NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Tivozanib for treating renal cell carcinoma [ID591]

Committee Papers

NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tivozanib for treating renal cell carcinoma [ID591]

Contents:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Pre-meeting briefing

Tivozanib for treating renal cell carcinoma

This slide set is the pre-meeting briefing for this appraisal. It has been prepared by the technical team with input from the committee lead team and the committee chair. It is sent to the appraisal committee before the committee meeting as part of the committee papers. It summarises:

- the key evidence and views submitted by the company, the consultees and their nominated clinical experts and patient experts and
- the Evidence Review Group (ERG) report

It highlights key issues for discussion at the first appraisal committee meeting and should be read with the full supporting documents for this appraisal

Please note that this document includes information from the ERG before the company has checked the ERG report for factual inaccuracies

The lead team may use, or amend, some of these slides for their presentation at the Committee meeting

Abbreviation	In full
AE	Adverse event
CHMP	Committee for Medicinal Products for Human Use
DIC	Deviance information criterion
ECOG	Eastern Cooperative Oncology Group
EQ-5D	EuroQol five dimensions questionnaire
ERG	Evidence review group
FP	Fractional polynomial
HR	Hazard ratio
HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
IFN	Interferon
IPCW	Inverse probability of censoring weights
ITT	Intention to treat
KM	Kaplan-Meier
MAIC	Matched adjusted indirect comparison
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	Mammalian target of rapamycin
NMA	Network meta-analysis
OS	Overall survival
PAS	Patient access scheme
PFS	Progression-free survival
QALY	Quality-adjusted life year
RCC	Renal cell carcinoma
RDI	Relative dose intensity
RPSFT	Rank preserving structural failure time
TKI	Tyrosine kinase inhibitor
VEGF(R)	Vascular endothelial growth factor (receptor)

Key issues – clinical effectiveness

- Where will tivozanib be used in the treatment pathway?:
  - treatment-naive population (1st line)
- Is the clinical trial TIVO-1 generalisable to UK practice in terms of baseline characteristics?
- Is the analysis using treatment-naive patients or the whole trial population most relevant?
- Do overall survival results in geographical subgroups support effectiveness of tivozanib in UK?
- What is the most appropriate method for crossover adjustment (IPCW, RPSFT, other [MAIC])?
  - Does the proportional hazards assumption hold?
- What is the most appropriate approach for extrapolation (e.g. fractional polynomial method, other)?
- Are results from the network meta-analysis plausible?
  - Are the other trials in the network generalisable to NHS clinical practice?
  - Should the trials be adjusted for crossover?
- Is tivozanib clinically effective?

Disease background and management

Kidney cancer

- More common in men than women
- Five-year survival is 56%, varying with age
- 86% of renal cancers are renal cell carcinoma

Renal cell carcinoma

- Estimated 9,045 new diagnoses in England per year
- Disease is often locally advanced or metastatic at point of diagnosis
- Early stage disease can be treated surgically – half of patients who have surgical treatment will develop metastatic disease
- Overall survival for people with metastatic disease is 8 months to 3.6 years

Tivozanib (Fotivda)
EUSAPharma

UK marketing authorisation	First line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC
Administration	Oral therapy
Mechanism of action	Tyrosine kinase inhibitor with affinity for all three vascular endothelial growth factor receptors, leading to reduced vascularisation of tumours
Dosage	1,340 micrograms (one tablet) tivozanib once daily for 21 days, followed by a 7-day rest period 890 micrograms capsule is available so that the dose can be reduced if necessary

Decision problem

	Final scope issued by NICE	Company's decision problem
Population	Adults with recurrent or metastatic renal cell carcinoma (RCC)	Adults with recurrent or metastatic RCC
Outcome	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment

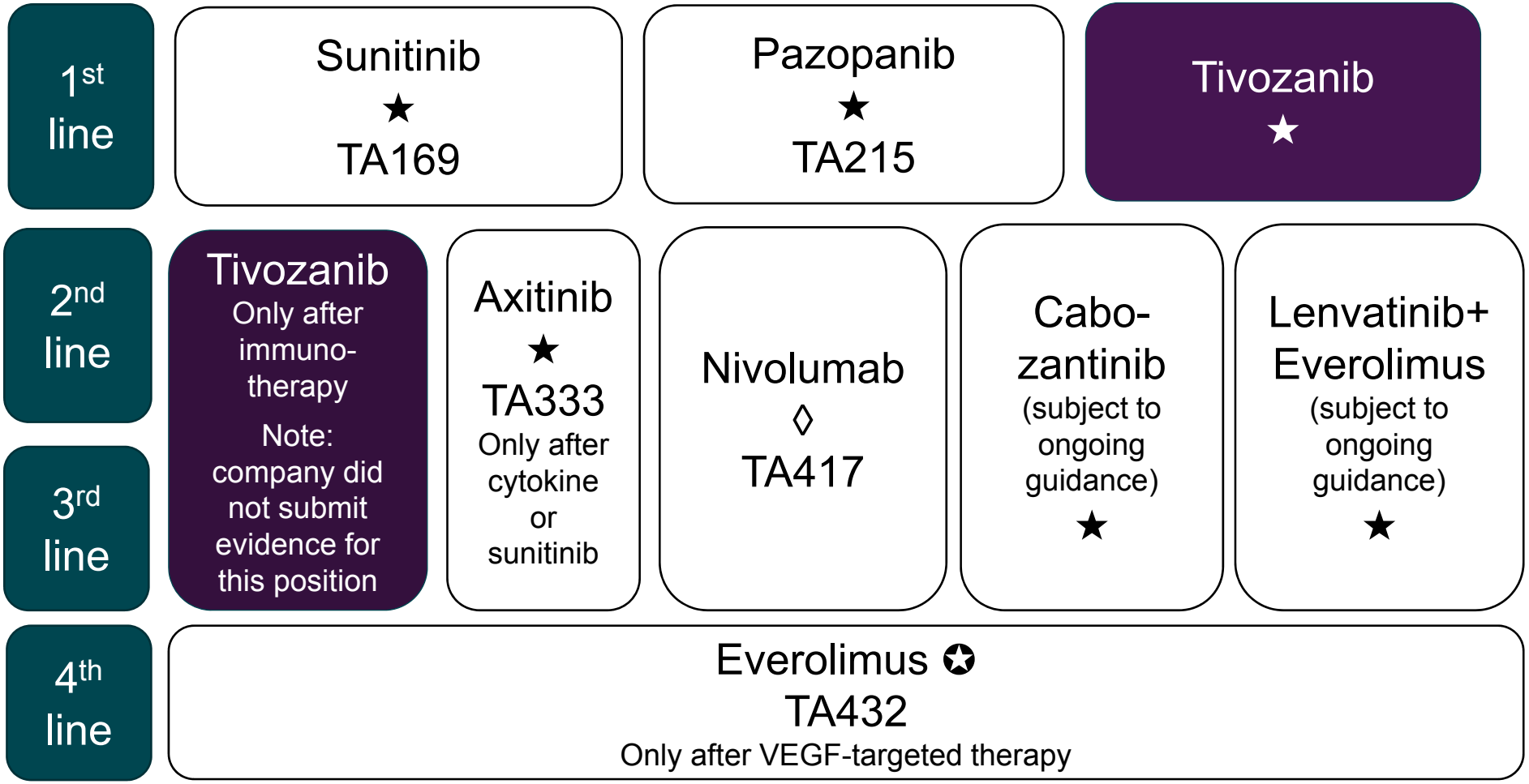
Company states there is insufficient data from trials for independent analysis of health-related quality of life

Decision problem

	Final scope issued by NICE	Company's decision problem
Comparator	Untreated disease: • Sunitinib • Pazopanib • Immunotherapy (interferon-alfa, interleukin-2) Previously treated disease: • Axitinib • Nivolumab • Everolimus • Cabozantinib • Best supportive care	Untreated disease: • Sunitinib • Pazopanib • Immunotherapy (interferon-alfa, interleukin-2)

- Company: Tivozanib will not be used for previously-treated disease in NHS clinical practice
- Marketing authorisation for tivozanib as 2nd line is for use after immunotherapy, which is not used in UK

Current treatment pathway



Key; VEGF, vascular endothelial growth factor

★: oral tyrosine kinase inhibitors; ✪: oral mammalian target of rapamycin (mTOR) inhibitor; ◊ **:** anti-programmed death 1 (PD-1) inhibitor

Comments from patient and professional groups

- Patient groups
  - People may experience constant pain as well as psychological effects e.g. depression, loss of confidence and self-worth
  - Many patients have to give up work due to debilitating effects of disease and treatments available – leads to financial pressures
  - Few treatment options available currently and adverse effects are significant e.g. extreme fatigue, severe hand and foot syndrome, chronic diarrhoea
  - No biomarkers to predict who will respond to each drug, therefore range of treatment options important
- Professional groups
  - Sunitinib or pazopanib currently used first line (sorafenib not used first line in UK)
  - Concern about study design, crossover rates and lack of a standard of care comparator in the first line setting in TIVO-1 study
  - Adverse event profile of tivozanib is comparable with other TKIs

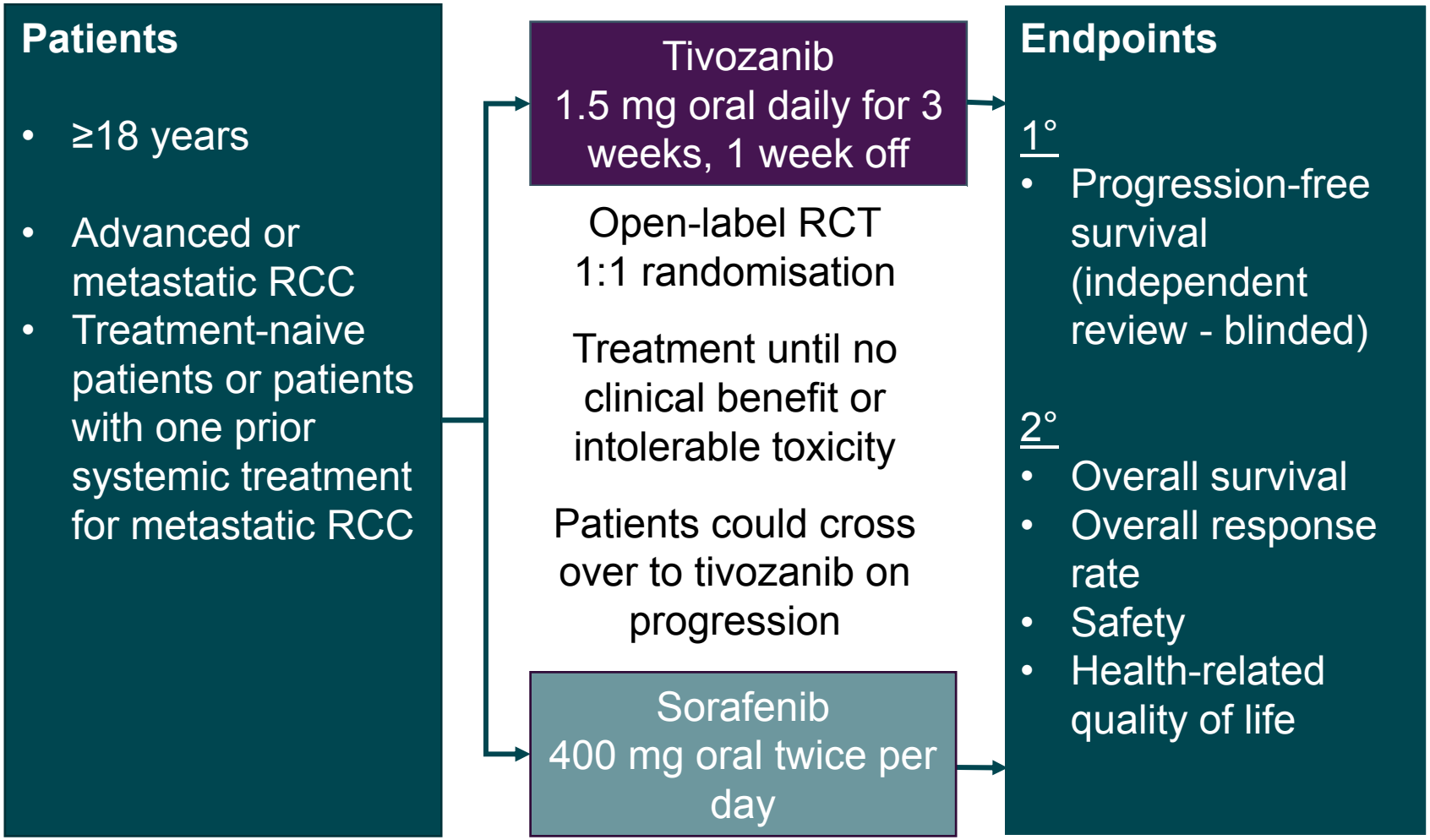
ERG comments

Agree with company about the appropriate comparators

- Agree that cytokines (immunotherapy) are not a relevant comparator for untreated disease as rarely used in UK
- Agree that axitinib, nivolumab, everolimus, cabozantinib and best supportive care are not relevant comparators given the evidence submitted and proposed marketing authorisation

Company's clinical evidence

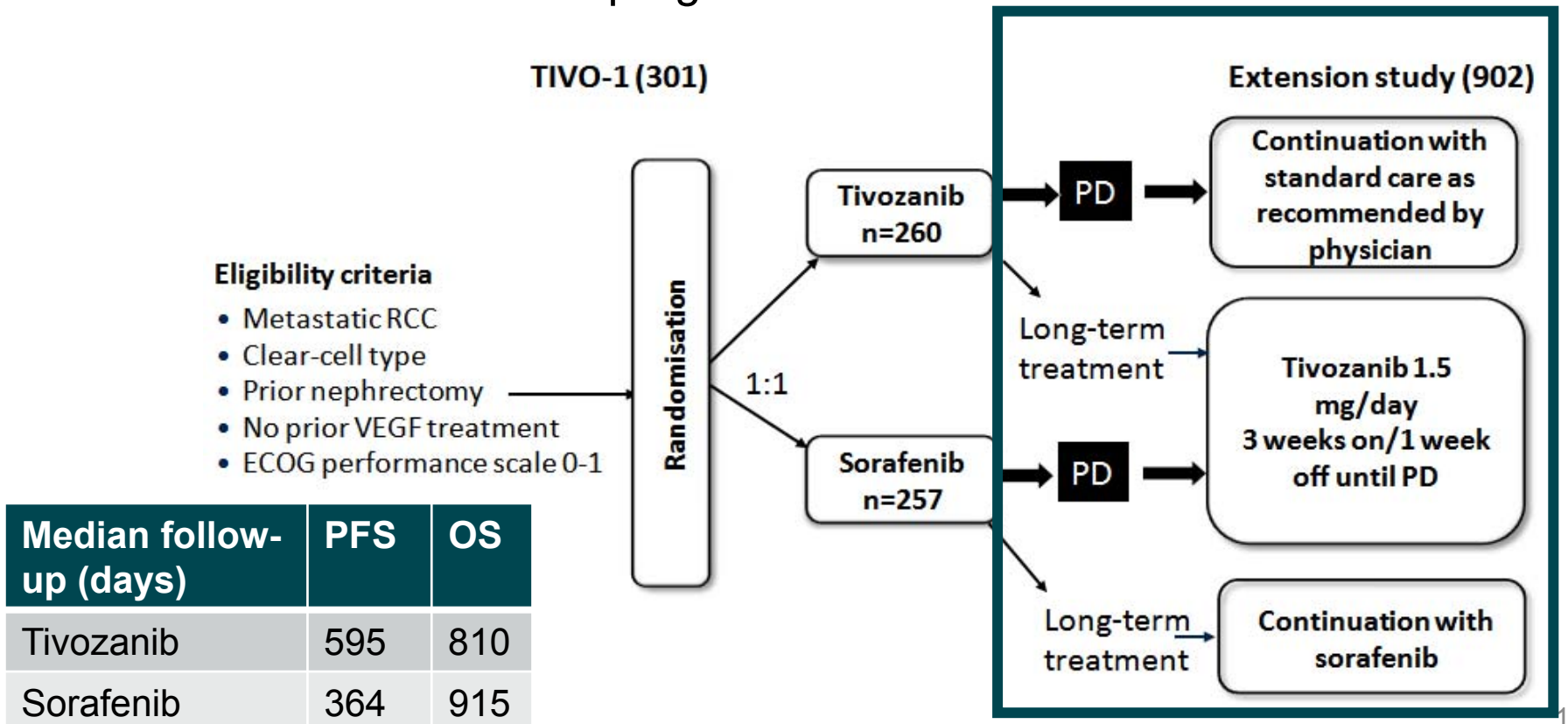
Tivozanib vs sorafenib: TIVO-1 trial (n=517)



RCT, randomised controlled trial; HR, hazard ratio; OR, odds ratio

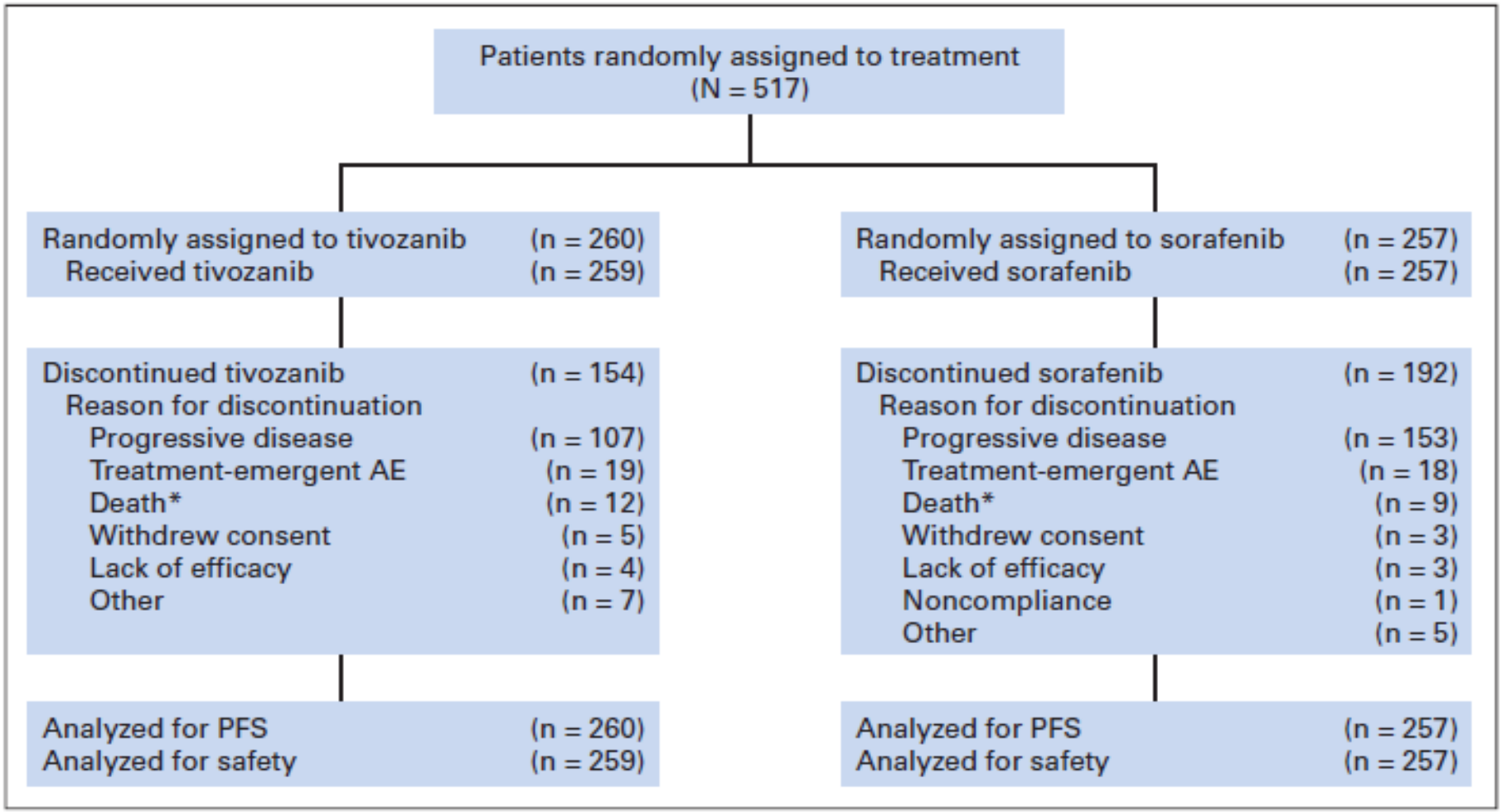
Company's clinical evidence
Extension study 902

- Extension study AV-951-09-902 **"902"**
  - allowed long-term access to tivozanib or sorafenib
  - one-way crossover study: patients in sorafenib arm could cross over to tivozanib arm after progression



Median follow-up (days)	PFS	OS
Tivozanib	595	810
Sorafenib	364	915

Participant flow in TIVO-1



TIVO-1 baseline characteristics

	Tivozanib (n=260)		Sorafenib (n= 257)	
Characteristic	No.	%	No.	%
Age, years				
Median		59		59
Range		23-83		23-85
Sex				
Male	185	71	189	74
Female	75	29	68	26
Race/ethnicity				
White	249	96	249	97
Asian	10	4	8	3
Black	1	<1	0	0
Time from diagnosis to study entry, years				
<1	109	42	105	41
>1	137	53	137	53
Most common sites of metastasis				
Lung	212	82	204	79
Lymph nodes	182	70	166	65
Adrenal gland	78	30	57	22
Liver	67	26	49	19
Bone	61	23	52	20

TIVO-1 baseline characteristics, cont.

	Tivozanib (n=260)		Sorafenib (n= 257)	
Characteristic	No.	%	No.	%
No. of organs involved				
1	76	29	88	34
2	99	38	106	41
>2	85	33	63	25
Eastern Cooperative Oncology Group performance score				
0	116	45	139	54
1	144	55	118	46
Memorial Sloan-Kettering Cancer Center prognostic group				
Favourable	70	27	87	34
Intermediate	173	67	160	62
Poor	17	7	10	4
Prior systemic therapy for metastatic renal cell carcinoma				
0	181	70	181	70
1	78	30	76	30
Prior systemic therapy by setting				
Metastatic	49	19	55	21
Adjuvant	23	9	22	9
Other	13	5	9	4

TIVO-1 baseline characteristics

Treatment-naive population

	Full population		Treatment-naive	
	Tivozanib	Sorafenib	Tivozanib	Sorafenib
N (% of randomised)	260 (100)	257 (100)	181 (70)	181 (70)
Median age (range)	59 (23-83)	59 (23-85)	59 (23-83)	59 (23-85)
Male, n (%)	185 (71)	189 (74)	134 (74)	135 (75)
ECOG performance status, n (%) 0	116 (45)	139 (54)	85 (47)	94 (52)
1	144 (55)	118 (46)	96 (53)	87 (48)
Region				
……North America /Western Europe	22 (9)	18 (7)	19 (11)	15 (8)
Central/Eastern Europe	229 (88)	228 (89)	154 (85)	155 (86)
Rest of world	9 (3)	11 (4)	8 (4)	11 (6)
Number of metastatic organs, n (%)				
1	76 (29)	88 (34)	53 (29)	65 (36)
≥2	184 (71)	169 (66)	128 (71)	116 (64)
MSKCC prognostic group, n (%)				
Favourable	70 (27)	87 (34)	48 (27)	60 (33)
Intermediate	173 (67)	160 (62)	121 (67)	112 (62)
Poor	17 (7)	10 (4)	12 (7)	9 (5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Center.

TIVO-1 subsequent therapies

	Full population		Treatment-naive	
	Tivozanib (N=259)* N (%)	Sorafenib (N=257) N (%)	Tivozanib (N=182)* N (%)	Sorafenib (N=181) N (%)
Received randomised therapy only	180 (69.5)**	83 (32.3)	128 (70.3)	57 (31.5)
Received subsequent therapy	79 (30.5)	174 (67.7)	54 (29.7)	124 (68.5)
Targeted therapy	53 (20.5)	169 (65.8)	37 (20.3)	120 (66.3)
First targeted therapy used:				
Tivozanib	0 (0.0)	161 (62.6)	0 (0.0)	114 (63.0)
Other VEGF inhibitor	24 (9.3)	4 (1.6)	17 (9.3)	2 (1.1)
mTOR inhibitor	29 (11.2)	4 (1.6)	20 (11.0)	4 (2.2)
Non-targeted therapy only	26 (10.0)	5 (1.9)	17 (9.3)	4 (2.2)
First non-targeted treatment used:				
Immunotherapy	13 (5.0)	3 (1.2)	NR	NR
Radiotherapy	5 (1.9)	2 (0.8)	NR	NR
Chemotherapy	1 (0.4)	0 (0.0)	NR	NR
Surgery	2 (0.8)	0 (0.0)	NR	NR
Other	5 (1.9)**	0 (0.0)	NR	NR

mTOR, mammalian target of rapamycin; N, number of patients; VEGF, vascular endothelial growth factor; NR, not reported

ERG comments on clinical trial

- Considerable uncertainty in estimate of overall survival introduced due to subsequent therapies received
- Inconsistencies in reported results due to multiple data cuts
- Population is generalisable to a UK population likely to be eligible for treatment with tivozanib in NHS
- However, population enrolled in TIVO-1 study may have better prognosis than full population in scope
- ERG clinical experts consider only treatment-naive population relevant to population eligible for tivozanib in England

History of company's analyses

Stage of process	TIVO-1 analysis	Network meta-analysis
Company's submission	• Full trial population • **PFS**: Kaplan-Meier with Cox hazard ratios • **OS**: Kaplan-Meier with Cox hazard ratios and IPCW adjustment for crossover	• Complex network • Both treatment-naive only and mixed analyses • Immunotherapy included as comparator • Calculated hazard ratios • No crossover adjustment
Clarification	• Treatment-naive population • **OS**: RPSFT adjustment for crossover	• Simplified network • Treatment-naive only • Immunotherapy not included • Based on parametric curves (Weibull) • No crossover adjustment
Post-clarification	• No change	• Fractional polynomial curves – **used in economic model** • No crossover adjustment

PFS, progression-free survival; OS, overall survival; IPCW, inverse probability of censoring weights; RPSFT, rank preserving structural failure time

Clinical effectiveness results – summary

Progression-free survival, December 2011 data cut

	Median, months		Hazard ratio	95% confidence intervals	P value
	Tivo	Sora			
Full population, unadjusted	11.9	9.1	0.797	0.639 to 0.993	0.042
Full population, adjusted for baseline demographics and geographical region; post-hoc analysis	NR	NR	0.725	0.58 to 0.91	0.006
Treatment-naive subgroup, unadjusted	12.7	9.1	0.756	0.581 to 0.985	0.037

NR, not reported.

ERG considers results from original PFS Cox analyses inappropriate as proportional hazards do not hold.

Clinical effectiveness results – summary

Overall survival

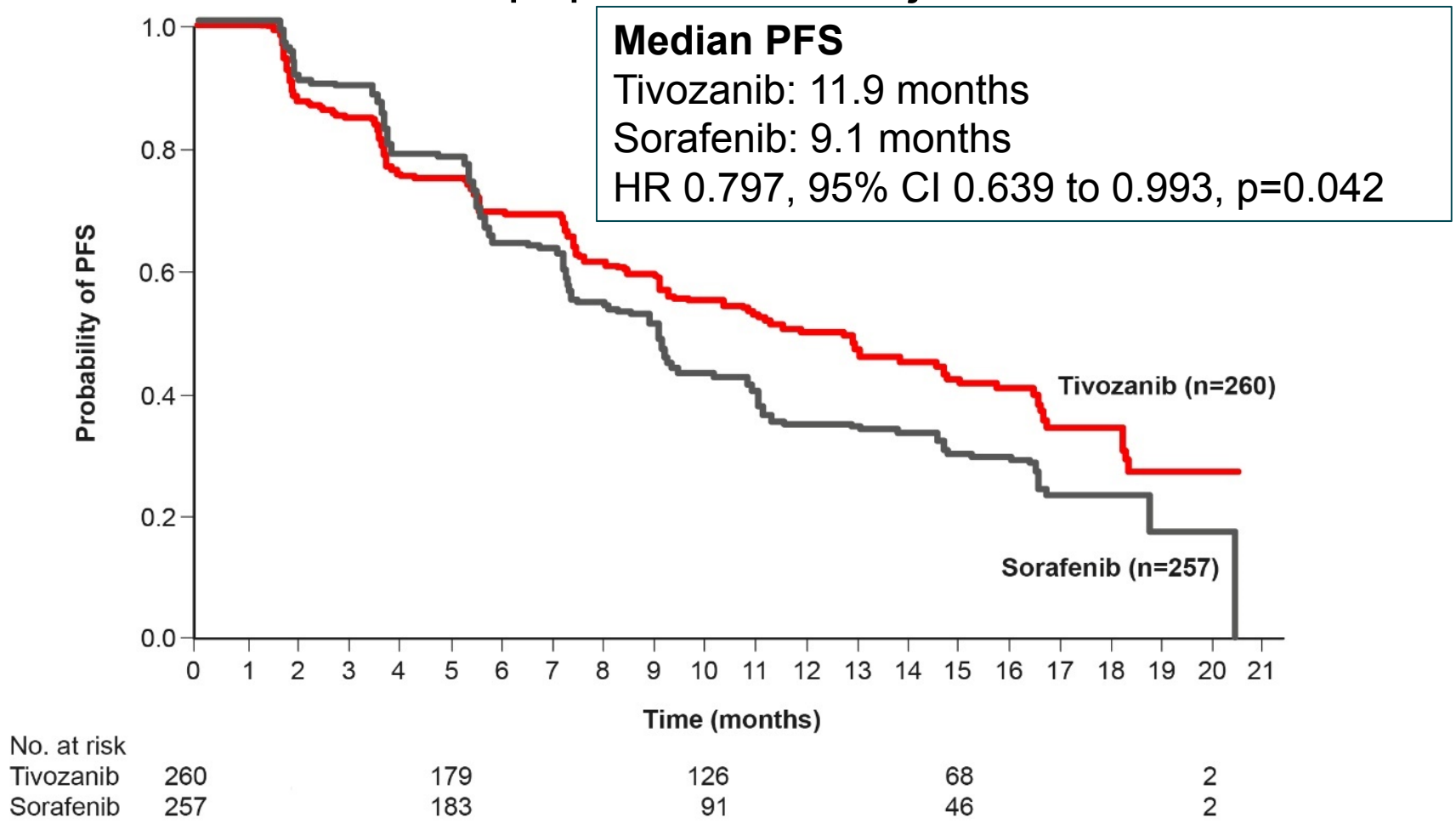
	Median, months		Hazard ratio	95% confidence intervals	P value
	Tivo	Sora			
Full population, Jan 2015 data cut, unadjusted for crossover	29.0	34.1	1.18	0.930 to 1.504	0.078
Full population, IPCW-adjusted*	NR	NR	1.021	0.671 to 1.553	0.923
Treatment-naive subgroup, unadjusted for crossover, Jul 2013 data cut	NR	NR	1.23	0.90 to 1.67	NR
Treatment-naive subgroup, RPSFT-adjusted*	Kaplan-Meier plot from independent curve fitting				
Subgroup analyses by geographical location, full population July 2013**					
N America & EU	32.9	29.5	0.846	NR	0.433
N America & EU5	NA	29.5	0.497	NR	0.136
Russia & Ukraine	26.3	32.0	1.383	NR	0.051

*Unclear which data cut used. NR, not reported; NA&EU: US, Canada, Bulgaria, Czech Republic, France, UK, Hungary, Italy, Poland, Romania. NA&EU5: US, Canada, Italy, France, UK

***amended after committee meeting*

Progression-free survival results

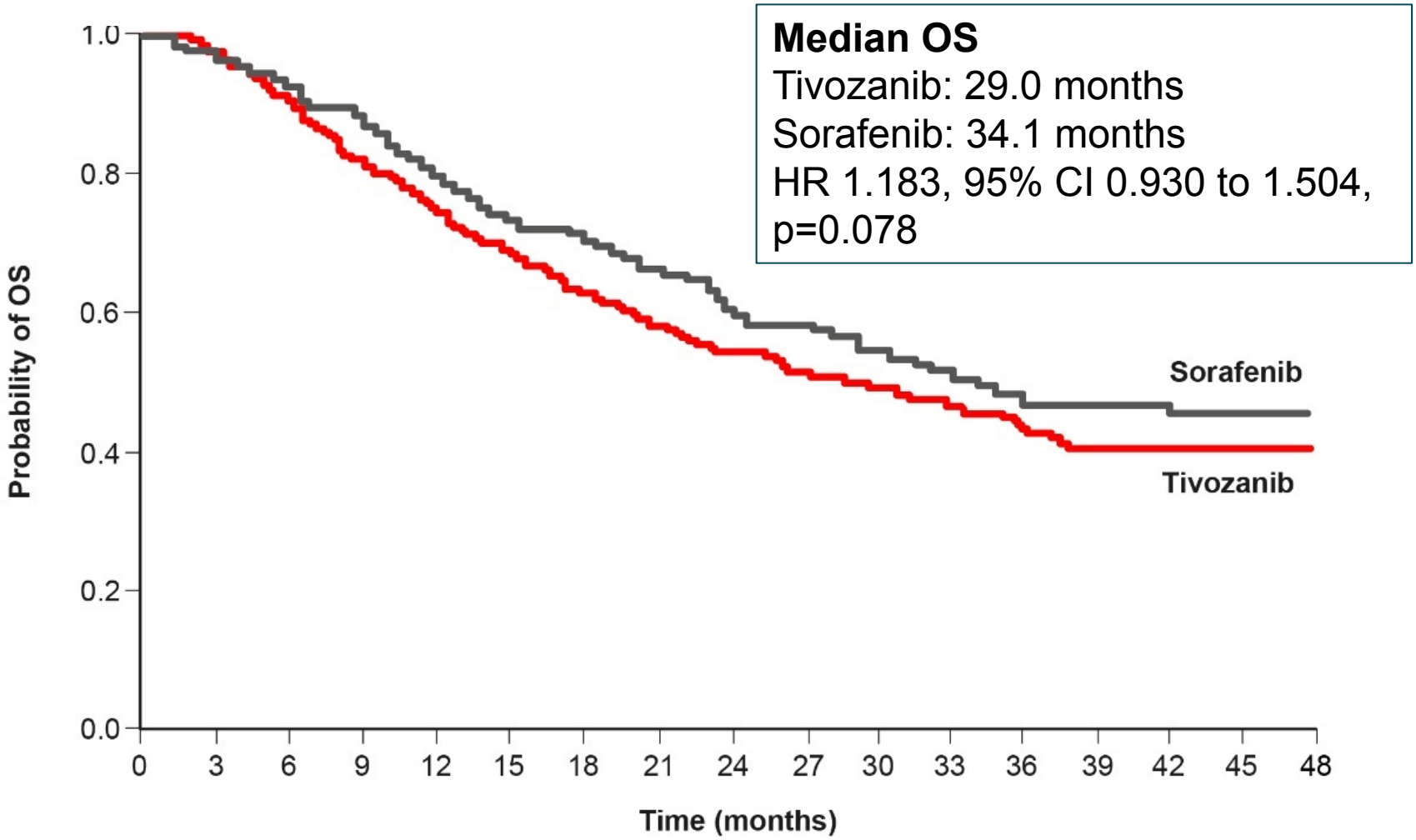
Full trial population, unadjusted



Kaplan-Meier plot of PFS as determined by independent radiology review (December 2011 data cut)

Overall survival results

Full trial population, unadjusted



Kaplan-Meier plot of overall survival, Jan 2015 data cut, unadjusted for crossover

Methods used to analyse overall survival
Substantial treatment switching causes confounding

- 161 patients who progressed on sorafenib crossed over to receive tivozanib (62.6%)
- Likely effect of crossover is to increase survival times for sorafenib group compared to no crossover
- To adjust for confounding effect of crossover, company employed two separate methods:
  - **Inverse probability of censoring weights method (IPCW)** → used in company's original submission and its preferred approach (based on full trial population)
  - **Rank preserving structural failure time method (RPSFT)** → in response to ERG suggestion at clarification stage (based on treatment-naive population)

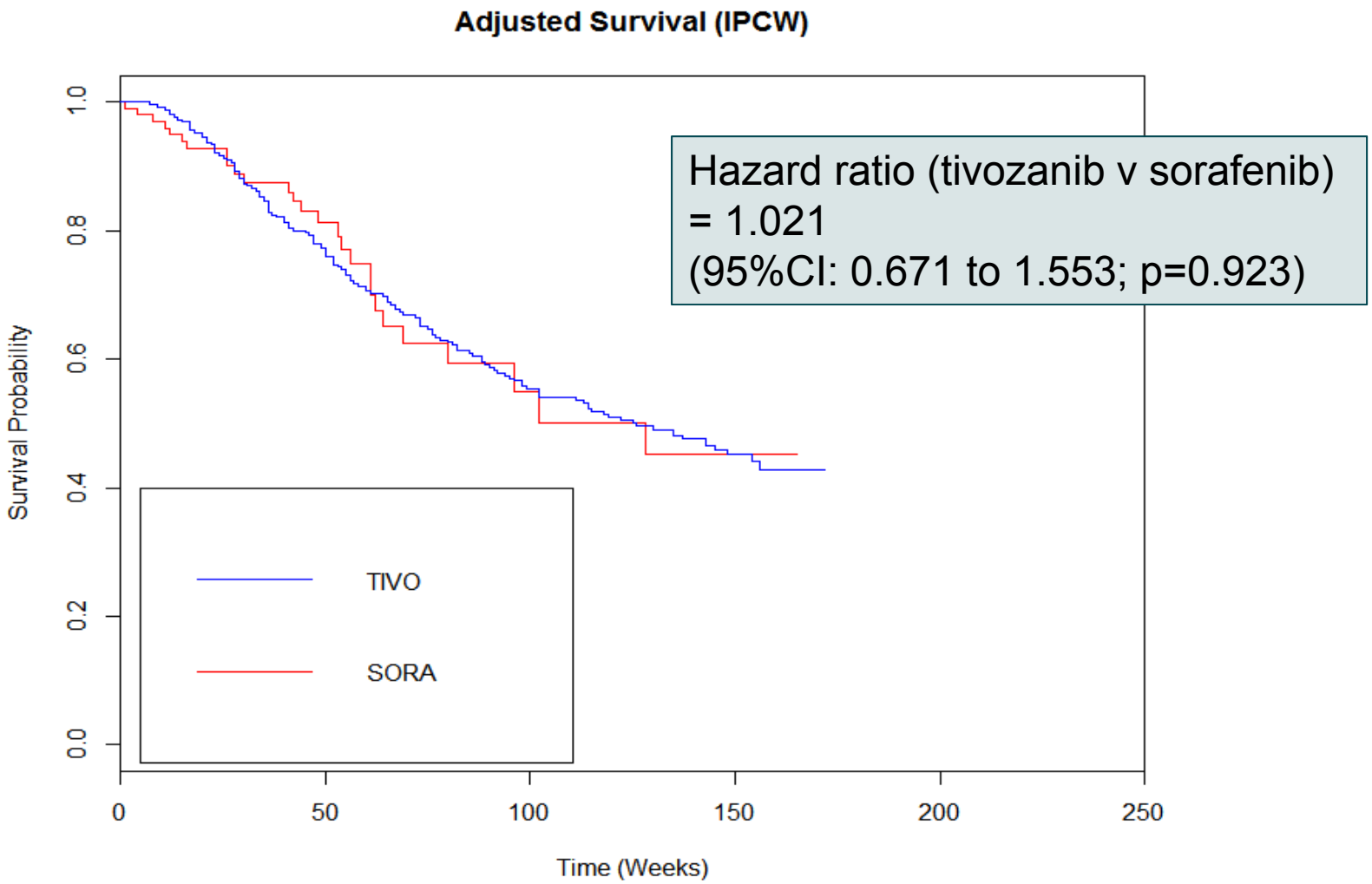
IPCW method for overall survival

Analysis methods – company's preferred approach

- Patients are artificially censored at the point of switch and remaining observations are weighted
- Aim is to remove bias associated with censoring
- Company used this method in its original submission (using full trial population) as RPSFT method assumes treatment benefit with tivozanib is the same regardless of patients' original randomisation
  - Company believes this is clinically implausible as patients who crossover are further along disease course

IPCW method for overall survival

Results of adjusted analysis – full trial population



Hazard ratio (tivozanib v sorafenib) = 1.021
(95%CI: 0.671 to 1.553; p=0.923)

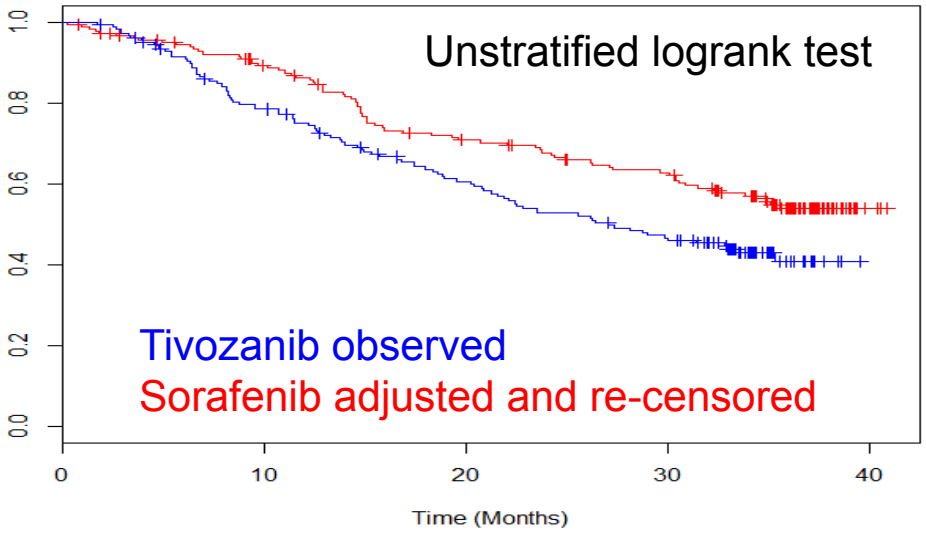
RPSFT method for overall survival

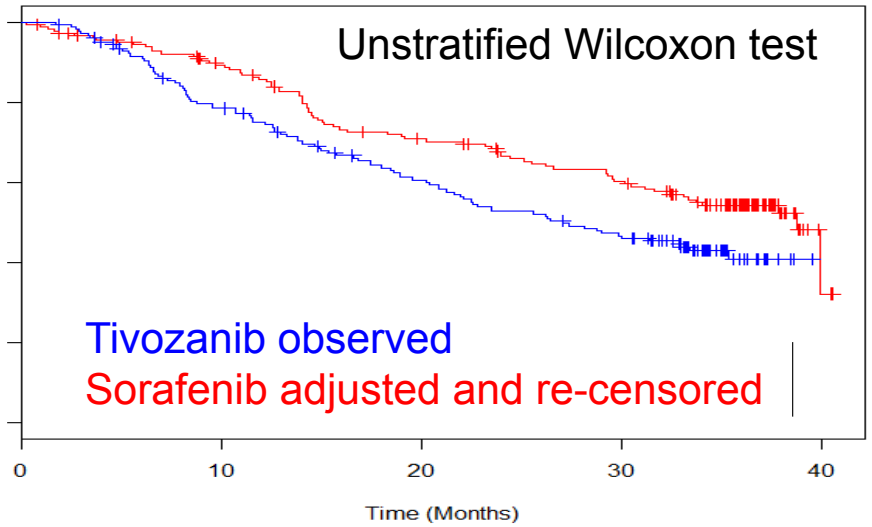
Analysis methods

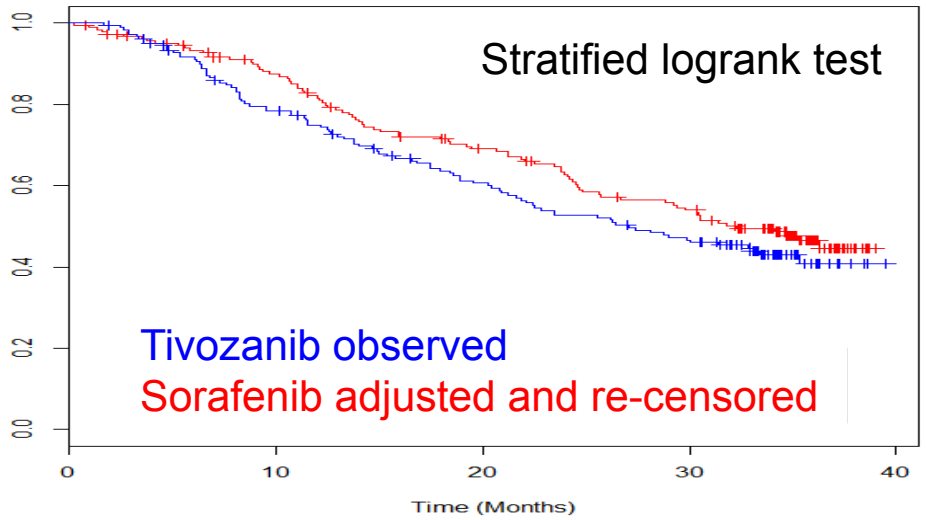
- Treatment-naive population used
- Effect of exposure to tivozanib on survival time estimated
- Failure times in sorafenib arm adjusted using the estimate of the effect of exposure to tivozanib, to model a scenario in which patients did not cross over to tivozanib
- Hazard ratio estimated (using Cox proportional hazards regression model) for the tivozanib arm compared to the simulated sorafenib arm
- Company modelled 4 separate analyses:
    1. Unstratified logrank test
    2. Unstratified Wilcoxon test
    3. Stratified logrank test
    4. Stratified Wilcoxon test
- Stratification based on patient baseline characteristics – ECOG performance status, MSKCC risk category and number of metastatic disease sites.

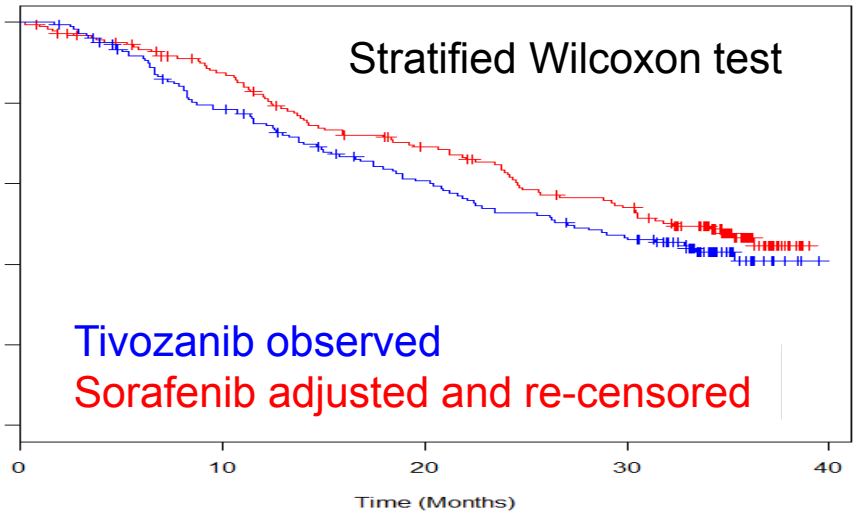
RPSFT method for OS

Adjusted survival distributions – treatment-naive population









RPSFT method for OS
Limitations

- Company note 3 limitations of using the RPSFT method:
  1. RPSFT suitable for placebo controlled trials, so if sequential treatment with sorafenib then tivozanib leads to a better or worse overall survival compared with only tivozanib, this would not be captured
  2. 3.7% of patients in sorafenib arm &13% of patients in tivozanib arm received anti-cancer treatments other than tivozanib after the study, which are not accounted for in this analysis
  3. 'Common treatment assumption' that average event times in each group would be the same if no patient were treated with tivozanib does not hold because:
     - Sorafenib is active treatment so if tivozanib removed from study, would not expect similar OS between the groups
     - Baseline characteristics differ between the two groups

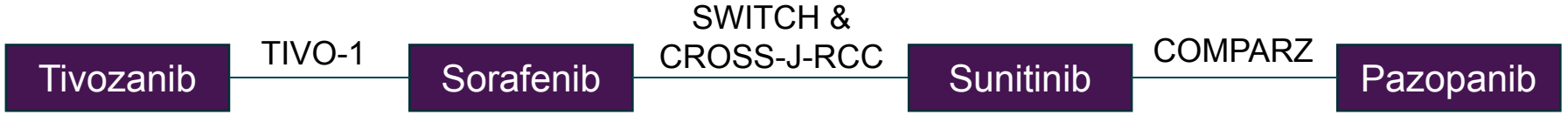
ERG comments on crossover adjustment
ERG prefers RPSFT approach

- Proportional hazard assumption does not hold – **see later**
- RPSFT-adjusted analyses do not support the IPCW-adjusted analyses
- ERG prefers RPSFT approach as is thought to be more reliable when large proportion of patients switch treatments, as in TIVO-1
- OS estimate unreliable despite adjustments for crossover
- Company suggest imbalance in subsequent therapies biased OS against tivozanib, but ERG states the bias caused by this imbalance cannot be quantified
- Crossover-adjusted results not used in network meta-analysis or model – ERG unable to predict direction and magnitude of bias

Network meta-analysis

To compare tivozanib to comparators without direct trial evidence

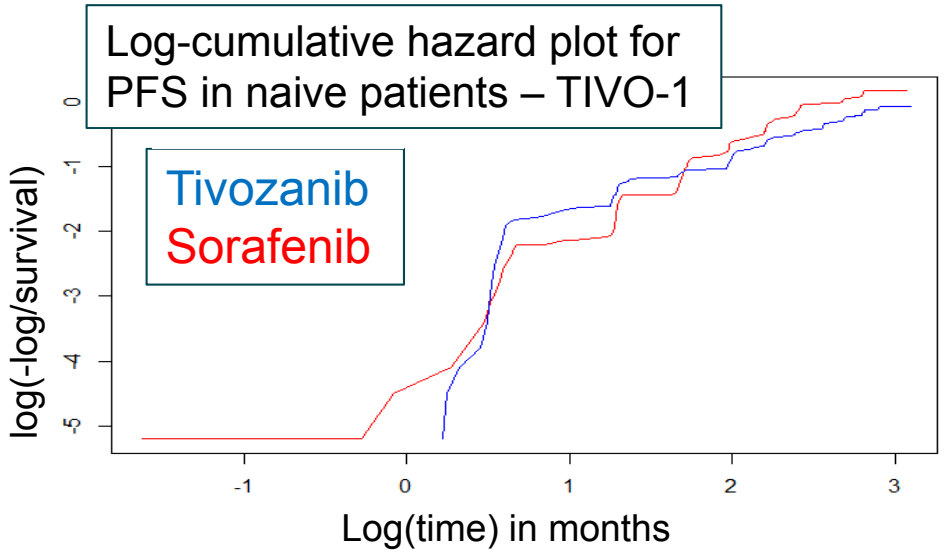
Company only consider patients who are **treatment-naive** in base case analysis

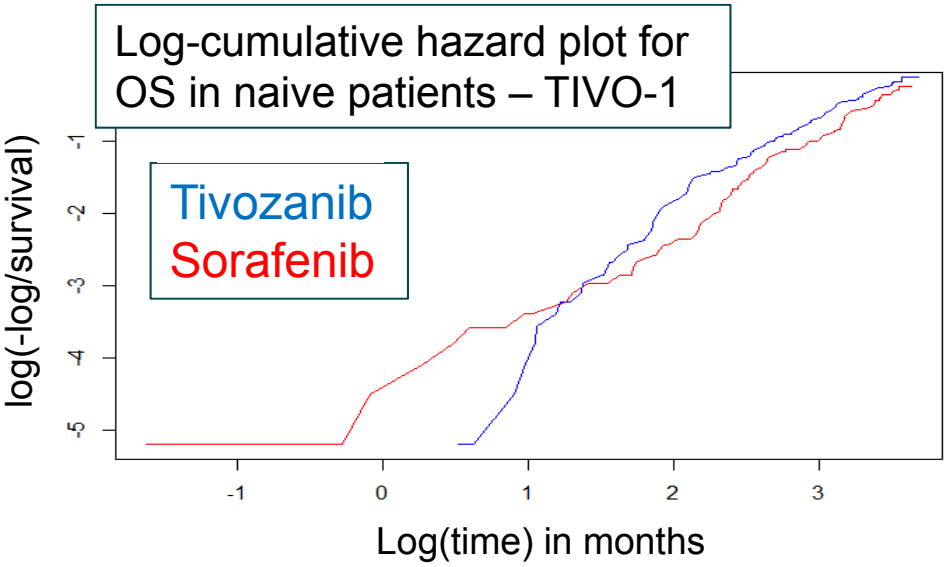


Trial number (acronym)	Population	Intervention	Comparator	Study methodology
COMPARZ Motzer et al. 2013	Clear cell metastatic RCC, treatment-naive	Pazopanib	Sunitinib **(crossover not reported)**	Open label phase III RCT, assessors partly blinded
Cross-J-RCC Tomita et al. 2014 and 2017	Clear cell metastatic RCC, treatment-naive	Sunitinib	Sorafenib **(planned crossover)**	Open label crossover RCT, abstract and poster only
SWITCH Eichelberg et al. 2015	Advanced/ metastatic RCC, treatment-naive or prior cytokine therapy	Sorafenib	Sunitinib **(planned crossover)**	Open label phase III crossover RCT
TIVO-1 Motzer et al. 2013	Clear cell recurrent/ metastatic RCC, treatment-naive or prior cytokines	Tivozanib	Sorafenib **(planned crossover)**	Open label phase III RCT, assessors partly blinded

Extrapolation & proportional hazards

- Proportional hazards assumption does not hold for PFS in TIVO-1
- Curves cross at around 5-7 months of follow up in the trial
- **Company use fractional polynomial method for extrapolation of PFS**
- OS – curves cross but then appear to have a linear trend
- Company state violation of proportional hazards in first 2-3 months unlikely to have meaningful impact on survival estimate and model results, but **use fractional polynomial method for extrapolation of OS as well**





Company's fractional polynomial model
Progression-free survival

- Company use fractional polynomial method to allow for a change in hazards over time
- Deviance information criterion (DIC) used to compare goodness of fit of fixed effects models with first and second order fractional polynomials
- Second-order fractional polynomial had lowest DIC so was used in base case

Power P1	Power P2	DIC
-2	-	973.724
-1	-	1026.39
-0.5	-	1103.31
0	-	1178.43
-2	-1	**932.832**

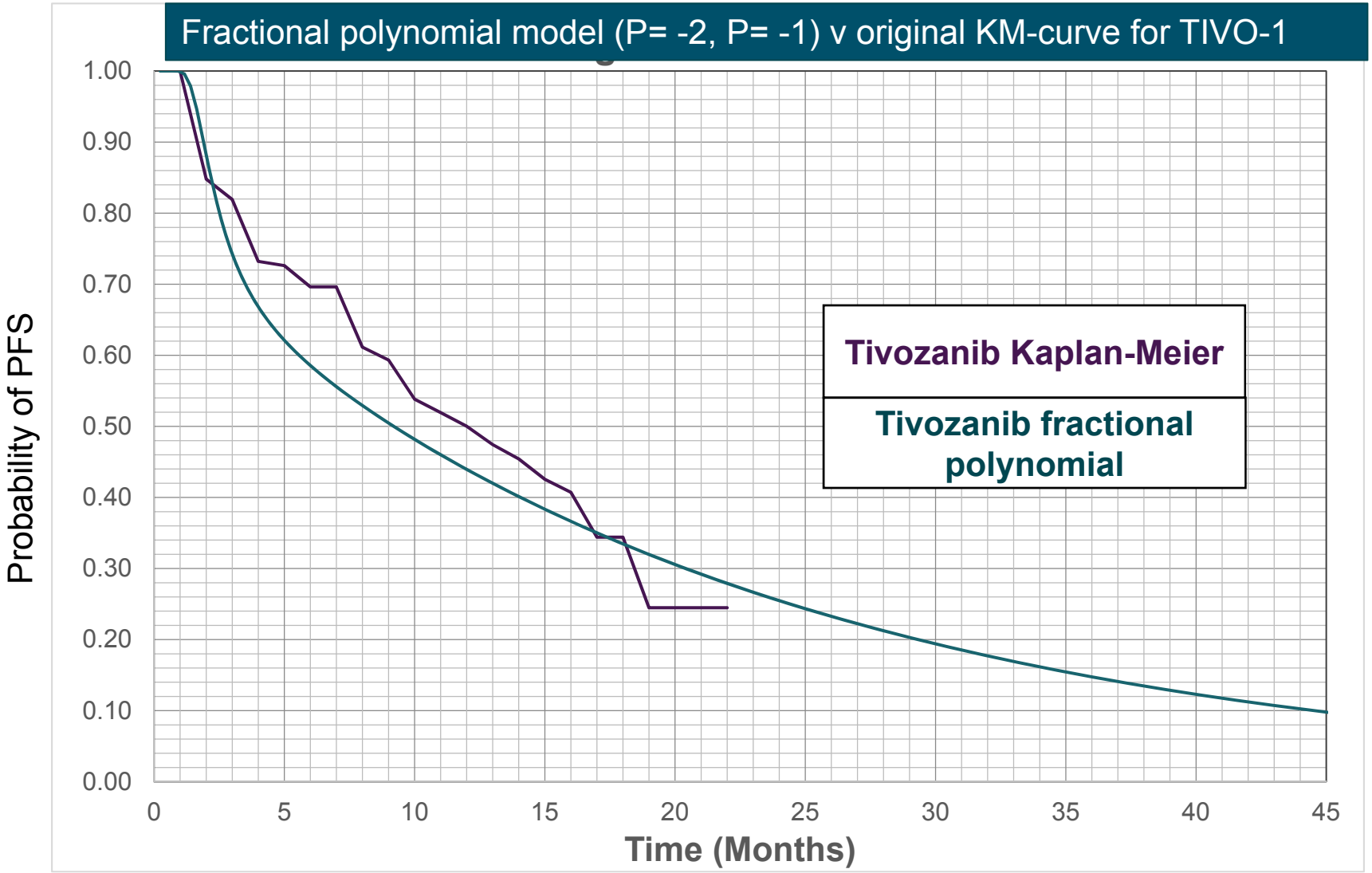
Goodness-of-fit estimates for fixed effects fractional polynomial models for different powers P1 and P2: Progression Free Survival

Power P1	Power P2	DIC
-2	-	864.418
-1	-	889.814
-0.5	-	921.329
0	-	957.12
-2	-1	**854.314**

Goodness-of-fit estimates for fixed effects fractional polynomial models for different powers P1 and P2: Overall Survival

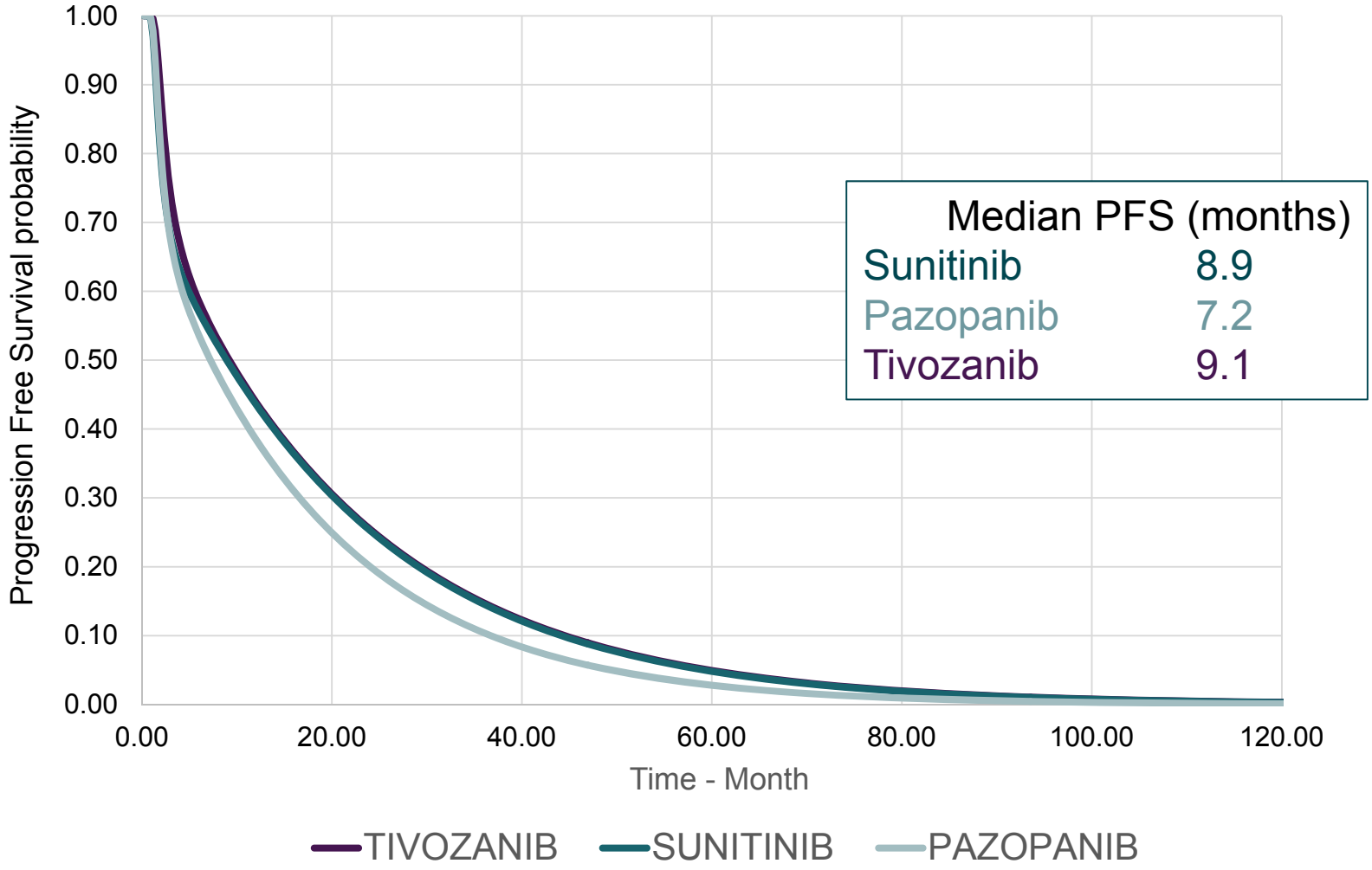
Company's fractional polynomial curve

Progression-free survival

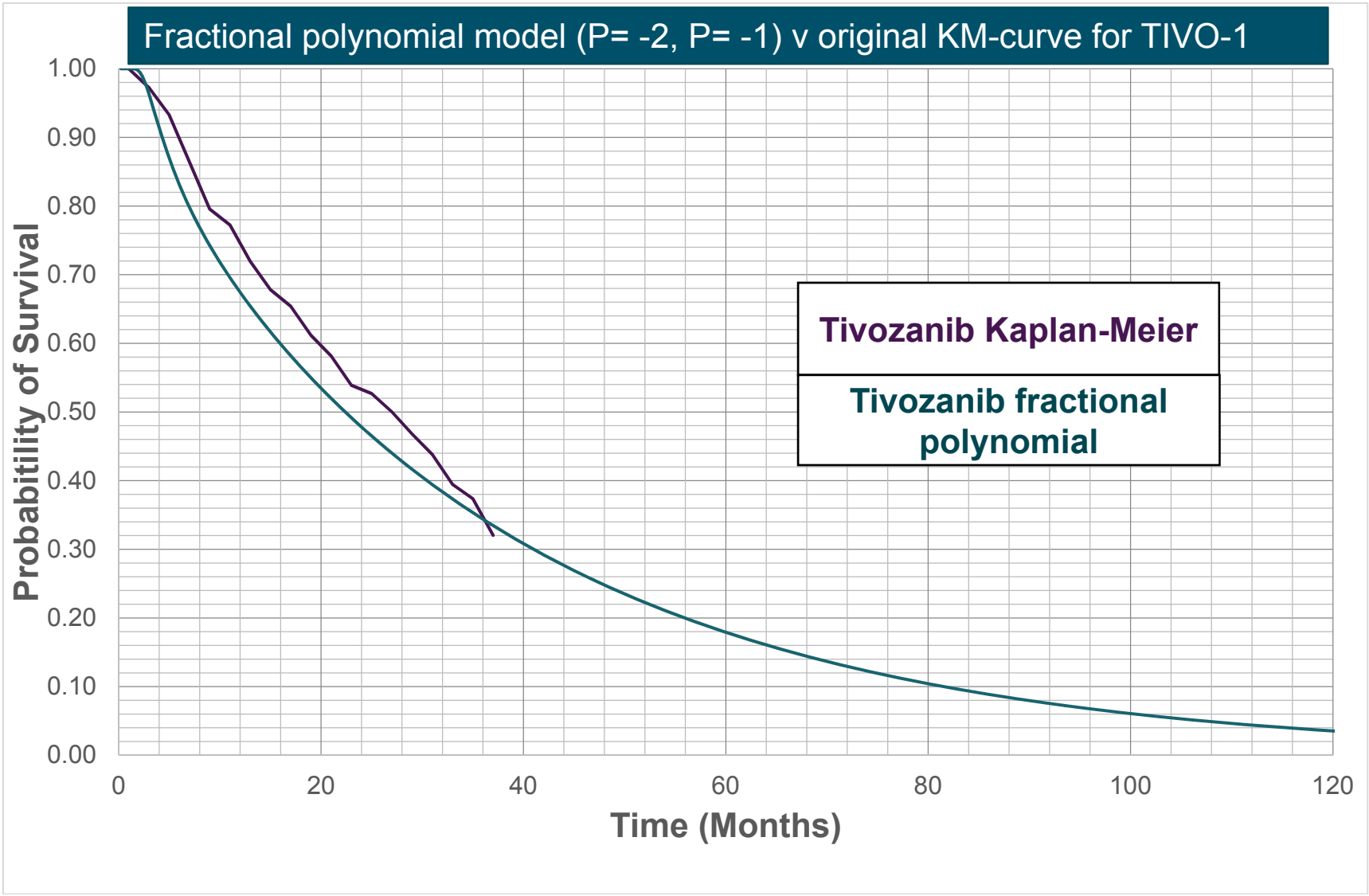


Network meta-analysis

Company's fractional polynomial method for PFS

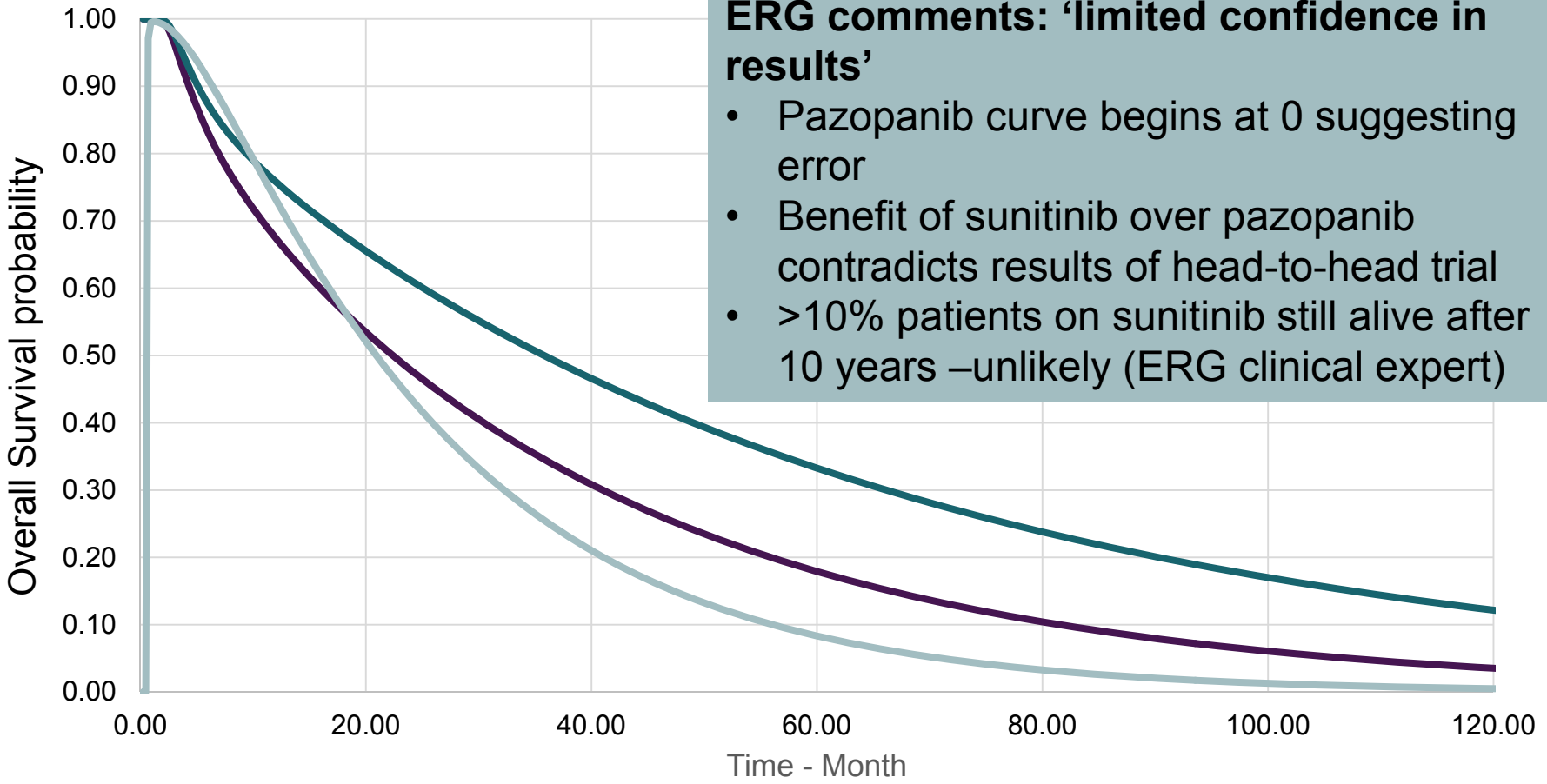


Company's fractional polynomial model – overall survival



Company's network meta-analysis for overall survival

Not adjusted for crossover



ERG comments: 'limited confidence in results'

- Pazopanib curve begins at 0 suggesting error
- Benefit of sunitinib over pazopanib contradicts results of head-to-head trial
- >10% patients on sunitinib still alive after 10 years –unlikely (ERG clinical expert)

Median OS:	TIVOZANIB 22.2 months	SUNITINIB 35.2 months	PAZOPANIB 20.8 months

ERG's comments on network-meta analysis and fractional polynomial approach

Issue	ERG's comments
Included trials	Inclusion criteria and population broadly similar
Crossover	• Company did not include crossover-adjusted data from TIVO-1 because it did not have crossover-adjusted data for SWITCH and CROSS-J-RCC • Treatment-switching more pronounced in TIVO-1 than in other studies • Incorporating RPSFT-adjusted results from TIVO-1 into the network would have been a useful scenario for comparison
Fractional polynomial method	• Fundamental flaw in calculation used to generate curves • Estimated within period hazard rather than cumulative hazard within model cycle → leads to implausible OS curves → **ERG corrects this** • Company only tested 1 second order fractional polynomial approach → **further scenarios conducted by ERG** • ERG's replication of the NMA did not match the company's results so additional exploratory analyses conducted

ERG DIC statistics for second order FPs

- PFS

	Power - P1	Power - P2	DIC
	-3	-3	**781**
ERG	-3	-2.5	**781**
	-3	-2	783
	-3	-1.5	785
	-3	-1	788
	-3	-0.5	792
	-2	-3	783
	-2	-2.5	783
	-2	-2	786
	-2	-1.5	789
	-2	-1	795

- OS

Power - P1	Power - P2	DIC
-3	-2.5	857
-3	-1.5	858
-3	-1	857
-3	-0.5	855
-3	0	853
-2	-3	858
-2	-2.5	857
-2	-2	858
-2	-1.5	855
-2	-1	855
-2	-0.5	852
-2	0	**849**
-2	0.5	850
-1	-1	851
-1	0	853

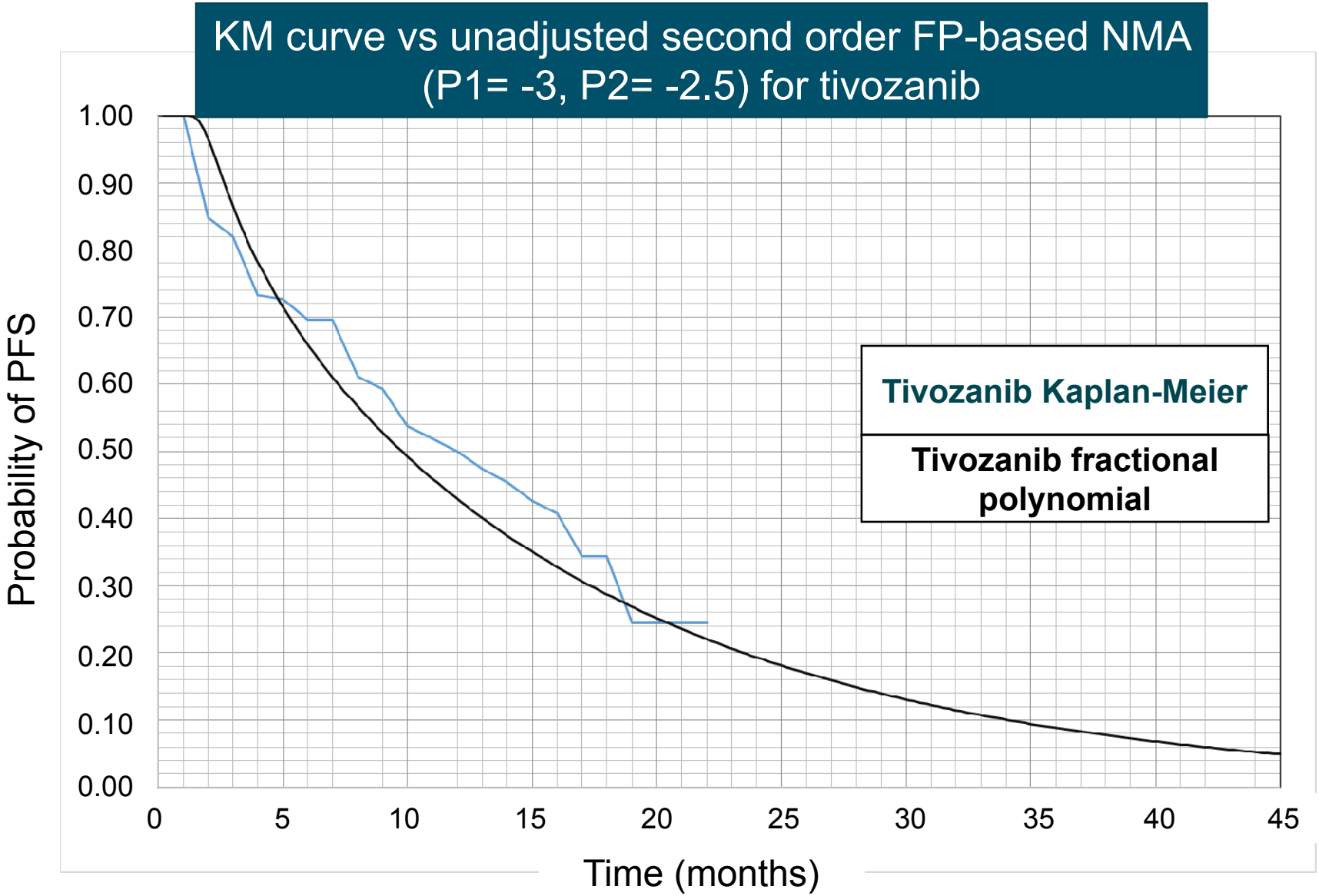
DIC, Deviance information criterion.

Note: Purple highlighted cells indicated company base case curve choice. Bold cells indicate lowest DIC. Blue rectangles indicate ERG curve choices.

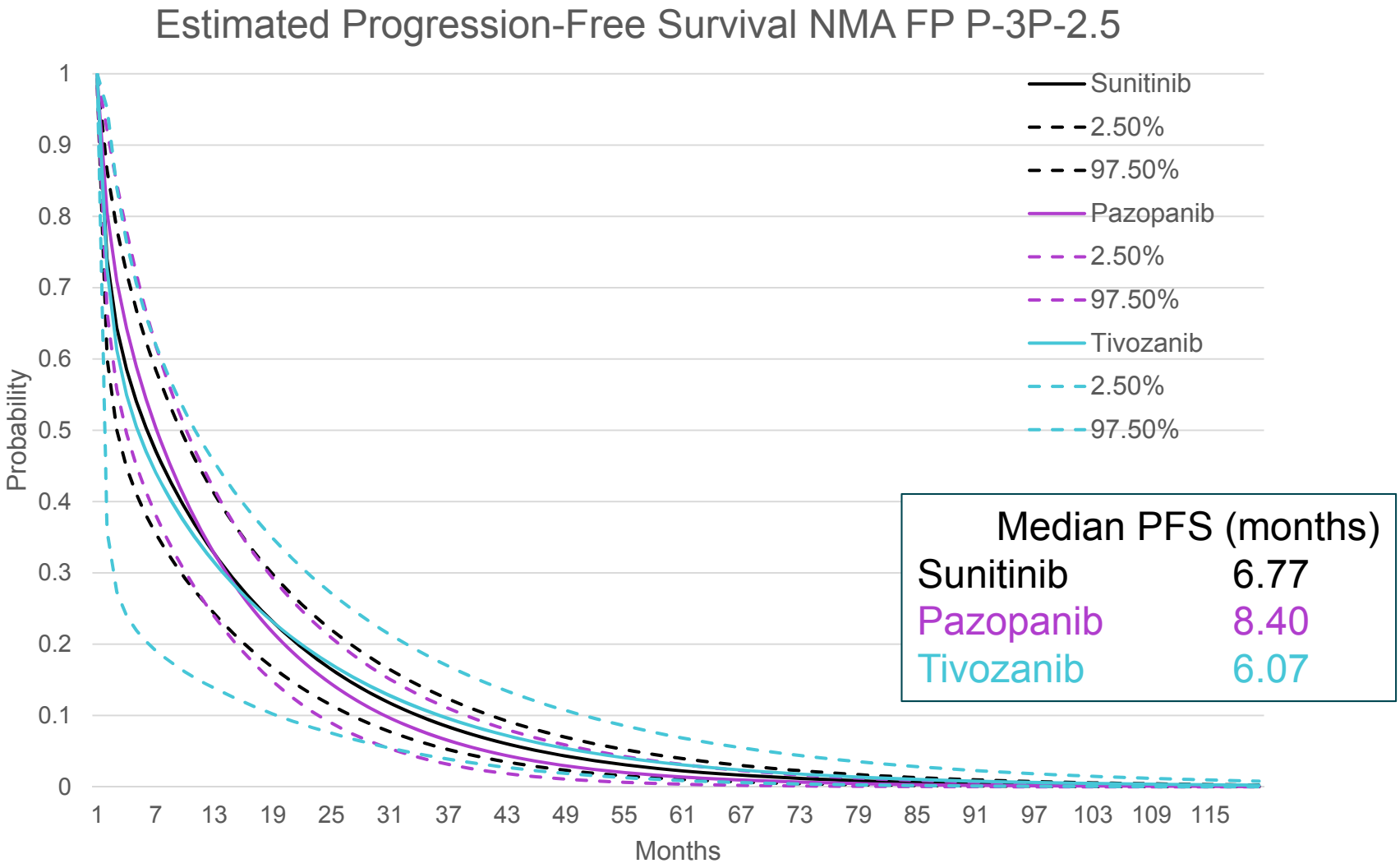
Summary of fractional polynomial NMA results

	Progression-free survival		Overall survival	
	Company	**ERG**	**Company**	**ERG**
Fractional polynomial order in base case	P= -2, P= -1	P= -3, P= -2.5	P= -2, P= -1	P= -2, P= -1.5
DIC statistic	795	781	855	855
Median (months)				
Tivozanib	9.1	6.1 ↓	22.2	25.0 ↑
Sunitinib	8.9	6.8 ↓	35.2	27.5 ↓
Pazopanib	7.1	8.4 ↑	20.8	29.2 ↑

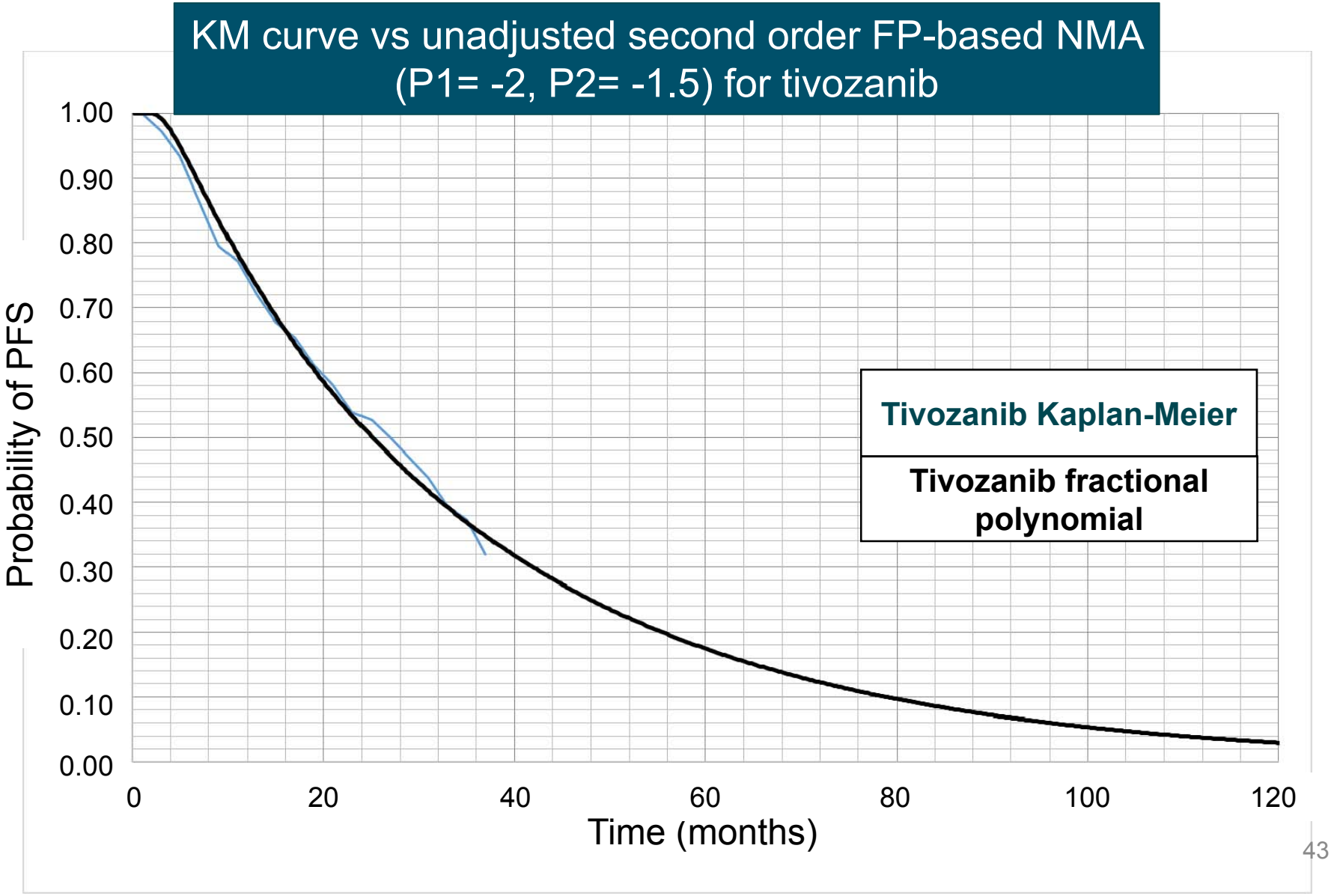
ERG's fractional polynomial curves - PFS



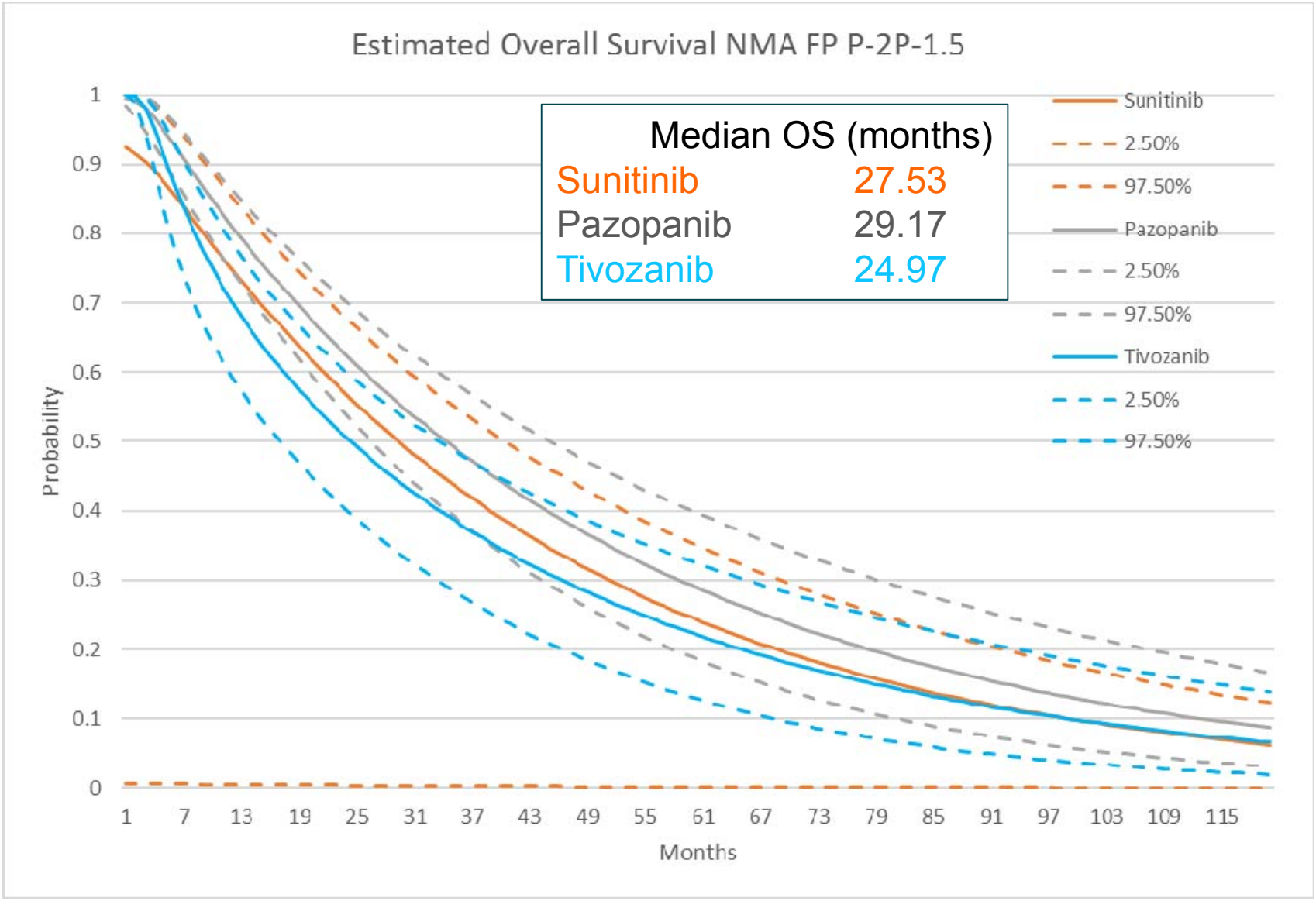
ERG's preferred NMA curves showing 95% credible intervals - PFS



ERG's fractional polynomial curves - OS



ERG's preferred NMA curves showing 95% credible intervals - OS



ERG comments on preferred curves

- Crossover-adjusted results not included
- Therefore, confounding seen for OS in TIVO-1 still an issue
  - ERG suggests use of matched adjusted indirect comparisons (MAIC) to adjust tivozanib group in TIVO-1 to match characteristics of population in COMPARZ trial (sunitinib v pazopanib) would overcome issue as would not rely on within-study comparison with sorafenib
  - ERG recognises several limitations but prefers MAIC to all methods explored by company so far

Health-related quality of life in TIVO-1

- Results for first 12 months of treatment from full trial population:

	FACT-G (27 items 0–4; range 0 to 108)			FKSI-DRS (9 items, 0–4; range 0 to 36)			EQ-5D-3L		
	Tivo n=256	Sora n=250	p	Tivo n=256	Sora n=250	p	Tivo n=256	Sora n=250	p
Baseline Mean	77.01	77.27		29.16	29.35		0.73	0.73	
SD	14.98	15.94		4.77	5.10		0.25	0.26	
Change from baseline			0.805			0.965			0.391
LS mean change	-2.83	-3.10		-0.94	-0.93		-0.05	-0.06	
SE	1.04	1.02		0.33	0.34		0.02	0.02	

Tivo, tivozanib; Sora, sorafenib; FACT-G: Functional Assessment of Cancer Therapy-General, FKSI-DRS: FACT Kidney Symptom Index–Disease-Related Symptoms; EQ-5D, EuroQol-5D; SD, Standard deviation; LS, least squares; SE, standard error

- FACT-G is a general cancer measure, FKSI-DRS is kidney cancer-specific

ERG comments: None of the results on any of the scales indicate a difference in HRQoL of patients treated with tivozanib compared with sorafenib.

Adverse effects in TIVO-1

- Almost all patients experienced at least one treatment emergent AE (91% in tivozanib group and 97% in sorafenib group)
- Grade 3 or above AEs reported by 61% in tivozanib group and 70% in sorafenib group
- Hypertension and dysphonia (altered voice sounds) more common with tivozanib, hand-foot syndrome and diarrhoea more common with sorafenib
- Company: well tolerated, lower rates of treatment-emergent adverse events than pazopanib and sunitinib

Adverse effects in TIVO-1

- Common treatment-emergent AEs (≥10% in either arm) in TIVO-1: all grades, full trial population

	Tivozanib (n=259)		Sorafenib (n=257)		Risk ratio	95% CI
Adverse effect	No.	%	No.	%		
Hypertension	115	44	88	34	1.30	1.04-1.61
Diarrhoea	59	23	84	33	0.7	0.52-0.93
Dysphonia	55	21	12	5	4.55	2.50-8.29
Fatigue	50	19	41	16	1.21	0.83-1.76
Weight decreased	47	18	53	21	0.88	0.62-1.25
Asthenia	40	15	43	17	0.92	0.62-1.37
HFS	36	14	139	54	0.26	0.19-0.36
Back pain	35	14	21	8	1.65	0.99-2.76
Nausea	31	12	19	7	1.62	0.94-2.79
Stomatitis	29	11	23	9	1.25	0.74-2.10
Dyspnoea	29	11	22	9	1.31	0.77-2.21
Decreased appetite	27	10	24	9	1.12	0.66-1.88
Alopecia	6	2	55	21	0.11	0.05-0.25

AE: Adverse event, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HFS: Hand-foot syndrome

Adverse effects in TIVO-1

- Common treatment-emergent AEs (≥10% in either arm) in TIVO-1: all grades

	Tivozanib (n=259)		Sorafenib (n=257)		Risk ratio	95% CI
Clinical chemistry	**No.**	**%**	**No.**	**%**		
Increased ALT	73	28	88	34	0.82	0.64-1.07
Increased AST	97	37	130	51	0.74	0.61-0.90
Increased amylase	104	40	135	53	0.76	0.63-0.92
Increased lipase	119	46	164	64	0.72	0.61-0.85
Hypophosphataemia	76	29	182	71	0.41	0.34-0.51
Proteinuria	186	72	187	73	0.99	0.89-1.10
Haematology						
Low haemoglobin	105	41	125	49	0.83	0.69-1.01
Neutropenia	28	11	27	11	1.03	0.62-1.70
Thrombocytopenia	47	18	31	12	1.50	0.99-2.29

AE, Adverse event; ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; HFS, Hand-foot syndrome

Network meta-analysis results for adverse effects

- Pairwise estimates of treatment effects (odds ratios) for specific AEs from Bayesian NMA (treatment-naive patients)

Treatment	Diarrhoea: Median [95% CrI]	Fatigue/ asthenia: Median [95% CrI]	Hypertension: Median [95% CrI]	ALT increased: Median [95% CrI]	AST increased: Median [95% CrI]
TIVO vs SUN	0.1131 [0.025; 0.43]	0.6846 [0.173; 2.849]	1.422 [0.639; 3.182]	0.2307 [0; 7.128]	0.134 [0; 3.215]
TIVO vs PAZ	0.09738 [0.02; 0.399]	1.22 [0.294; 5.294]	1.421 [0.598; 3.391]	0.05841 [0; 1.873]	0.0295 [0; 0.753]

CrI, credible interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase

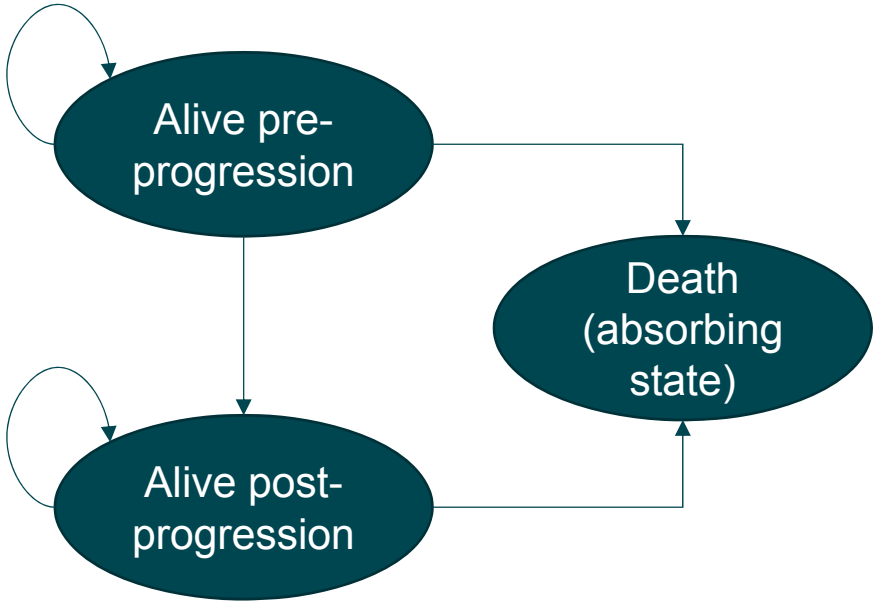
ERG comments: results of NMA do not provide robust evidence to support company's assertion that tivozanib has a favourable safety profile compared with pazopanib and sunitinib

Cost effectiveness

Key issues – cost effectiveness

- Which fractional polynomial-based extrapolation is most appropriate to use in the model? (from range of 1st and 2nd order options)
- Are the results from the model reliable without inclusion of crossover-adjusted data?
- How should subsequent therapy be accounted for in the model? (company's approach, ERG's approach, other?)
  - % of patients receiving each treatment, benefits and costs
- How should adverse effects be incorporated into the model?
  - Include decrements to utility values for adverse effects (company) or not (ERG)?
- Are the end-of-life criteria met?
- Is tivozanib an innovative treatment?
- Are there any equality issues?

Modelling approach and structure



- Partitioned-survival model
- Estimated proportions in each health state based on parametric survival curves fitted to clinical trial data on PFS and OS
- Based on NMA with fractional polynomial method
- Time horizon: 10 years
- Cycle length: 1 week

Treatment	Dosage regimen
Tivozanib (oral)	1,340 µg daily for 3 weeks followed by 1 week without treatment
Sunitinib (oral)	50 mg daily for 4 weeks followed by 2 weeks without treatment
Pazopanib (oral)	800 mg daily, continuously administered

ERG comments: appropriate structure, cycle length and time horizon

Model inputs
Utility values

- Utility values are derived from health-related quality of life data from EQ-5D-3L questionnaires given to patients in TIVO-1 study
- Based on full trial population (not on treatment-naive population)
- Utility values assumed same for each treatment arm

	Utility value (mean)	Source	Measure
Pre-progression	0.726	TIVO-1	EQ-5D-3L
Post-progression	0.649	TIVO-1	EQ-5D-3L

ERG comments:
- assuming same utility values for each treatment → reasonable
- satisfied with company's approach of using conservative utility estimates → ERG base case is based on treatment-naive population

Model inputs

Utility values including decrements from adverse events

- Decrements from adverse events derived from published cost-effectiveness analysis of pazopanib
- Each decrement applied to pre-progression utility estimate
- Incidence of AEs in tivozanib arm identified from TIVO-1 and odds ratio from NMA applied to calculate expected incidence in each comparator group

Adverse effect (all grade 3+)	Utility value including decrement
Anaemia	0.61
Asthenia/fatigue	0.60
Hand-foot syndrome	0.68
Hypertension	0.66

ERG comments on company model inputs

Issue	ERG comment
Treatment effectiveness	• Data for median PFS and OS used in fractional polynomial NMA is inconsistent between different iterations of the model provided by the company – without explanation • Crossover-adjusted data not used in NMA or model
Utility values	• Health state utility values based on full trial population (not treatment-naive) • Decrements for adverse effects (from pazopanib STA) actually estimated from a vignette study of a sample from UK general population, **not** people with RCC (→ ERG removes in base case)
Adverse events	• Odds ratios used to produce incidences of adverse effects were taken from the NMA carried out by company before clarification, instead of post-clarification NMA – however, odds ratios from both NMAs associated with uncertainty → ERG uses post-clarification NMA in base case • These odds ratios were applied to the incidence rates of AEs for tivozanib in the overall population instead of the treatment-naive population (→ERG uses treatment-naive in base case)

Costs + resources used in company model

Drug costs

Treatment	Dose regimen	PAS discount	List price	Mean cost per week
Tivozanib	1,340 µg daily for 3 weeks followed by 1 week rest	None	[redacted]	[redacted]
Sunitinib	50 mg daily for 2 weeks followed by 2 weeks rest	No charge for first cycle. List price thereafter	50 mg caps x 28: £3,138.80[94]	First 6 weeks: nil Thereafter: £523.13
Pazopanib	800 mg daily administered continuously	12.5% discount on all doses	400 mg tabs x 30: £1,121[94]	£457.74

Costs and resources used in company model

Company includes only 1 2nd line therapy

- Pre-progression service/monitoring costs
  - consultant appointment on starting treatment
  - monthly outpatient follow-up
  - CT scan every 3 months
- Post-progression service/monitoring costs
  - 60% treated with axitinib (ongoing monitoring requirement same as in pre-progression state)
  - 40% receive supportive care only (same monthly follow-up but no CT scans)
- Adverse events: Company obtained advice from UK clinician to estimate resources for managing AEs – anaemia, fatigue, hand-foot syndrome, hypertension and diarrhoea

ERG comments on costs and resource use

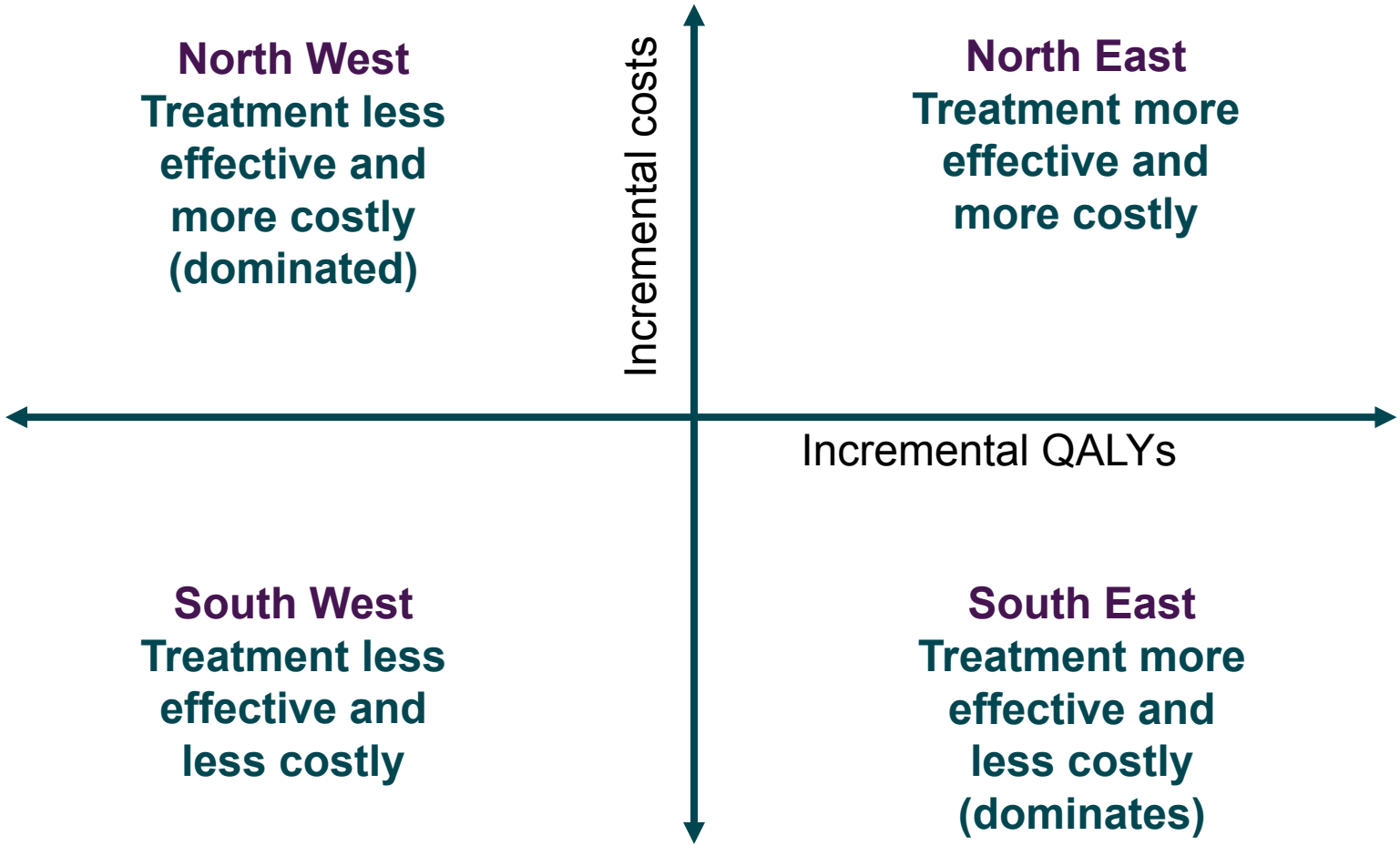
- Month assumed to have 4 weeks when converting monthly to weekly disease management costs, instead of 4.35 (→ ERG corrected company's base case)
- Relative dose intensities (RDI) not included in company's model
  - ERG considers RDIs used in previous NICE technology appraisals to be relevant (→ included in ERG base case)
- ERG clinical experts
  - patients would have monthly blood tests – not included in company's model (→ included in ERG base case)
    - full blood count and liver function tests
    - thyroid function tests every 3 months
  - disagree with resource use assumptions for managing AEs
    - → included in ERG base case (but 'negligible impact on ICER')

ERG comments on subsequent therapy costs

	Proportion of patients	
	Company's base-case assumptions (based on TA333 and expert opinion)	Proposed by ERG clinical expert* (→ included in ERG base case)
Axitinib	60%	50%
Everolimus	0%	10%
Nivolumab	0%	30%
Best supportive care	40%	10%
*in line with clinical experts views in NICE TA on cabozantinib [ID931]		

- ERG's clinical experts disagree with company's assumption that all patients who receive axitinib will continue taking it until they die
- Company did not discount subsequent treatment disease management costs in the model (→ ERG corrected company base case)
- Modelling does not include any assumptions around the treatment effectiveness of subsequent therapies on OS

Cost-effectiveness plane



Company's base-case results, deterministic

All the ICERs reported in the next slides include the non-confidential PAS discounts for sunitinib and pazopanib but **do not include** confidential PAS discounts for the subsequent treatments axitinib, everolimus and nivolumab.

Drug	Total costs (£)	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER £/QALY
Pazopanib	£58,537	1.432		-	**-**
Tivozanib	£70,476	1.757	£11,938	0.325	**£36,757**
Sunitinib	£105,566	2.425	£47,029	0.99	**£52,533**

Inc., incremental; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years

- Based on fractional polynomial distribution (P1= -2, P2= -1)

Company's probabilistic sensitivity analysis

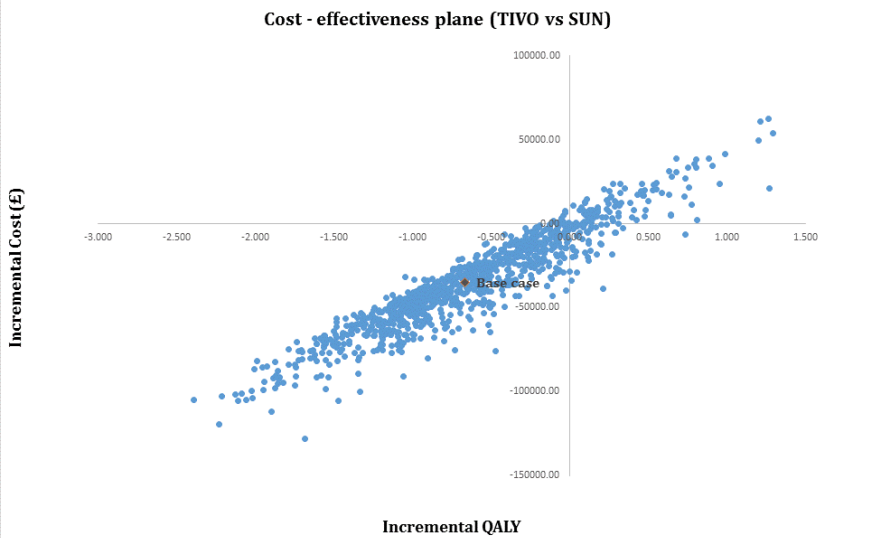
Pairwise results

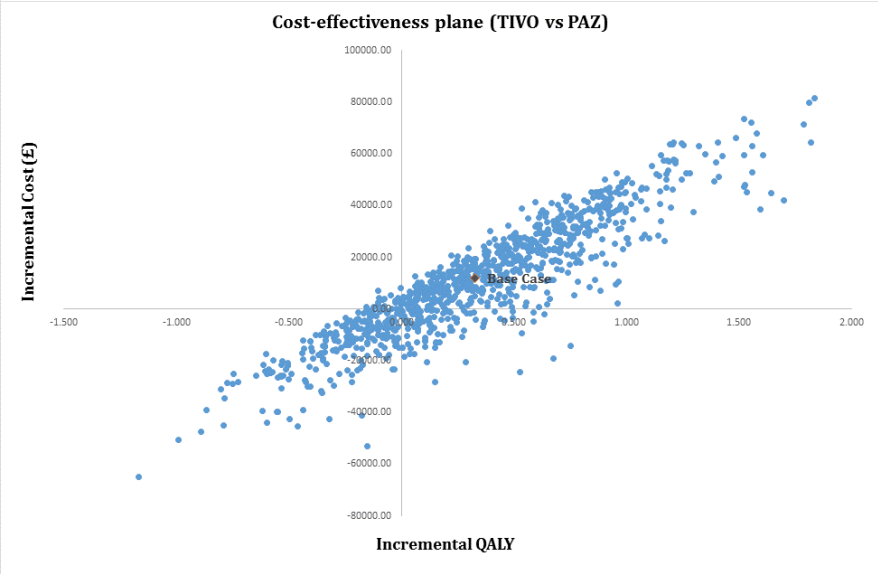
Therapy	Tivozanib versus sunitinib	Tivozanib versus pazopanib
Deterministic ICER	£52,533 (SW Quadrant)	£36,757
Mean probabilistic ICER	£55,039 (SW Quadrant)	£32,336

ICER, incremental cost-effectiveness ratio; SW, south west

Company's probabilistic sensitivity analysis

Cost-effectiveness plane

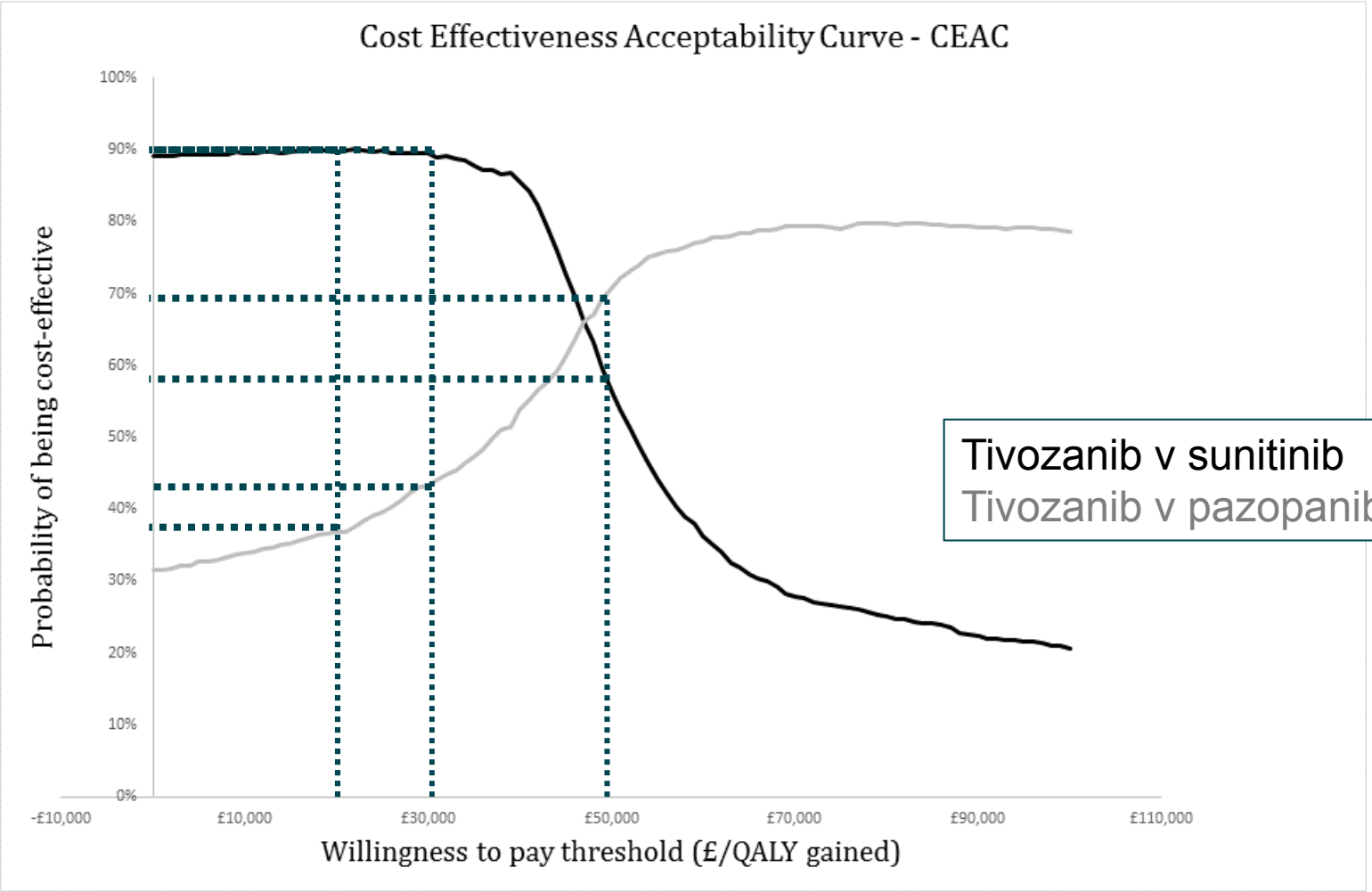




At a willingness to pay threshold of £30,000 per QALY:

- 89.6% probability that tivozanib will be cost effective versus sunitinib
- 43.4% probability that tivozanib will be cost effective versus pazopanib

Company's cost-effectiveness acceptability curve



Company's scenario analyses

Scenario analyses carried out on the base-case model:

1. Use of alternate utility for pre-progression and post-progression health states
   - Using utility values from previous NICE TAs
2. Reduction in post-progression treatment costs
   - Exploring assumption that 60% of patients will be treated with axitinib post-progression
3. Lowest deviance information criterion (DIC) for 1st order fractional polynomial used for efficacy data
   - Lowest DIC for 2nd order fractional polynomial used in base case

Company's scenario deterministic pairwise analyses results

Base case assumption	Scenario	Tivozanib vs sunitinib ICER	Tivozanib vs pazopanib ICER
Base case ICER	**-**	**£52,533 (SW Quadrant)**	**£36,757**
2nd order fractional polynomial-based NMA	1st order fractional polynomial-based NMA	£59,247 (SW Quadrant)	£70,865
Pre-progression utility of 0.73	Pre-progression: 0.78, Post-progression: 0.70 based on TA169	£48,728 (SW Quadrant)	£34,292
Post-progression utility of 0.65	Pre-progression: 0.70, Post-progression: 0.59 based on TA215	£58,060 (SW Quadrant)	£39,275
2nd line treatment received by 60% patients with axitinib being the only 2nd line treatment option	% of patients receiving 2nd line axitinib is increased to 90%	£74,977 (SW Quadrant)	£46,526
	Mean cost of 2nd line treatment reduced by 50%	£30,371 (SW Quadrant)	£27,124

ICER, incremental cost-effectiveness ratio; SW, south-west; TA, technology appraisal

ERG corrections to company's base case

- Corrected fundamental flaw in calculation of treatment effectiveness based on parameters generated in fractional polynomial analysis
- Weekly costs derived from monthly costs by dividing by 4.35 instead of 4
- Discounting included in costs for subsequent therapy disease management

ERG corrected company's base case ICERs – 2nd order fractional polynomial (P1= -2, P2= -1) incremental analysis, deterministic

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Tivozanib	£71,281	1.839	-	-	-
Pazopanib	£71,369	1.783	£88	-0.056	Tivozanib dominates pazopanib
Sunitinib	£99,073	2.415	£27,792	0.576	£48,222

ERG corrections to company's scenario analyses

Base case assumption	Scenario	Tivozanib vs Sunitinib ICER	Tivozanib vs Pazopanib ICER
Base case ICER	-	£48,222 (SW quadrant)	Tivozanib dominates pazopanib
Second-order fractional polynomial	First-order fractional polynomial	£56,176 (SW quadrant)	£74,693
Pre-progression utility of 0.73	Pre-progression utility of 0.78, Post-progression utility of 0.70 based on values used in TA169	£44,678 (SW quadrant)	Tivozanib dominates pazopanib
Post-progression utility of 0.65	Pre-progression utility of 0.70, Post-progression utility of 0.59 based on values used in TA215	£53,700 (SW quadrant)	Tivozanib dominates pazopanib

ICER, incremental cost-effectiveness ratio; SW, south-west; TA, technology appraisal.

ERG's base case analysis

- Based on corrected company's base-case ICER and incorporates:
  - Alternative second order FP-based NMA (P1= -2, P2= -1.5) for OS (slide 44)
  - Alternative second order FP-based NMA (P1= -3, P2= -2.5) for PFS (slide 42)
  - Alternative modelling of adverse events (AE) (slides 56 and 93)
    - Treatment naive AE incidence rates for tivozanib from TIVO-1
    - ERG estimates of AE odds ratios based on network meta-analysis
    - ERG clinical expert resource use assumptions for AEs
    - Removal of AE health state utility value decrements
  - Inclusion of blood tests for disease management costs (slide 59)
  - Inclusion of relative dose intensities for treatments (slide 59)
  - Alternative modelling of subsequent therapy costs (slide 60)
- Includes PAS discounts for pazopanib and sunitinib but not confidential PAS for subsequent therapies

ERG's results

Deterministic, pairwise analyses

Change to corrected company base case	ICER tivozanib vs. sunitinib	ICER tivozanib vs. pazopanib
Corrected company base case	**£48,222 (SW quadrant)**	**Tivozanib dominates pazopanib**
2nd order FP-based (P1= -2, P2= -1.5) for OS	£55,586 (SW quadrant)	£49,094 (SW quadrant)
2nd order FP-based (P1= -3, P2= -2.5) for PFS	£47,180 (SW quadrant)	£5,161
Alternative modelling for adverse effects	£47,640 (SW quadrant)	Tivozanib dominates pazopanib
Inclusion of blood tests for PFS disease management costs	£48,214 (SW quadrant)	Tivozanib dominates pazopanib
Inclusion of relative dose intensities for treatments	£44,478 (SW quadrant)	£27,756
Alternative modelling of subsequent therapy costs	£5,162 (SW quadrant)	£32,570

ERG base case ICER

Deterministic

- Incremental analyses

	Total		Incremental		ICER (£/QALY)
	Cost	QALYs	Cost	QALYs	Incremental
Pazopanib	£43,644	2.35	-	-	-
Tivozanib	£43,742	1.97	£98	-0.38	Pazopanib dominates tivozanib
Sunitinib	£44,174	2.24	£530	-0.11	Pazopanib dominates sunitinib

QALY, quality-adjusted life year, ICER, incremental cost-effectiveness ratio

- Pairwise analyses

	ICER (£/QALY)
Tivozanib vs sunitinib	£1,624 (SW quadrant)
Tivozanib vs pazopanib	Pazopanib dominates tivozanib

QALY, quality-adjusted life year, ICER, incremental cost-effectiveness ratio; SW, south west

Scenario analyses on ERG base case

- Alternative PFS scenario (P1= -3, P2= -3), incremental analysis

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Sunitinib	£42,228	2.23	-	-	-
Pazopanib	£43,019	2.35	£791	0.12	£6,714
Tivozanib	£44,111	1.97	£1,093	-0.37	Pazopanib dominates tivozanib

ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year

- Cost minimisation scenario assuming equal efficacy for PFS and OS for all treatments

Therapy	Total costs	Incremental costs
Tivozanib	£43,742	-
Sunitinib	£43,736	£6
Pazopanib	£42,656	£1,087

End of life considerations

- Company did not submit information about end of life considerations

Criterion	Data source	Sorafenib	Pazopanib	Sunitinib
		Median OS (months)		
Short life expectancy, normally < 24 months	TIVO-1 trial and extension study (unadjusted, full trial)	34.1	-	-
	IPCW analysis (full trial)	Not reported	-	-
	RPSFT analysis (treatment-naive): Unstratified logrank test Unstratified Wilcoxon test Stratified logrank test Stratified Wilcoxon test	Not reached 38.7 32.3 32.3	-	-
	Company's NMA	-	20.8	35.2
	Company's NMA - corrected	-	27.8	35.7
	ERG's NMA	-	34.8	33.1
Extension to life, normally of a mean value of ≥ 3 months		Median OS increase with tivozanib, (months)		
	Company's base case model	-	1.4	-13.0
	ERG base case model	-	-4.2	-2.6

Equality considerations & innovation

- No equality issues related to the use of tivozanib were identified
- Company stated innovation ‘not applicable’ to tivozanib
- Patient groups highlighted that tivozanib is thought to be more specific in targeting all 3 VEGF receptors and therefore to be more effective with fewer side effects than other treatments for metastatic renal cell carcinoma

Key issues – clinical effectiveness

- Where will tivozanib be used in the treatment pathway?:
  - treatment-naive population (1st line)
- Is the clinical trial TIVO-1 generalisable to UK practice in terms of baseline characteristics?
- Is the analysis using treatment-naive patients or the whole trial population most relevant?
- Do overall survival results in geographical subgroups support effectiveness of tivozanib in UK?
- What is the most appropriate method for crossover adjustment (IPCW, RPSFT, other [MAIC])?
  - Does the proportional hazards assumption hold?
- What is the most appropriate approach for extrapolation (e.g. fractional polynomial method, other)?
- Are results from the network meta-analysis plausible?
  - Are the other trials in the network generalisable to practice?
  - Should they be adjusted for crossover?
- Is tivozanib clinically effective?

Key issues – cost effectiveness

- Which fractional polynomial-based extrapolation is most appropriate to use in the model? (from range of 1st and 2nd order options)
- Are the results from the model reliable without inclusion of crossover-adjusted data?
- How should subsequent therapy be accounted for in the model? (company's approach, ERG's approach, other?)
  - % of patients receiving each treatment, benefits and costs
- How should adverse effects be incorporated into the model?
  - Include utility decrements (company) or not (ERG)?
- Are the end-of-life criteria met?
- Is tivozanib an innovative treatment?
- Are there any equality issues?

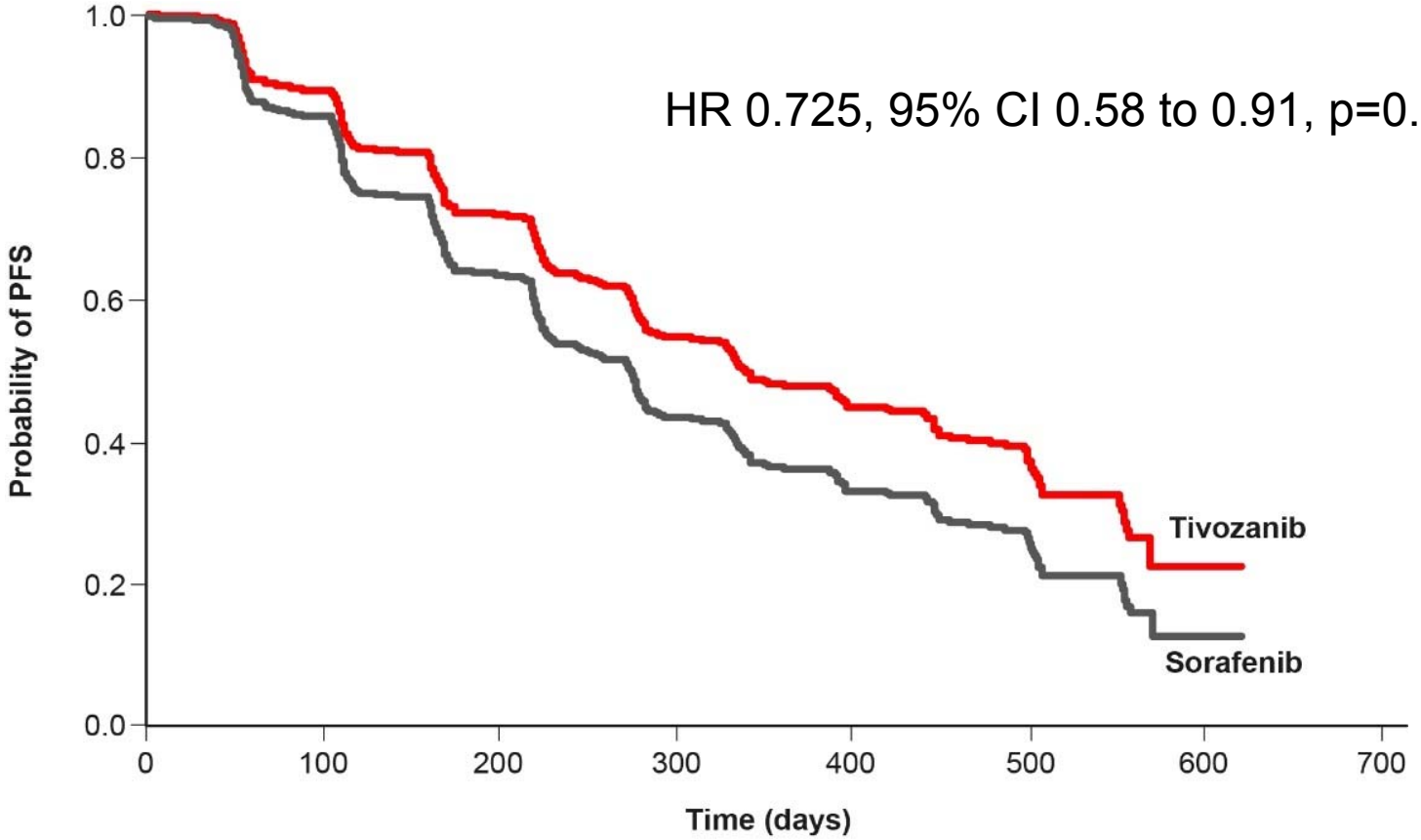
Authors

- **Kirsty Pitt**
  Technical Lead
- **Jasdeep Hayre**
  Technical Adviser
- with input from the Lead Team (Stephen Palmer, Sanjay Kinra and Nigel Westwood)

Additional slides

Progression-free survival results

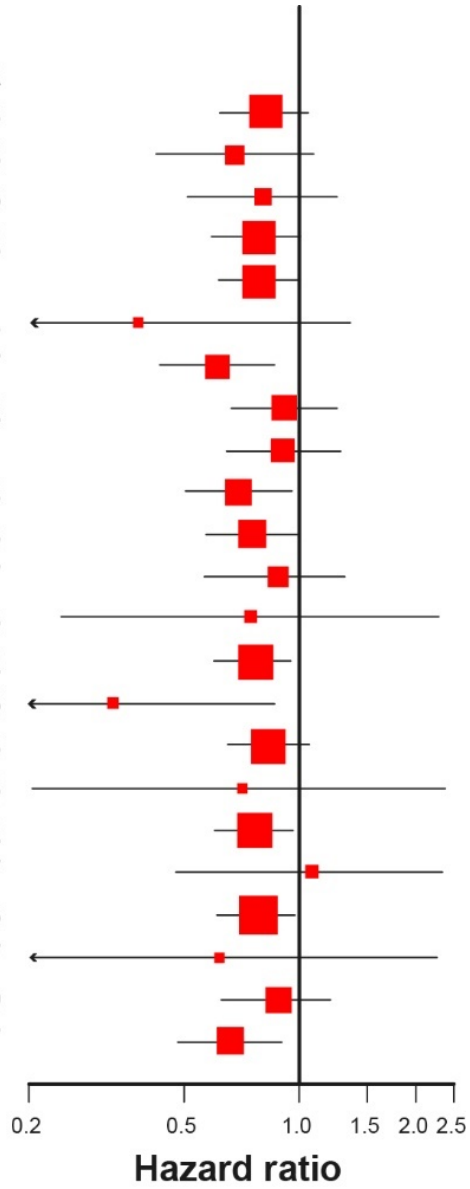
Full trial population, adjusted for baseline demographics and geographical region



Kaplan-Meier plot of PFS as determined by independent radiology review, adjusted for baseline demographics and geographical region

Pre-planned subgroup analyses - PFS

Subgroup	Tivozanib Event/N	Sorafenib Event/N	HR
<65 years	119/195	131/193	0.818
≥65 years	34/65	37/64	0.686
Female	40/75	42/68	0.805
Male	113/185	126/189	0.782
White	146/249	161/249	0.791
Non-white	7/11	7/8	0.384
ECOG status 0	57/116	92/139	0.617
ECOG status 1	96/144	76/118	0.92
<1 year since diagnosis	71/109	71/105	0.911
≥1 year since diagnosis	73/137	84/137	0.698
No prior systemic therapy for met disease	104/181	118/181	0.756
1 prior systemic therapy for met disease	48/78	50/76	0.877
1 metastatic site	5/16	8/17	0.753
≥2 metastatic sites	148/244	160/240	0.772
North America/Western Europe	8/22	11/18	0.335
Central/Eastern Europe	140/229	149/228	0.836
Rest of World	5/9	8/11	0.706
SBP at Baseline ≤140	143/243	151/233	0.772
SBP at Baseline >140	10/17	17/24	1.067
DBP at Baseline ≤90	150/254	157/238	0.785
DBP at Baseline >90	3/6	11/19	0.627
MSKCC Intermediate	79/118	70/101	0.879
MSKCC Favourable	72/140	98/155	0.67



Subgroup analyses - OS

- Prespecified analysis by next-line therapy and region

	Discontinued patients on next-line therapy			Median OS (months)	
Region	**Tivozanib**	**Sorafenib**	**OS HR**	**Tivozanib**	**Sorafenib**
Full trial (n=517)	38.4%	75.7%	1.147 (p=ns)	28.2	30.8
NA & EU (n=186)	55.6%	79.5%	0.846 (p=ns)	32.9	29.5
NA & EU5 (n=40)	84.2%	82.4%	0.497 (p=ns)	NA	29.5
Russia & Ukraine (n=291)	28.4%	71.0%	1.383 (p=0.051)	26.3	32.0

OS: Overall survival; HR: Hazard ratio; RCC: Renal cell carcinoma; EU: European Union ; NA: North America; EU includes Bulgaria, Czech Republic, France, United Kingdom, Hungary, Italy, Poland, Romania; EU5 includes UK, Italy, and France

Subgroup analyses - OS

- Post-hoc analysis – 2 year survival by next-line therapy

	Tivozanib		Sorafenib	
	n	2 year survival (%), 95% CI	n	2 year survival (%), 95% CI
Any next-line anti-cancer therapy	68	50 (38-62)	168	64 (56-71)
Next-line VEGFR-TKI	18	55 (31-78)	158 (156 receiving tivozanib)	63 (56-71)
Still on study treatment or no next-line treatment	192	56 (48-63)	89	54 (43-65)

VEGFR-TKI: Vascular endothelial growth factor receptor-tyrosine kinase inhibitor

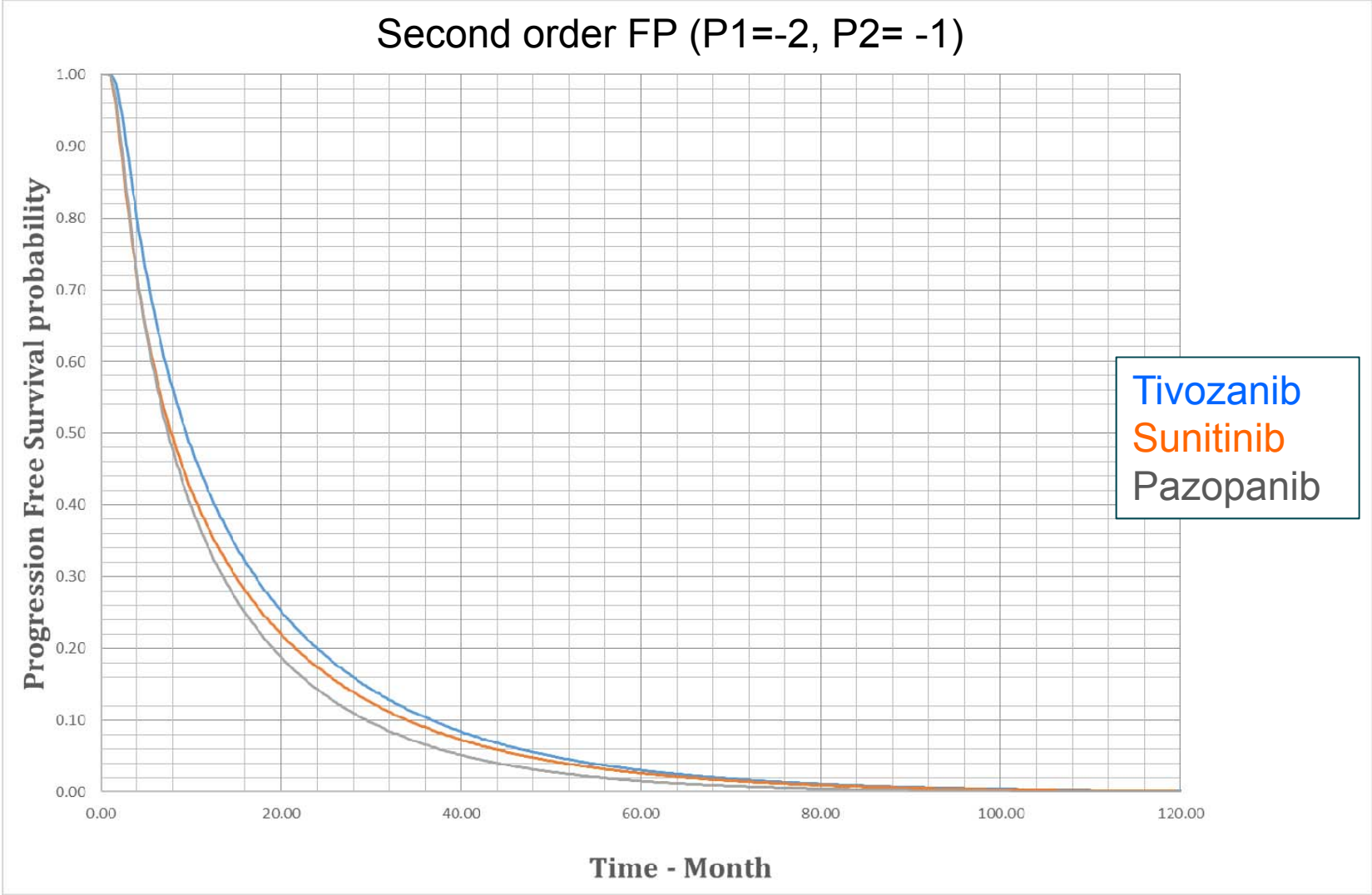
- Company state this analysis supports concept that survival benefit seen among sorafenib group may have been partly due to treatment with tivozanib

Fractional polynomial method

- Uses parametric survival functions, including survival distributions such as Weibull or Gompertz, together with more flexible fractional polynomials (FP)
- Use of FPs allows for change of hazards over time and offers more freedom in distribution selection
- With first or second order FPs, hazard functions of the interventions compared in a trial are modelled and the difference in the parameters of these fractional polynomials within a trial are considered the multidimensional treatment effect and synthesised (and indirectly compared) across studies
- Therefore, the treatment effects are represented with multiple parameters rather than a single parameter or outcome

Network meta-analysis

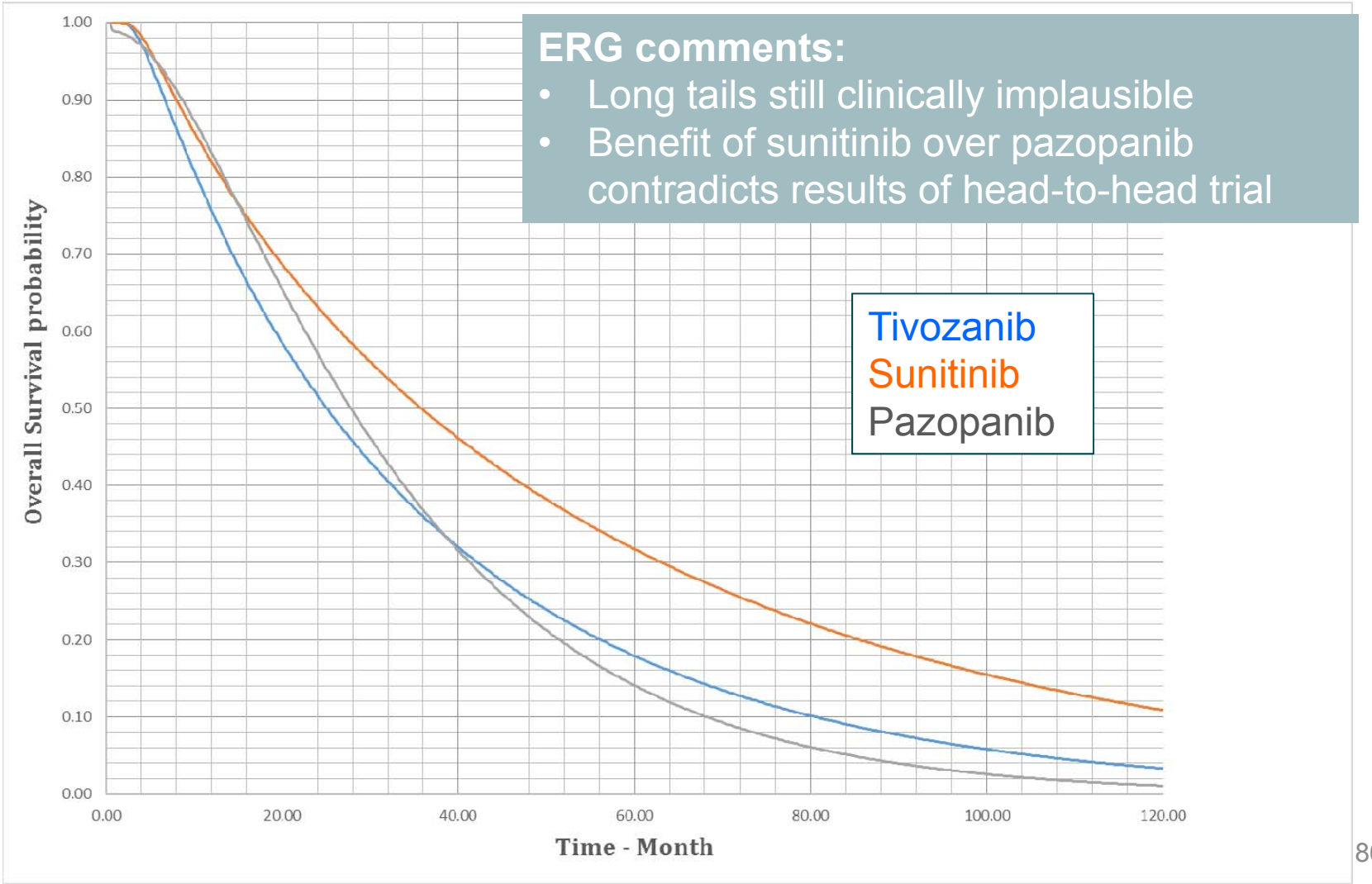
Company's results corrected by ERG – fractional polynomial method for PFS



Network meta-analysis

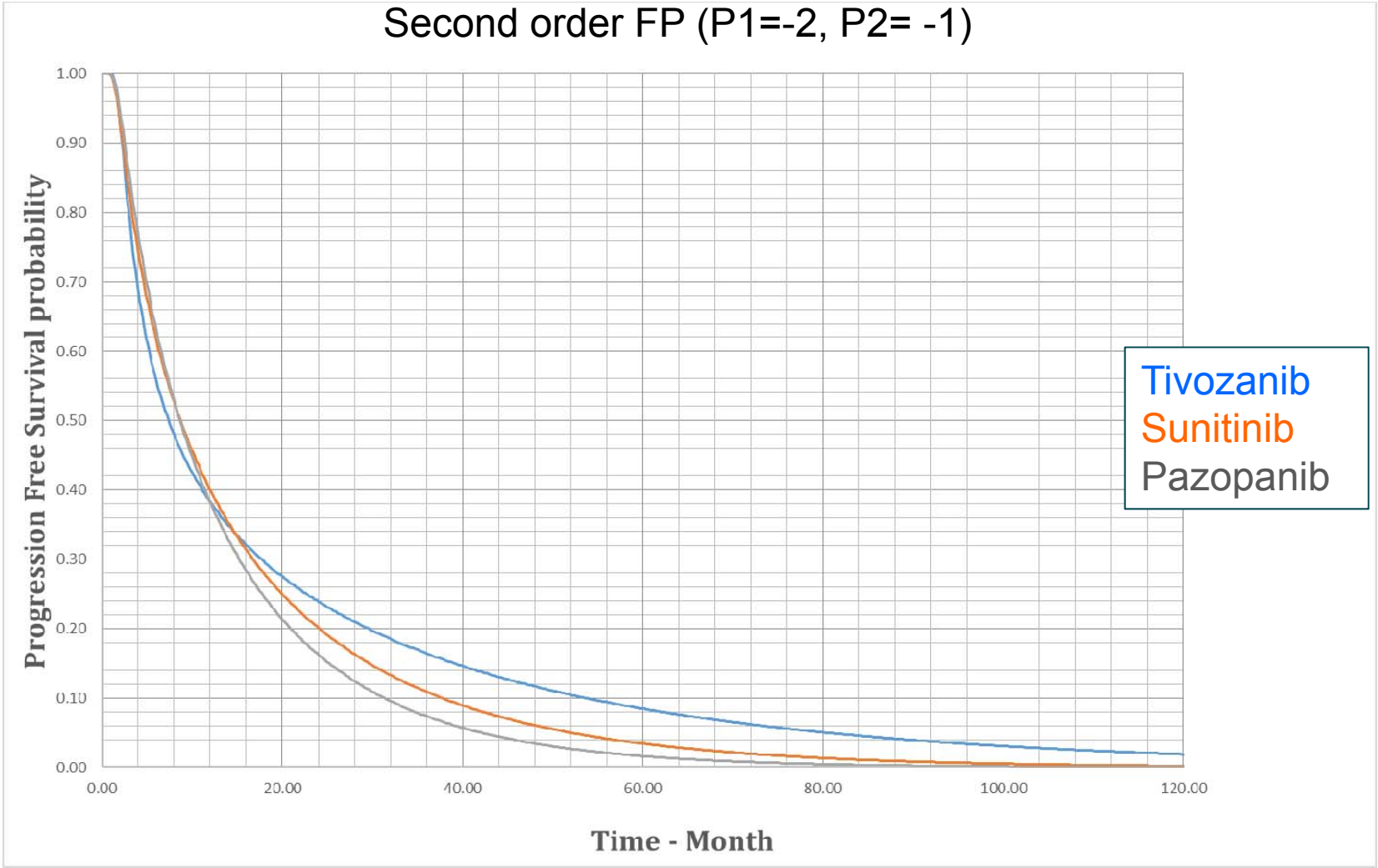
Company's results corrected by ERG – fractional polynomial method for OS

Second order FP (P1=-2, P2= -1)



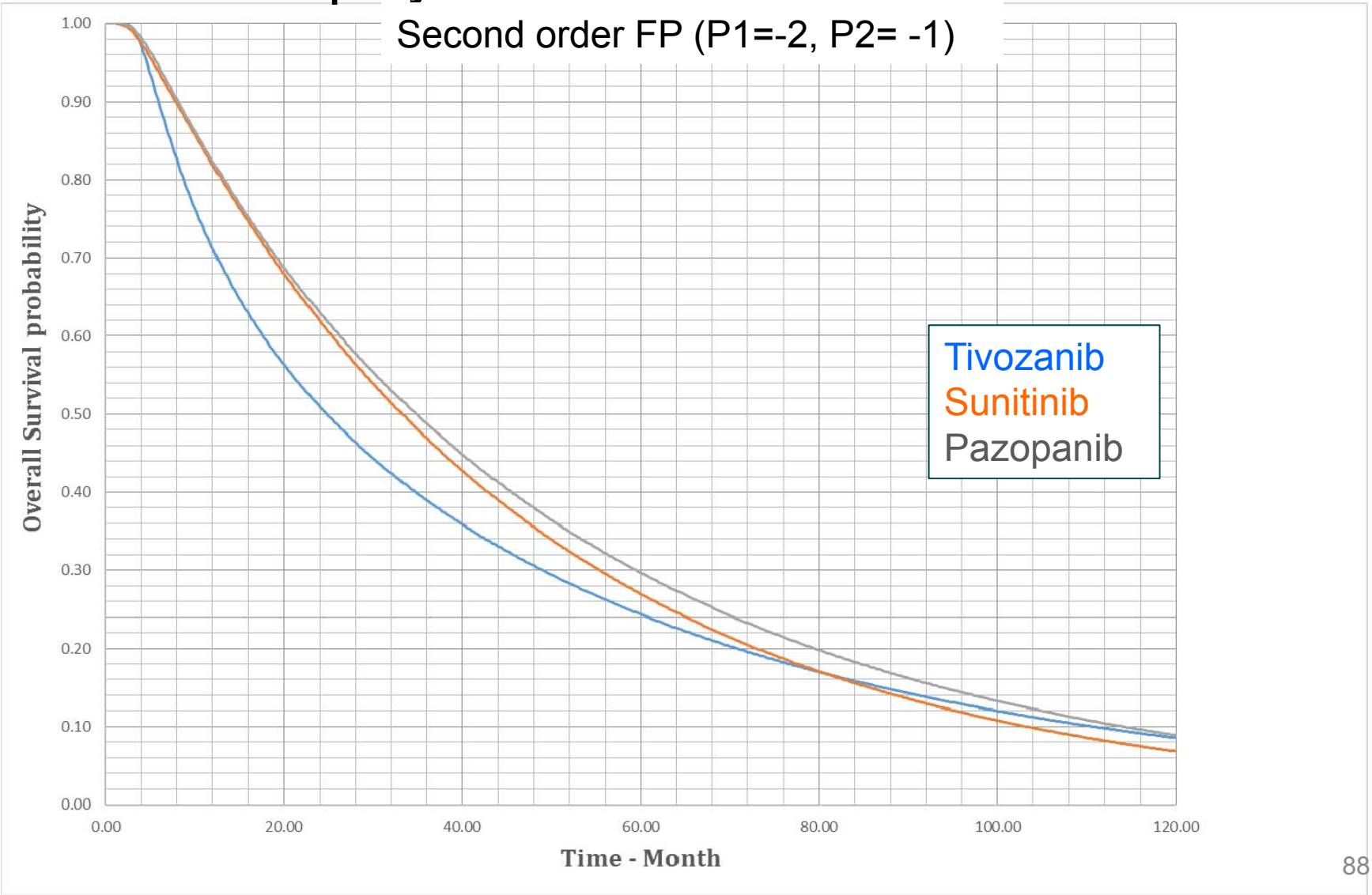
Network meta-analysis

Results using ERG's parameter estimates – fractional polynomial method for PFS

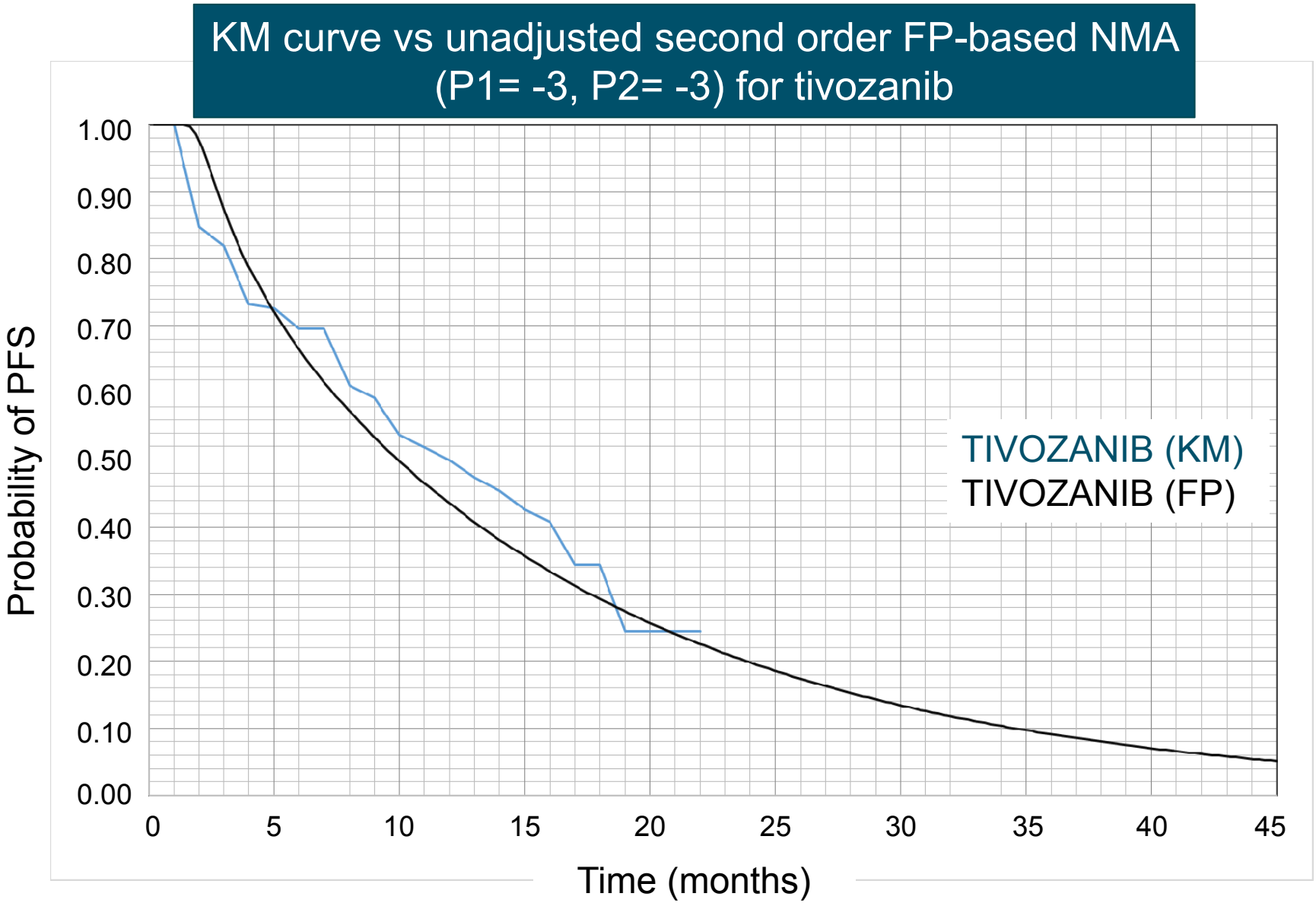


Network meta-analysis

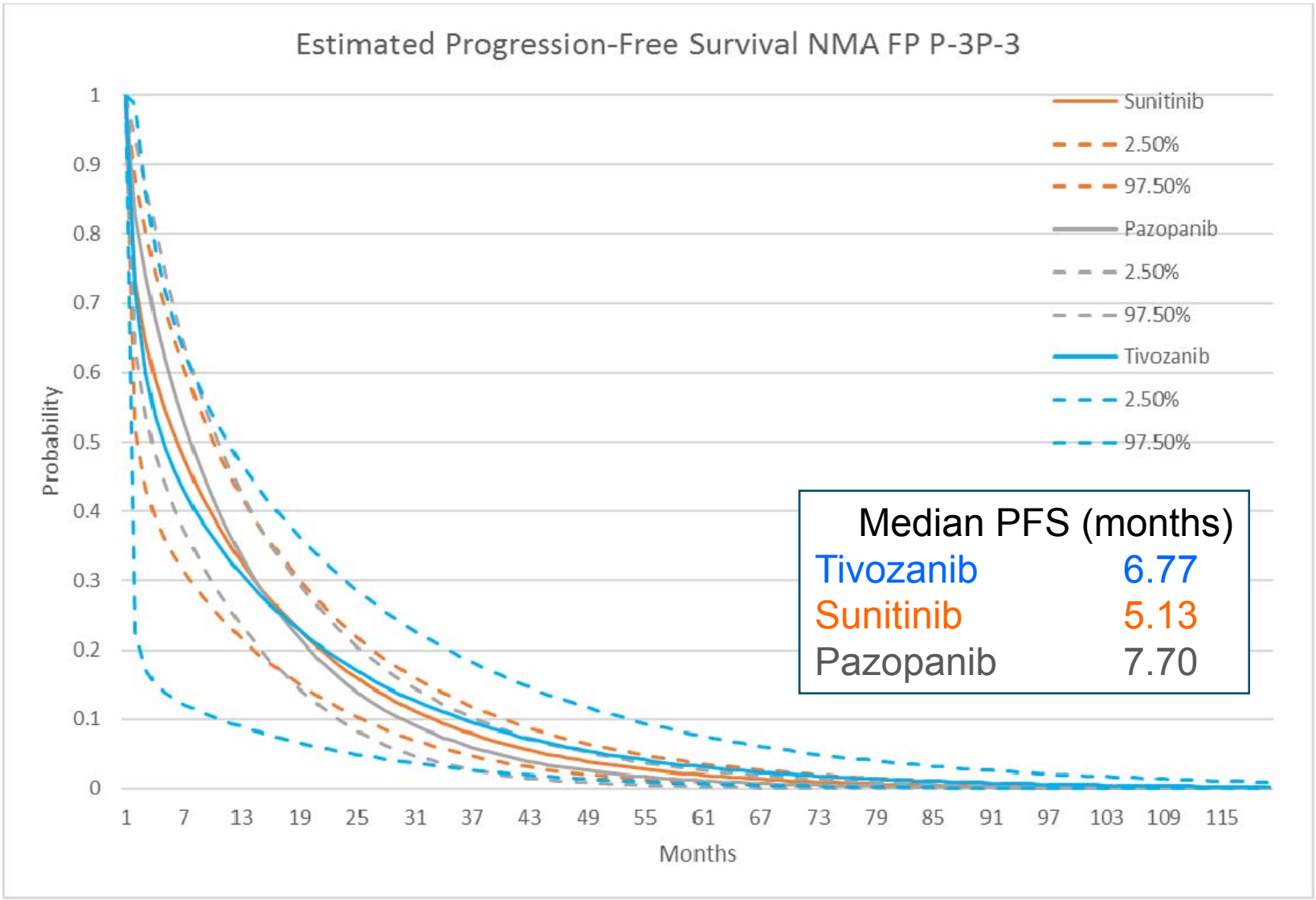
Results using ERG's parameter estimates – fractional polynomial method for OS



ERG's fractional polynomial curves - PFS



ERG's preferred NMA curves showing 95% credible intervals - PFS



Disease management costs in the model

Cost Item	Frequency – stable disease	Frequency – progressive disease	Unit cost	Reference
Oncologist Examination (first visit)	First visit	N/A	£197	NHS Reference Costs 2015/6 HRG WF01B: service code 370 Medical Oncology
Oncologist Examination (subsequent visits)	Monthly	Monthly	£163	NHS Reference Costs 2015/6 HRG WF01A: service code 370 Medical Oncology
CT Scan	Every 3 months	Every 3 months (for patients on subsequent active therapy only)	£115	RD27Z Computerised Tomography Scan of more than three areas (Source: NHS Reference costs 2015/16)

GP, General Practitioner; HFS: Hand-foot syndrome; HRG, Health Resources Group; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Adverse event costs in the model (1)

Adverse event	Service	Proportion of patients	Unit cost	Reference
Anaemia	Day case transfusion	50%	£306	NHS reference costs 2015/6
	Short stay transfusion	50%	£509	Weighted mean of HRG SA04G-SA04L[126]
	Mean expected cost:		£407.50	
Fatigue	Additional outpatient attendance	50%	£163	NHS Reference Costs 2015/6 HRG WF01A: service code 370 Medical Oncology[126]
	Mean expected cost		£81.50	

Adverse effects costs in the model (2)

Adverse event	Service	Proportion of patients	Unit cost	Reference
Hand-foot syndrome	Additional outpatient attendance	60%	£163	NHS reference costs 2015/6
	Short stay admission	30%	£526	NHS reference costs 2015/6
	Mean expected cost		£255.60	
Hypertension	GP attendance x3	100%	£109	PSSRU costs of health and social care 2016
	Treatment with antihypertensive	100%	£28	Assumes treatment with ramipril 5mg + bendroflumethiazide 2.5mg for 1 year
	Mean expected cost		£137	
Diarrhoea	Not reported	100%	£752	Not reported

Estimated resource use assumptions for managing adverse events

Company's and ERG's assumptions

Adverse event	Service	Company's assumption	ERG's clinical expert
Anaemia	Day case transfusion	50%	80%
	Short stay transfusion	50%	20%
Fatigue	Additional outpatient attendance	50%	20%
Hand-foot syndrome	Additional outpatient attendance	60%	60%
	Short stay admission	30%	0

ERG scenario analyses

- Subsequent therapy costs
  - Calculated the proportion of newly-progressed patients in a cycle and multiplied by one-off total weighted cost of subsequent therapy
    - Weighted cost based on distribution of patients across second line treatments (clinical expert advice), mean duration, list price, recommended dose and relative dose intensities of treatments obtained from published literature
  - One-off cost for disease management also applied to proportion newly-progressed in a cycle
    - Estimated based on company's original costs and mean duration of treatment
- Relative dose intensity
  - Based on previous NICE TAs

ERG scenario analyses pairwise results

Scenario	ICER tivozanib v sunitinib	ICER tivozanib v pazopanib
0. Corrected company base case	£48,222*	Tivo dominates
1. Second order FP-based NMA (P1= -2, P2= -1.5), OS	£55,586*	£49,094*
2a. Second order FP-based NMA (P1= -3, P2= -3), PFS	£47,746*	£2,311
2b. Second order FP-based NMA (P1= -3, P2= -2.5), PFS	£47,180*	£5,161
3. 1+2a	£54,691*	£47,709*
4. 1+2b	£53,144*	£46,763*
5. Equal efficacy for OS and PFS based on company's preferred second order FP (ERG estimates)	Tivo dominates	Tivo dominates
6. Treatment-naive AE incidence for tivozanib	£47,823*	Tivo dominates

ICER, incremental cost effectiveness ratio; FP, fractional polynomial; NMA, network meta-analysis; AE, adverse effects; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity

*** ICER is in south-west quadrant**

ERG scenario analyses pairwise results

Scenario	ICER tivozanib v sunitinib	ICER tivozanib v pazopanib
7. ERG estimates of AE ORs based on simplified NMA	£48,540*	Tivo dominates
8. ERG clinical expert resource use assumptions for AEs	£48,200*	Tivo dominates
9. Removal of AE health state utility value decrements	£47,609*	Tivo dominates
10. 6 to 9	£47,640*	Tivo dominates
11. Equal incidence of AEs based on tivozanib incidence	£47,577*	Tivo dominates
12. Inclusion of blood tests for PFS disease management costs	£48,214*	Tivo dominates
13. Inclusion of relative dose intensities	£44,478*	£27,756
14. ERG's remodelling of subsequent therapy costs	£5,162*	£32,570

ICER, incremental cost effectiveness ratio; AE, adverse effects; OR, odds ratio; OS, overall survival; PFS, progression-free survival; RDI, relative dose intensity

*** ICER is in south-west quadrant**

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Tivozanib for treating renal cell carcinoma

Final scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of tivozanib within its marketing authorisation for renal cell carcinoma.

Background

Renal cell cancer (RCC) is a cancer that usually originates in the lining of the tubules of the kidney (the smallest tubes inside the nephrons) that help filter the blood and make urine. RCC is the most common type of kidney cancer (approximately 90% of the cases).[i] There are several different types of RCC, with the main ones divided into 5 categories: clear cell, papillary (types 1 and 2), chromophobe, oncocytic and collecting duct carcinoma. Clear cell is the most common form of RCC accounting for approximately 80–90% of cases.[ii]

In 2014, 9,023 new kidney cancer cases were diagnosed in England.[iii] In 2014, approximately 44% of people diagnosed with kidney cancer had stage III or IV disease and 25% had stage IV disease.[iv] The 5-year survival rate for metastatic RCC is approximately 10%.[v]

The aim of treatment is to stop the growth of new blood vessels within a tumour. In untreated RCC NICE technology appraisal guidance 169 recommends sunitinib a 'first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.' NICE technology appraisal guidance 215 recommends pazopanib as a first-line treatment option for people with advanced renal cell carcinoma and who have not received prior cytokine therapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

After failure of prior systemic treatment with a tyrosine kinase inhibitor or cytokine, NICE technology appraisal guidance 333 recommends axitinib. Because the remit referred to NICE by the Department of Health for axitinib only includes adults who have been previously treated with sunitinib, the use of axitinib with other tyrosine kinase inhibitors, such as pazopanib (NICE technology appraisal guidance 215) is not subject to statutory funding. NICE technology appraisal guidance 417 recommends nivolumab as an option for previously treated advanced renal cell carcinoma in adults. Everolimus is available in England for metastatic RCC through the Cancer Drugs Fund (at the time the final scope was written) for people who have had prior treatment with only one previous tyrosine kinase inhibitor, and where axitinib is contraindicated or there is excessive toxicity to axtinib and no evidence of disease progression. Everolimus is subject to ongoing NICE CDF transition

review [ID1016]. Cabozantinib is subject to ongoing NICE appraisal for previously treated advanced RCC.

The technology

Tivozanib (Fotivda, EUSA Pharma) is a selective inhibitor of vascular endothelial growth factor (VEGF) receptors pathway. Inhibition of VEGF driven angiogenesis has been demonstrated to reduce vascularisation of tumours, thereby supressing tumour growth. Tivozanib is administered orally.

Tivozanib does not currently have a marketing authorisation in the UK. It has been studied in a clinical trial compared with sorafenib in adults with recurrent or metastatic RCC who have untreated disease or who have received no more than 1 prior systemic regimen for metastatic RCC. It is also being studied in a clinical trial compared with sorafenib in adults with metastatic RCC whose disease has not responded to 2 or 3 prior systemic regimens.

Intervention(s)	Tivozanib
Population(s)	Adults with recurrent or metastatic renal cell carcinoma
Comparators	Untreated disease: • Sunitinib • Pazopanib • Immunotherapy (interferon-alfa, interleukin-2) Previously treated disease: • Axitinib • Nivolumab • Everolimus (NICE guidance is in development, funded by the Cancer Drugs Fund in the interim) • Cabozantinib (subject to ongoing NICE appraisal [ID931]) • Best supportive care
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rates • adverse effects of treatment • health-related quality of life.

Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention and comparator technologies should be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Technology Appraisals: 'Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma' (2009). NICE technology appraisal 169. Guidance on the static list. 'Pazopanib for the first-line treatment of advanced renal cell carcinoma' (2011) NICE technology appraisal 215. Guidance on the static list. 'Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment' (2015). NICE technology appraisal 333. Review date to be confirmed. 'Cabozantinib for treating renal cell carcinoma'. NICE technology appraisals guidance [ID931]. Publication expected June 2017. 'Everolimus for the second-line treatment of advanced renal cell carcinoma' (2011). NICE technology appraisal guidance 219. Everolimus subject to ongoing NICE CDF transition review [ID1016], expected date of publication February 2017. 'Bevacizumab (first-line), sorafenib (first- and second line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' (2009). NICE technology appraisal guidance 178. Review date to be confirmed.

	'Nivolumab for previously treated advanced renal cell carcinoma'. NICE technology appraisal guidance 417. Review date November 2019 Terminated appraisals 'Pazopanib for the second line treatment of metastatic renal cell carcinoma (discontinued)' NICE technology appraisals guidance [ID70]. Appraisals in development (including suspended appraisals) 'Axitinib, everolimus, sorafenib and sunitinib for treated advanced or metastatic renal cell carcinoma'. NICE technology appraisals guidance [ID897]. Suspended appraisal. 'Cabozantinib for previously treated advanced renal cell carcinoma'. NICE technology appraisal guidance [ID931]. Publication expected June 2017 'Lenvatinib in combination with everolimus for previously treated advanced renal cell carcinoma' Proposed NICE technology appraisal [ID1029]. Publication expected December 2017. Related Guidelines: 'Suspected cancer: recognition and referral' (2015) NICE guideline 12 'Improving outcomes in urological cancers' (2002). NICE guideline CSGUC. Review date to be confirmed. Related Interventional Procedures: 'Irreversible electroporation for treating renal cancer' (2013). NICE interventional procedures guidance 443. 'Laparoscopic cryotherapy for renal cancer' (2011). NICE interventional procedures guidance 405. 'Percutaneous cryotherapy for renal cancer' (2011). NICE interventional procedures guidance 402. 'Percutaneous radiofrequency ablation for renal cancer' (2010). NICE interventional procedures guidance 353. Related NICE Pathways: Renal cancer (2016) NICE pathway
Related National Policy	NHS England (January 2017) National Cancer Drugs Fund List. https://www.england.nhs.uk/cancer/cdf/cancer-drugs-fund-list/

	NHS England (May 2016) Manual for prescribed specialised services. Section 15. https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2016/06/pss-manual-may16.pdf Department of Health (April 2016) NHS Outcomes Framework 2016-2017. Domain 1. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017 Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020 http://www.cancerresearchuk.org/about-us/cancer-strategy-in-england Department of Health (2014) The national cancer strategy: 4th annual report https://www.gov.uk/government/publications/the-national-cancer-strategy-4th-annual-report NHS England (2013/14) B14. Specialised Urology. NHS Standard Contract. http://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b14/

References

[i] American Cancer Society. Kidney Cancer (Adult) - Renal Cell Carcinoma. Accessed October 2016.
[ii] Patient.co.uk Renal Cancer. Accessed October 2016.
[iii] Office for National Statistics Cancer Registration Statistics. Accessed October 2016.
[iv] Cancer Research UK Kidney cancer incidence statistics. Accessed October 2016.
[v] GP Notebook Clear Cell Cancer. Accessed October 2016.

Appendix C

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tivozanib for the treatment of renal cell carcinoma [ID591]

Final matrix of consultees and commentators

Consultees	Commentators (no right to submit or appeal)
Company • EUSA Pharma (tivozanib) Patient/carer groups • Black Health Agency • British Kidney Patient Association • Cancer Black Care • Cancer Equality • Cancer 52 • HAWC • Helen Rollason Cancer Charity • Independent Cancer Patients Voice • Kidney Cancer Support Network • Kidney Cancer UK • Kidney Research UK • Macmillan Cancer Support • Maggie's Centres • Marie Curie • Muslim Council of Britain • National Kidney Federation • Rarer Cancers Foundation • South Asian Health Foundation • Specialised Healthcare Alliance • Tenovus Cancer Care Professional groups • Association of Cancer Physicians • British Association of Urological Nurses • British Association of Urological Surgeons • British Geriatrics Society • British Institute of Radiology • British Psychosocial Oncology Society (BPOS) • British Society of Urogenital Radiology • British Renal Society • Cancer Research UK	General • Allied Health Professionals Federation • Association of Renal Industries • Board of Community Health Councils in Wales • British National Formulary • Care Quality Commission • Department of Health, Social Services and Public Safety for Northern Ireland • Healthcare Improvement Scotland • Medicines and Healthcare products Regulatory Agency • National Association of Primary Care • National Pharmacy Association • NHS Alliance • NHS Commercial Medicines Unit • NHS Confederation • Scottish Medicines Consortium • Welsh Kidney Patients Association Possible comparator companies • Bristol-Myers Squibb (nivolumab) • Novartis Pharmaceuticals (everolimus, interleukin-2, pazopanib) • Pfizer (axitinib, sunitinib) • Roche Products (interferon alfa 2a) Relevant research groups • Cochrane Urology • Institute of Cancer Research • MRC Clinical Trials Unit • National Cancer Research Institute • National Cancer Research Network • National Institute for Health Research Associated Public Health Groups • Public Health England • Public Health Wales

Consultees	Commentators (no right to submit or appeal)
• Renal Association • Royal College of General Practitioners • Royal College of Nursing • Royal College of Pathologists • Royal College of Physicians • Royal College of Radiologists • Royal Pharmaceutical Society • Royal Society of Medicine • Society and College of Radiographers • Society for DGH Nephrologists • UK Clinical Pharmacy Association • UK Health Forum • UK Oncology Nursing Society • UK Renal Pharmacy Group • Urology Foundation <u>Others</u> • Department of Health • NHS Greater Huddersfield CCG • NHS England • NHS Wigan Borough • Welsh Government	

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people who share a protected characteristic and those who do not. Please let us know if we have missed any important organisations from the lists in the matrix, and which organisations we should include that have a particular focus on relevant equality issues.

PTO FOR DEFINITIONS OF CONSULTEES AND COMMENTATORS

Definitions:

Consultees

Organisations that accept an invitation to participate in the appraisal; the company that markets the technology; national professional organisations; national patient organisations; the Department of Health and the Welsh Government and relevant NHS organisations in England.

The company that markets the technology is invited to make an evidence submission, respond to consultations, nominate clinical experts and has the right to appeal against the Final Appraisal Determination (FAD).

All non company consultees are invited to submit a statement[1], respond to consultations, nominate clinical or patient experts and have the right to appeal against the Final Appraisal Determination (FAD).

Commentators

Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement, are able to respond to consultations and they receive the FAD for information only, without right of appeal. These organisations are: companies that market comparator technologies; Healthcare Improvement Scotland;; related research groups where appropriate (for example, the Medical Research Council [MRC], National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Alliance and NHS Commercial Medicines Unit, and the British National Formulary.

All non company commentators are invited to nominate clinical or patient experts.

[1] Non company consultees are invited to submit statements relevant to the group they are representing.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Tivozanib for treating renal cell carcinoma [ID591]

Company evidence submission

EUSA Pharma Ltd

May 2017

File name	Version	Contains confidential information	Date
ID591 tivozanib manufacturers submission CAIC_final_no PAS	3	Yes	25 May 2017

Instructions for companies

This is the template for submission of evidence to the National Institute for Health and Care Excellence (NICE) as part of the single technology appraisal (STA) process. Please note that the information requirements for submissions are summarised in this template; full details of the requirements for pharmaceuticals and devices are in the user guide.

This submission must not be longer than 250 pages, excluding appendices and the pages covered by this template.

Companies making evidence submissions to NICE should also refer to the NICE guide to the methods of technology appraisal and the NICE guide to the processes of technology appraisal.

Contents

List of tables

List of figures

Abbreviations

AE	Adverse events
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ATE	Arterial thrombotic events
CI	Confidence interval
CR	Complete response
CrI	Credible interval
CEAC	Cost effectiveness acceptability curve
CSR	Clinical study report
DSU	Decision support unit
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
EQ-5D	EuroQol-5D
ESMO	European Society for Medical Oncology
FACT-G	Functional Assessment of Cancer Therapy-General
FCE	Finished consultant episodes
FE	Fixed effect
FKSI-DRS	FACT Kidney Symptom Index–Disease-Related Symptoms
HFS	Hand-foot syndrome
HIF	Hypoxia-inducible factor 1α
HR	Hazard ratio
HRQOL	Health related quality of life
IFN	Interferon

IL	Interleukin
IMDC	International Metastatic Renal Cancer Database Consortium
IPCW	Inverse Probability of Censoring Weighed
ITT	Intention to treat
IVR/IWR	Interactive Voice Response/Interactive Web Response
KPS	Karnofsky performance status
MSKCC:	Memorial Sloan-Kettering Cancer Center
MTC	Mixed treatment comparison
mTOR	Mammalian target of rapamycin
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PD	Progressive disease
PFS	Progression free survival
PPS	Post-progression survival
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria in Solid Tumors
RPSFT	Rank Preserving Structural Failure Time
SBP	Systolic blood pressure
SEER	Surveillance, Epidemiology and End Results
SmPC	Summary of Product Characteristics
TK	Tyrosine kinase
TNM	Tumor node metastases
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor

VEGFR-TKI	Vascular endothelial growth factor receptor-tyrosine kinase inhibitor
VEGFR	Vascular endothelial growth factor receptor
VHL	von Hippel-Landau
VTE	Venous thrombotic events
WTP	Willingness to pay

1 Executive summary

1.1 Statement of decision problem

Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with recurrent or metastatic renal cell carcinoma (RCC)	Adults with recurrent or metastatic RCC	
Intervention	Tivozanib	Tivozanib	
Comparator (s)	Untreated disease: • Sunitinib • Pazopanib • Immunotherapy (interferon-alfa, interleukin-2) Previously treated disease: • Axitinib • Nivolumab • Everolimus • Cabozantinib • Best supportive care	Untreated disease: • Sunitinib • Pazopanib • Immunotherapy (interferon-alfa, interleukin-2)	Tivozanib was not compared in patients with previously treated disease because there are insufficient data for independent analysis of tivozanib and other vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) in pre-treated patients and the mixed treatment comparison (MTC) cannot give reliable estimates. Furthermore, we believe that tivozanib will not be used in clinical practice in patients with previously treated disease. The VEGFR-TKIs pazopanib and sunitinib are recommended by NICE as first-line treatment options for advanced and metastatic disease[1] [2]. VEGFR-TKIs have replaced cytokines to become the standard of care at first-line and evidence provided to NICE by clinical experts in the course of several recent Technology Appraisals (axitinib, Technology Appraisal 333[3] and nivolumab Technology Appraisal 417[4]) supports this view. Clinical experts in the axitinib appraisal which was issued in February 2015 suggested that <1% of patients would receive cytokines as first-line treatment[3].

			Clinical opinion elicited for the nivolumab appraisal issued 21 months later in November 2016[4] reinforced this view …*The committee heard from the clinical experts that most people in the NHS with newly diagnosed advanced renal cell carcinoma would be offered one of two tyrosine kinase inhibitors; either pazopanib or sunitinib, as recommended in NICE's technology appraisal guidance…* Supportive real world data comes from the RECCORD registry which gathered UK data on the use of targeted therapies in locally advanced or metastatic RCC from seven UK hospitals (five in England) from March 2009 to October 2012. Anonymised data was collected through an online registry and data was included on 415 patients[5]. Sunitinib and pazopanib accounted for 90.3% of all first-line treatments, cytokines for 1% and everolimus, sorafenib, temsirolimus for the balance. Expert opinion from the UK confirms this approach, we are aware of only one hospital in the UK (The Christie, Manchester) which routinely uses cytokines first-line in a highly selected subgroup of patients who receive high dose IL-2. We understand that around 20 patients per year receive treatment in this way (Dr Robert Jones, Personal Communication). Axitinib is recommended by NICE as an option for treating adults with advanced RCC after failure of treatment with a first-line VEGFR-TKI or a cytokine (immunotherapy)[3]. Nivolumab is

			licensed as monotherapy for the treatment of advanced RCC after prior therapy in adults[6] and is recommended by NICE in that population[4].We believe that that axitinib and nivolumab are not relevant comparators since tivozanib will not be licensed in patients pre-treated with VEGFR-TKI or mammalian target of rapamycin (mTOR) inhibitors and very few people in UK clinical practice will receive cytokines first line and be eligible for treatment with tivozanib, axitinib or nivolumab at second line. Everolimus is recommended by NICE for second-line treatment[7]. It is licensed for treatment of patients with advanced RCC, whose disease has progressed on or after treatment with VEGF-targeted therapy[8]. Treatment of patients previously treated with VEGFR pathway inhibitors is outside the product licence for tivozanib. Cabozantinib is not recommended by NICE for previously treated RCC[9]. It is licensed for the treatment of advanced RCC in adults following prior VEGF-targeted therapy[10]. Treatment of patients previously treated with VEGFR pathway inhibitors is outside the product licence for tivozanib. Best supportive care is not a relevant comparator, since if patients are eligible for tivozanib then they would also be eligible for sunitinib and pazopanib. Best supportive care

			is used in patients in whom targeted therapy is inappropriate.
Outcomes	• Overall survival (OS) • Progression free survival (PFS) • Response rates • Adverse effects (AE) of treatment • Health-related quality of life (HRQOL)	• OS • PFS • Response rates • AE of treatment	HRQOL data for tivozanib versus sorafenib from the pivotal clinical trial (TIVO-1)[11] is presented. There are insufficient data for independent analysis of HRQOL and the MTC cannot give reliable estimates.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	As per the scope: With regard to time horizon, we believe that a 10-year horizon is the most appropriate one to use in this case, in that it approximates to lifetime. Survival duration in advanced RCC is relatively limited, with a median overall survival duration of around 3 years. Individual patients, however, may survive for considerably longer, perhaps up to 10 years.	
Subgroups to be considered	Not applicable		
Special considerations including issues related	Not applicable		

to equity or equality			

1.2 Description of the technology being appraised

Table 2: Technology being appraised

UK approved name and brand name	UK approved name: Tivozanib Brand name: Fotivda
Marketing authorisation/CE mark status	Tivozanib was submitted to the Committee for Human Medicinal Products (CHMP) in March 2016 and marketing approval is anticipated in May 2017.
Indications and any restriction(s) as described in the summary of product characteristics	The indication for tivozanib is for the treatment of adult patients with advanced RCC who are VEGFR and mTOR pathway inhibitor-naïve and are either untreated or who have failed prior therapy with interferon-alpha (IFN-α) or interleukin-2 (IL-2)[12]. Contra-indications to tivozanib are hypersensitivity to the active substance or any of the excipients and coadministration with herbal preparations containing St. John's wort (Hypericum perforatum)[12]. Tivozanib is not recommended in patients with severe hepatic impairment and should be used with caution in patients with mild/moderate hepatic impairment with close monitoring of tolerability[12].
Method of administration and dosage	Tivozanib is an oral medication given once daily at a dose of 1,340 µg for 21 days, followed by a 7-day rest period making one complete treatment cycle of 4 weeks. This treatment schedule should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs[12]. A 890 µg capsule is available so that the dose can be reduced if necessary to 890 µg once daily within the normal treatment schedule of 21 days of dosing, followed by a 7-day rest period[12]. The dose of tivozanib used in the TIVO-1 study is the licenced dose for tivozanib. Recent EMA/CHMP guidelines state that the declaration of dose in the Summary of Product Characteristics should reflect the amount of active substance (1,340 µg). The dose in the TIVO-1 study is described as a 1.5 mg capsule, which consists of 1,340 µg of tivozanib, with the balance being made up of excipients.

1.3 Summary of the clinical effectiveness analysis

The systematic review identified one phase III randomised controlled trial (RCT) of tivozanib versus sorafenib in patients with metastatic RCC (TIVO-1), reported in 13 publications, plus a phase II randomised discontinuation study of tivozanib reported in six publications. An additional phase II study assessing potential biomarkers is unpublished and is also included in this submission.

TIVO-1 (AV-951-09-301) was an open-label, randomised phase III trial. Patients were randomly assigned 1:1 to either tivozanib (n=260) or sorafenib (n=257) as their initial targeted therapy[11].

TIVO-1 was a planned one-way crossover study. On progression, patients assigned to sorafenib were given the option to crossover to receive tivozanib or receive next-line treatment as recommended by their physician. Patients on tivozanib who progressed received next-line routine treatment as recommended by their physician. There was no planned crossover from tivozanib to sorafenib[11].

Patients received treatment until disease progression, unacceptable toxicity or death. On discontinuation of treatment patients were permitted to receive further treatment. Almost two-thirds (63%) of patients in the sorafenib arm and 13% in the tivozanib arm received a next-line targeted therapy[11].

Tivozanib is an efficacious treatment for advanced and metastatic RCC. The primary analysis of PFS data from TIVO-1 trial versus sorafenib revealed a benefit with tivozanib over sorafenib (median PFS, based on independent radiology review 11.9 months versus 9.1 months, hazard ratio [HR], 0.797; 95% CI, 0.639 to 0.993; p=0.042)[11].

Baseline characteristics were well balanced between the two arms, except for the Eastern Cooperative Oncology Group (ECOG) performance score; more patients had a favourable ECOG performance score of 0 in the sorafenib arm compared with the tivozanib arm (54% versus 45%), this was most apparent in the Ukraine and Russia. A post-hoc analysis using Cox proportional hazards models adjusted for baseline demographics (age, sex, race, baseline ECOG score, number of metastatic sites/organs, Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic group, prior treatments and time since diagnosis) and geographical region resulted in a highly significant difference in PFS (HR 0.725, 95% CI 0.58-0.91, p=0.006)[13]. Median PFS in patients receiving tivozanib during the two phase II studies was 11.7 months[14] and 9.7 months[15].

Sorafenib is not specified as a comparator in the scope for this submission. Data from pivotal trials of other VEGFR-TKIs used as first-line treatment show that tivozanib has a longer median PFS compared with pazopanib (8.4 months in COMPARZ versus sunitinib[16] and 9.2 months in the pivotal study versus placebo[17]) and sunitinib (9.5 months in COMPARZ[16] and 11 months in the pivotal trial versus IFN[18]). Indeed, tivozanib is the only licenced VEGFR-TKI with superior efficacy to an active targeted therapy in first-line treatment.

An MTC was carried out for this submission and revealed that tivozanib has a comparable PFS to sunitinib and pazopanib, with a HR close to 1 in both untreated disease (treatment-naïve) and mixed (treatment-naïve and previously treated) populations. PFS with tivozanib is significantly longer than with IFN, with a HR of 0.61.

OS was not significantly different between tivozanib and sorafenib (median OS, 28.8 months with tivozanib versus 29.3 months with sorafenib; HR: 1.245; 95% CI, 0.954 to 1.624, p=ns) in the primary analysis[11]. Median OS was 28.2 months for tivozanib and 30.8 months for sorafenib, HR 1.147, p=ns at the final 10 July 2013 data cut (TIVO-1 and the extension study)[19].

OS in the TIVO-1 study is difficult to interpret due to the planned one-way crossover design, which resulted in an imbalance in access to next-line targeted therapies. The authors of the TIVO-1 publication attributed the discordant OS seen in the TIVO-1 study to a crossover effect[11]. Analysis adjusted for crossover carried out for this submission confirms this hypothesis (HR of 1.021; 95% CI 0.671 to 1.553; p=0.923).

Imbalance in access to next-line targeted therapy varied considerably by geography and was most marked in Ukraine and Russia. A pre-specified analysis of OS by next-line therapy by region revealed that if use of next-line therapy is balanced as was the case in North America and Western Europe then the OS trend favours tivozanib (HR 0.846 for North America and European Union and 0.497 for North America and UK, Italy and France)[12].

It should be noted that none of the analyses, either pre-specified or post-hoc, suggested a detrimental effect of tivozanib on OS.

OS was not reported in the phase II studies[14 15].

Data from pivotal trials of other VEGFR-TKIs approved by NICE as first-line treatment in RCC show that tivozanib has a comparable median OS to pazopanib (28.4 months in COMPARZ[16] and 22.9 months in the pivotal study versus placebo[20]) and sunitinib (29.3 months in COMPARZ[16] and 26.4 months in the pivotal trial versus IFN[18]). The MTC revealed

that tivozanib has a comparable OS to sunitinib (HR, 0.92) and pazopanib (HR, 0.98) and that OS with tivozanib is longer than with IFN (HR, 0.86).

In TIVO-1 most patients remained on the full dose of treatment with tivozanib for the duration of the trial, discontinuations due to AE were relatively low in both arms: 4% versus 5%. However, significantly fewer patients had treatment interruptions due to AE (19% versus 36%, p<0.001) and dose reductions due to AE (14% versus 43%, p<0.001) in the tivozanib arm compared with the sorafenib arm[11]. The discontinuation rate with tivozanib compares favourably versus pazopanib (24% in COMPARZ versus sunitinib[16] and 14% in the pivotal study versus placebo[17]) and sunitinib (20% in COMPARZ[16] and 19% in the pivotal trial versus IFN[18]). Dose reductions and interruptions were more common with pazopanib and sunitinib than with tivozanib. In the COMPARZ study dose reductions were 44% with pazopanib and 51% with sunitinib; dose interruptions were 44% and 49% respectively[16]. Real world evidence from a retrospective medical record review of patients receiving sunitinib for first-line treatment of RCC across Europe (41% of patients from the UK) revealed that patients with reduced dose intensity (<70%) or treatment discontinuation had significantly reduced survival times illustrating the importance of maintaining patients on the full dose[21].

Tivozanib is well tolerated with lower rates of the AEs which RCC patients find troublesome (fatigue/tiredness, diarrhoea and hand-foot syndrome [HFS])[22] than pazopanib and sunitinib. Very few patients receiving tivozanib had fatigue/tiredness, diarrhoea and HFS which was grade 3 and above. Most patients experienced mild to moderate symptoms which reduced over time[11]. The MTC revealed that tivozanib was less likely to result in AE, of all grades, than sunitinib and pazopanib, with the exception of hypertension. HFS was significantly less likely with tivozanib compared to sunitinib, with a clear trend favouring tivozanib over pazopanib.

In both the pivotal phase III and the phase II studies, hypertension was the most common AE with tivozanib (44% in the phase III study [TIVO-1][11], 46% in the discontinuation study [AV-951-10-201][14] and 64% in the biomarker study [AV-951-10-202][15]). In TIVO-1, hypertension was controlled with medication in most patients, only 2% of patients required dose reduction and <1% required dose interruption due to hypertension[11]. Data indicate that the development of hypertension with VEGF-targeted therapy is associated with improved efficacy and may suggest an on-target effect[23 24].

Overall on treatment QOL was similar with tivozanib and sorafenib and maintained at a level comparable to baseline[11], [redacted][25]

TIVO-1 was a well conducted study; the risk of bias was low. The only concern was the imbalance in ECOG at baseline; however, post-hoc analyses using Cox proportional hazards models was carried out to determine the impact of differences in baseline characteristics on PFS.

The evidence-base for tivozanib is limited by a lack of direct head-to-head evidence versus the comparators in the scope. TIVO-1, the pivotal trial for tivozanib[11], is versus sorafenib which was routinely used in Europe and North America when the study was initiated (first patient was dosed in 2010). However, sorafenib is not approved by NICE[26], therefore evidence for tivozanib versus sunitinib, pazopanib and cytokines in treatment naïve patents was provided via an MTC.

In TIVO-1 around 30% of patients had received one prior treatment (not VEGFR-TKI or mTOR inhibitor), therefore the patient population is mixed. The number of prior treatments for metastatic RCC was a pre-specified subgroup (0 or 1). The HR for PFS of 0.756 in the treatment naïve population is comparable to the primary analysis of PFS in the overall population (HR 0.797; 95% CI, 0.639 to 0.993). We used data from trials in treatment naïve patients plus data reported from treatment naïve subgroups in trials which included mixed populations to inform the MTC in treatment naïve patients.

Tivozanib will also be licensed to treat patients who have failed prior cytokine therapy[12]. It should be noted that the patients in the pivotal TIVO-1 study who were exposed to prior treatment were not assessed for treatment response before study entry; therefore we cannot be certain that they failed their initial therapy.

There are insufficient data for independent analysis of tivozanib or other VEGFR-TKI in cytokine pre-treated patients and none in VEGFR-TKI pre-treated patients, as this was a specific exclusion criterion for the TIVO-1 study. This means that the MTC cannot give reliable estimates and therefore we have not carried out a comparison in a pure previously treated population, as recommended in the scope. However, we have used data from all relevant studies identified in the SLR to inform a MTC in the mixed population (treatment naïve and pre-treated).

We believe that the results of the TIVO-1 study are generalisable to the UK population. TIVO-1 was carried out in Bulgaria, Canada, Chile, Czech Republic, France, Hungary, India,

Italy, Poland, Romania, Russia, Serbia, UK, Ukraine and the US. Four patients from two sites were enrolled from the UK (Leicester and Cambridge).

The median age of patients in TIVO-1 was 59 years; most patients were male and white and the most common metastatic sites were lung and lymph nodes. Patient characteristics in the pivotal trials for pazopanib[17] and sunitinib[27] were similar and we believe reflect the characteristics of patients with advanced or metastatic RCC in the UK.

To conclude, we believe that there are no reasons why the clinical benefits of tivozanib demonstrated in TIVO-1 would not be applicable to suitable patients in the UK.

1.4 Summary of the cost-effectiveness analysis

We used a similar approach to that used for NICE TA215 for pazopanib[1 28 29] in the same indication, extended to allow the capture of post-progression treatment costs, in line with current NICE guidance for the treatment of advanced RCC.

For the economic model, the base case was based on the study population who had not received prior immunotherapy (70% of the total recruited patients in TIVO-1), which allows the “Untreated disease” (treatment naïve) comparator subset in the NICE Scope to be addressed. Lack of data meant that we were unable to model the “Previously treated disease” (pre-treated population).

The analysis uses a partitioned-survival model to estimate expected clinical and economic outcomes for patients with metastatic RCC receiving treatment with tivozanib, sunitinib, pazopanib or IFN. The model quantifies transition over time through three discrete mutually exclusive health states (“Alive pre-progression”, “Alive post-progression” and “Dead”) and estimates proportions in each health state based on parametric survival curves fitted to clinical trial data on PFS and OS over time.

The pivotal study for tivozanib was an active comparator study versus sorafenib, therefore, clinical efficacy data was obtained via a MTC. The derived HR versus tivozanib for each outcome and comparator were then used to inform the partitioned survival model. Using the reported Kaplan-Meier curves from the TIVO-1 study, parametric survival functions for both PFS and OS were calculated, using Weibull survival functions. Based on these outcome and treatment-specific survival curves, the proportion of patients in any of the three health states at any given time point can be estimated.

Estimates for the relative incidence of AEs were derived from the MTC. For the purposes of the economic model, in keeping with previous practice in NICE STAs, only AEs of severity grade 3 or above that had an incidence of 5% or more in any treatment arm were incorporated in the analysis. Since the cost and utility impact of lesser AE grades or lower incidence, is likely to be insignificant in this clinical and financial context.

Individual patient data from the TIVO-1 trial was used to derive estimates for utilities for both pre-progression and post-progression health states. An analysis carried out as part of the manufacturer's submission to NICE in support of pazopanib[29] was used to assess the potential impact of AEs on utilities.

Drug costs in the base case are the PAS price for pazopanib and sunitinib and the list price for IFN and tivozanib.

Costs of management, follow-up and AE are in line with UK practice and are derived from UK sources. The model incorporates post-progression treatment costs based on the use of axitinib, in line with NICE guidance. Clinical advice suggests that 60% of patients who progress on a VEGFR-TKI will receive this treatment and we have modelled on this basis.

Using the list price for tivozanib, the results of the base case show none of the three targeted therapies is associated with an incremental cost effectiveness ratio (ICER) versus IFN that would be below the conventionally accepted willingness to pay threshold of £30,000/QALY (quality-adjusted life year) (see Table 6). Of the three, tivozanib offers the lowest ICER versus IFN (£112,050/QALY). When compared with the other targeted therapies, at list price tivozanib is cost-effective versus sunitinib (ICER of £1,500/QALY) and pazopanib (ICER dominated), see Table 4 and Table 5.

Sensitivity and scenario analyses show that the model is highly sensitive to the estimates used for relative PFS and OS, which in turn impact on the cost of post-progression treatment – a major component of the overall cost. None of the other model inputs tested exert an effect on the results that would affect the qualitative conclusions.

The cost-effectiveness analysis is generalisable to clinical practice in England. We have used UK data wherever possible for inputs into the model and have taken expert clinical advice from UK clinicians practising in the field.

The model confirms that, under any reasonable set of assumptions, tivozanib cannot be considered a cost effective alternative to IFN, in line with previous health economic analyses of VEGFR-TKIs[1 2]. In current UK practice, however, few patients are treated with IFN. In this

context, tivozanib is comparable to sunitinib and pazopanib in efficacy and offers a cost effective treatment alternative to sunitinib at list price.

Table 3: Base-case results: pairwise comparisons – tivozanib versus IFN

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£84,351	2.085	
IFN	£59,585	1.864	
Increment (TIVO - IFN)	£24,767	0.221	£112,050
TIVO: Tivozanib, IFN: Interferon, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio.			

Table 4: Base-case results: pairwise comparisons – tivozanib versus sunitinib

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£84,351	2.085	
SUN	£84,199	1.983	
Increment (TIVO - SUN)	£152	0.101	£1,500
TIVO: Tivozanib, SUN: Sunitinib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio,			

Table 5: Base-case results: pairwise comparisons – tivozanib versus pazopanib

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£84,351	2.085	
PAZO	£85,094	2.063	
Increment (TIVO - PAZ)	-£742	0.022	Dominated
TIVO: Tivozanib, PAZ: Pazopanib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio,			

Table 6: Incremental cost-effectiveness results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus IFN (QALYs)	ICER (£) incremental (QALYs)
Tivozanib at list price								
IFN	£59,585	2.756	1.864					
Sunitinib	£84,199	2.876	1.983	£24,615	0.120	0.120	£205,840	£205,840
Tivozanib	**£84,351**	**3.028**	**2.085**	**£24,767**	**0.272**	**0.221**	**£112,050**	**£1,500**
Pazopanib	£85,094	2.997	2.063	£25,509	0.241	0.199	£128,228	£11,272
ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALYs: Quality-adjusted life years; IFN: Interferon								

2 The technology

- Tivozanib (Fotivda) is a VEGFR pathway inhibitor, specifically it is VEGFR tyrosine kinase inhibitor (VEGFR-TKI) and potently inhibits VEGFR 1, 2, and 3[30]. Inhibition of VEGFR-TKI and hence VEGF-driven angiogenesis has been demonstrated to reduce vascularisation of tumours, thereby suppressing tumour growth[30].
- The indication for tivozanib is for the treatment of adult patients with advanced RCC who are VEGFR and mTOR pathway inhibitor-naïve and are either untreated or who have failed prior therapy with IFN-α or IL-2[12].
- Tivozanib is an oral medication given once daily at a dose of 1,340 µg for 21 days, followed by a 7-day rest period making one complete treatment cycle of 4 weeks. This treatment schedule should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs[12].
- At list price, tivozanib is priced at [redacted].
- Tivozanib is taken in the patient's own home, minimising the need for hospital visits. The dose regimen is simple (one tablet once daily) and there are clear and straightforward instructions in the case of a missed dose. The resource use to the NHS is low.
- The most common AE with tivozanib in the clinical trial programme was hypertension, which can be managed using standard antihypertensive medication or dose reduction, interruption or discontinuation[12]. In the pivotal TIVO-1 study[11], hypertension was controlled with medication in most cases, with 2% of patients requiring dose reduction and <1% of patients requiring dose discontinuation for hypertension.

2.1 Description of the technology

Brand name: Fotivda

UK approved name: Tivozanib

Therapeutic class: Anti-neoplastic agents, protein kinase inhibitor

2.1.1 Mechanism of action

Angiogenesis, the development of a new blood supply, plays an essential role in tumour development and growth. It is particularly important in RCC, since the majority of patients

have dysfunction of a gene which plays an important part in the regulation of angiogenesis; the von Hippel-Landau (VHL) gene.

VHL regulates hypoxia-inducible factor 1α (HIF), a transcription factor which controls cellular response to low oxygen levels (hypoxia), including the expression of vascular endothelial growth factor (VEGF) and other factors responsible for angiogenesis. Under normal oxygen conditions (normoxia) the VHL protein forms complexes with other proteins to degrade HIF and regulate angiogenesis[30 31].

Under normal circumstances the VHL protein breaks down HIF, however, in patients with the VHL mutation or inactivation the cell is unable to degrade HIF effectively. Accumulation of HIF leads to an increase in VEGF, platelet derived growth factor and fibroblast growth factor, all of which are responsible for angiogenesis, tumour cell survival and proliferation[30 31].

The cellular response to VEGF is mediated by VEGF binding to tyrosine kinase (TK) receptors (the VEGFRs) on the surface of endothelial cells resulting in the formation of new blood vessels.

Tivozanib is a VEGFR pathway inhibitor, specifically it is a VEGFR-TKI and potently inhibits VEGFR 1, 2, and 3[30]. Inhibition of VEGFR-TKI and hence VEGF-driven angiogenesis has been demonstrated to reduce vascularisation of tumours, thereby suppressing tumour growth[30].

Of all the available VEGFR-TKIs, tivozanib is the most potent and most selective[32] which has positive implications for both efficacy and tolerability.

2.2 Marketing authorisation/CE marking and health technology *assessment*

Tivozanib was submitted to the Committee for Human Medicinal Products (CHMP) in March 2016 and marketing approval is anticipated in May 2017. The expected launch date is August 2017.

Information in this section is from the proposed Summary of Product Characteristics.

The indication for tivozanib is for the treatment of adult patients with advanced RCC who are VEGFR and mTOR pathway inhibitor-naïve and are either untreated or who have failed prior therapy with IFN-α or IL-2[12].

Contra-indications to tivozanib are hypersensitivity to the active substance or any of the excipients and coadministration with herbal preparations containing St. John's wort (Hypericum perforatum) due to the risk of reduced plasma levels and reduced time to reach steady-state of tivozanib[12].

Hypertension is a recognised side effect of tivozanib treatment; therefore, blood pressure should be well controlled prior to initiation of treatment. Patients' blood pressure should be monitored during treatment and antihypertensive medication initiated to control blood pressure if required. If hypertension persists despite antihypertensive treatment the dose of tivozanib should be reduced or the treatment interrupted and re-initiated at a lower dose once the blood pressure is controlled, according to clinical judgment. Treatment discontinuation should be considered if patients have severe and persistent hypertension[12].

Tivozanib should be used with caution in patients at risk of, or with a history of, arterial thrombotic events (ATE) for example myocardial infarction or stroke, and also in patients with venous thrombotic events (VTE) and bleeding[12].

The Summary of Product Characteristics recommends that tivozanib is used with caution in patients undergoing dialysis.

Hepatic function should be monitored before and during treatment. Tivozanib is not recommended in patients with severe hepatic impairment and should be used with caution in patients with mild/moderate hepatic impairment with close monitoring of tolerability. The dose in patients with moderate hepatotoxicity should be reduced to every other day[12].

The dose should be reduced, interrupted or discontinued depending on the severity of events if patients develop cardiac failure or proteinuria. In patients who develop bleeding which requires medical intervention then tivozanib should be temporarily interrupted[12].

Tivozanib should be used with caution in patients with or who may develop QT interval prolongation, in those at risk of gastrointestinal perforation/fistula[12].

There are a number of side effects which are class effects of VEGFR-TKIs – these include HFS, QT interval prolongation, gastrointestinal perforation/fistula, wound healing complications and hypothyroidism[12].

Temporary discontinuation or dose reduction should be considered in patients with troublesome HFS with permanent discontinuation recommended in severe or persistent cases[12].

Temporary interruption of tivozanib is recommended in patients undergoing major surgical procedures[12].

Tivozanib should not be used during pregnancy, effective methods of contraception should be used by male and female patients and their partners during therapy, and for at least one month after completing therapy. Female partners of men taking tivozanib should also avoid pregnancy. Tivozanib should not be taken by breast-feeding women[12].

The proposed Summary of Product Characteristics provides further details and may be found in Appendix 1.

The two VEGFR-TKIs approved by NICE for first-line use in advanced RCC – sunitinib and pazopanib – have similar restrictions for use within their Summaries of Product Characteristics[33 34].

The draft European public assessment report (EPAR) has not yet been issued; therefore, we are unable to summarise the main issues discussed by the regulatory authorities at the time of submission of this dossier to NICE.

The US Food and Drug Administration (FDA) considered a submission for tivozanib for the treatment of advanced RCC in 2013, based on the pivotal phase III study (TIVO-1). They did not approve tivozanib in this indication, since they felt that the results of the study were unclear as to whether the benefit-to-risk evaluation was favourable. Although there was a significant benefit for tivozanib in terms of PFS, the primary outcome, there was a non-significant decrease in OS versus the comparator (sorafenib).

At the time of the FDA submission no analysis of crossover was available. We have carredo out an analysis adjusted for crossover which confirms that the difference in OS reflects imbalance in access to next-line targeted therapies.

Tivozanib is NOT subject to any other health technology assessment in the UK.

2.3 Administration and costs of the technology

Tivozanib is an oral medication given once daily at a dose of 1,340 µg for 21 days, followed by a 7-day rest period making one complete treatment cycle of 4 weeks. This treatment schedule should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs[12].

Tivozanib may be taken with or without food, the capsules should be swallowed whole with a glass of water and not be opened[12].

Side effects may require temporary interruption and/or dose reduction of tivozanib therapy. When dose reduction is necessary, a 890 µg capsule is available so that the dose can be reduced to 890 µg once daily within the normal treatment schedule of 21 days of dosing, followed by a 7-day rest period[12].

No dose adjustment is required for patients aged 65 or over or patients with mild, moderate or severe renal impairment. Patients with hepatic impairment have reduced tivozanib clearance and a dose reduction may be considered to help manage adverse reactions[12].

Table 7: Costs of the technology being appraised

	Cost	Source
Pharmaceutical formulation	Hard capsule	Summary of Product Characteristics[12]
Acquisition cost (excluding VAT) *	[redacted]	EUSA Pharma
Method of administration	Oral	Summary of Product Characteristics[12]
Doses	1,340 µg[1] 890 µg in patients requiring dose reduction	Summary of Product Characteristics[12]
Dosing frequency	Once daily	Summary of Product Characteristics[12]
Average length of a course of treatment	Until disease progression or unacceptable toxicity	Summary of Product Characteristics[12]
Average cost of a course of treatment	[redacted]	Based on cost per month x median PFS in TIVO-1(11.9 months)[11] Calculated as 13 x price
Anticipated average interval between courses of treatments	Given for 3 weeks in a 4 week cycle	Summary of Product Characteristics[12]
Anticipated number of repeat courses of treatments	N/A	Summary of Product Characteristics[12]
Dose adjustments	Dose adjustments may be required to manage side effects or in patients with hepatic impairment. Dose reduction is recommended for uncontrolled hypertension, cardiac failure, proteinuria and troublesome HFS. Dose interruption or discontinuation is recommended In patients with severe/persistent hypertension or HFS. Management of cardiac failure may require dose interruption or discontinuation. Patients with grade 2 or 3 proteinuria may benefit from temporary discontinuation, in those with grade 4 proteinuria tivozanib should be discontinued. Temporary discontinuation of tivozanib is recommended in patients undergoing major surgical procedures	Summary of Product Characteristics[12]
Anticipated care setting	Secondary care, medication taken in the patient's home	Summary of Product Characteristics[12]
PAS: Patient access scheme, PFS: Progression free survival		

2.4 Changes in service provision and management

The tests and monitoring for the use of tivozanib are outlined below[12], they are all standard tests and are not additional to usual care.

The two VEGFR-TKIs approved by NICE for first-line use in advanced RCC – sunitinib and pazopanib – have similar testing and monitoring requirements[33] [34]. Tivozanib use is unlikely to result in additional monitoring or hospital visits compared with sunitinib and pazopanib. Indeed, the adverse event (AE) profile with tivozanib seen in the pivotal TIVO-1 trial[11] suggests that patients receiving tivozanib may require fewer hospital visits than those receiving pazopanib or sunitinib.

The tests required prior to initiation of tivozanib are as follows

- Blood pressure: patients should have controlled blood pressure prior to initiation of tivozanib.
- Proteinuria: all patients should undergo dipstick urinalysis before starting treatment.
- Liver tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin).
- Thyroid function.

The monitoring requirements for tivozanib are as follows:

- Blood pressure: during treatment, patients should be monitored for hypertension and treated as needed with anti-hypertensive therapy according to standard medical practice.
- Cardiac failure: signs or symptoms of cardiac failure should be periodically monitored throughout treatment with tivozanib.
- Proteinuria: should be monitored periodically throughout treatment. In clinical practice this will generally be at each cycle.

[1] The dose of tivozanib used in the TIVO-1 study is the licenced dose for tivozanib. Recent EMA/CHMP guidelines state that the declaration of dose in the Summary of Product Characteristics should reflect the amount of active substance (1,340 µg). The dose in the TIVO-1 study is described as a 1.5 mg capsule, which consists of 1,340 µg of tivozanib, with the balance being made up of excipients.

- Liver tests: should be monitored periodically throughout treatment. Unlike with pazapanib[33] there is no specific liver toxicity signal necessitating explicit monitoring with tivozanib.

- Gastrointestinal perforation/fistula: symptoms of gastrointestinal perforation/fistula should be monitored during treatment.

- Thyroid function: should be monitored periodically throughout treatment.

The most common AE with tivozanib in the clinical trial programme was hypertension, which can be managed using standard antihypertensive medication or dose reduction, interruption or discontinuation as detailed above[12]. In the pivotal TIVO-1 study, hypertension was controlled with medication in most cases, with 2% of patients requiring dose reduction and <1% of patients requiring dose discontinuation for hypertension[11].

No concomitant therapies are specified within the Summary of Product Characteristics.

Tivozanib should only be initiated by an oncologist with experience of managing patients with RCC.

Tivozanib is an oral medication and is taken in the patient's own home, minimising the need for hospital visits. The dose regimen is simple (one tablet once daily) and there are clear and straightforward instructions in the case of a missed dose. The resource use to the NHS is low.

Tivozanib does not require additional infrastructure in the NHS to be put in place, as the resources required are the same as those required for the technologies it displaces.

2.5 Innovation

Not applicable.

3 Health condition and position of the technology in the treatment pathway

- Around 90% of renal cancers are RCC[2] – there are around 7,760 new cases of RCC each year in England[35 36].
- Incidence increases with age, around three-quarters of new cases are diagnosed in people aged 60 and over[36].
- The majority of cases of RCC present incidentally. Almost one-half of those patients with advanced disease present late in the course of the disease; often as an emergency[36 37].
- There is no cure for advanced or metastatic disease, and life expectancy is poor. OS varies from 8 months to 3.6 years depending on prognostic factors[38].
- Late stage RCC has a considerable impact on HRQOL, particularly in patients with progressive disease who may suffer unpleasant symptoms and in patients undergoing treatment who may suffer AE[39 40].
- The financial burden of RCC is considerable in terms of hospital stay and the management of AE associated with treatment[41 42].
- Advanced disease is treated medically with a focus on the targeted therapies. VEGFR-TKIs [sunitinib, pazopanib, sorafenib, axitinib]) and mTOR) inhibitors (temsirolimus and everolimus. Newer agents include nivolumab (an anti-programmed death 1 [PD-1] inhibitor) and cabozantinib (small molecule inhibitor of the tyrosine kinases c-Met and VEGFR2)[38 43].
- VEGFR-TKIs are the standard of care at first-line and NICE approve the use of the VEGFR-TKIs pazopanib[1] and sunitinib[2] as the only first-line treatment options for advanced and metastatic disease.
- Tivozanib will be a first-line treatment option as an alternative to pazopanib and sunitinib.
- NICE-approved second-line treatments post-VEGFR-TKI include everolimus[7], nivolumab [4] and axitinib (a VEGFR-TKI)[3]. Sorafenib, sunitinib[26] and cabozantinib [9] are not recommended by NICE for second-line treatment.

- The number of patients in England suitable for treatment with tivozanib each year is estimated at 2,967.

3.1 Overview of RCC

Renal cancer is the eighth most common cancer in the UK (2012), accounting for 3% of all new cases of cancer. In 2013, there were 9,023 cases of renal cancer in England[35]. RCC is the most common form of renal cancer, accounting for around 90% of renal cancers[2] and we estimate that there are 7,760 new RCC cases each year in England (Table 8).

RCC encompasses a number of different types of tumours found in the kidney, each derived from the lining of the nephron. There are three main types: clear cell (70-80% of cases), papillary (10-15%) and chromophobe (3-5%) and several other rarer types[37].

Risk factors for RCC include cigarette smoking (active and passive), obesity and hypertension, although most patients do not have an identifiable risk factor and the pathological mechanisms underlying the disease remain unclear[37]. Around 2-3% of cases are familial with an underlying genetic basis, the most common of which is VHL syndrome (1 in 36,000 births) which is associated with a number of tumours including clear cell RCC. Clear cell RCC in people with VHL syndrome is generally early in onset and multifocal. In contrast, in patients with non-inherited clear cell RCC onset tends to be late and unifocal. However, most patients with RCC will have somatic defects in the VHL gene[37].

RCC is more common in men than in women with a ratio of 1:1.6[36]. RCC incidence also increases with age; in the UK between 2010 and 2012, three-quarters (76%) of cases were diagnosed in people aged 60 and over[36].

Patients may present with local or systemic symptoms, although most presentations are incidental and found on unrelated abdominal imaging. Local signs and symptoms include the classic triad of flank pain, gross haematuria and palpable abdominal mass, however, this is rare (6-10%) and correlates with aggressive histology and advanced disease[38]. Systemic symptoms can be due to metastases or paraneoplastic events related to secreted proteins, for example parathyroidhormone-related protein (causing hypercalcaemia), renin (causing hypertension), erthyropoietin (causing an increase in red blood cells known as erythrocytosis) and fever or wasting syndromes[37].

The American Joint Committee on Cancer (AJCC) tumor node metastases (TNM) system is used to grade RCC into stages I to IV. Locally advanced RCC, in which the tumour is either locally invasive and/or has spread to regional lymph nodes, is generally defined as stage III.

Metastatic RCC, in which the tumour has spread beyond the regional lymph nodes to other parts of the body, is generally defined as stage IV[38].

In many cases the disease is locally advanced or metastatic at the point of diagnosis. A quarter of RCC cases in England are diagnosed after presenting as an emergency. The proportion of patients presenting as an emergency rises with increasing age, reaching a peak in 85+ year-olds (50%)[36].

Indeed, of those patients recorded with a known stage at diagnosis in 2013 (71%), 18% presented with stage III (locally advanced disease) and 28% with stage IV (metastatic disease)[36]. If we assume that the distribution is similar in patients without a recorded stage at diagnosis then this equates to around 3,570 patients each year in England (46% of 7,760 patients with RCC).

Treatment of early stage disease is surgical, and around one-half of patients who undergo surgical treatment will subsequently develop metastatic disease[26].

At present there is no cure for patients with locally advanced or metastatic disease and prognosis in patients with late stage disease is generally poor, varying according to prognostic factors.

OS in patients with metastatic disease is of the order of 8 months in patients with a poor prognosis according to the International Metastatic Renal Cancer Database Consortium (IMDC) model[2] rising to 3.6 years in those with a favourable prognosis[38].

In the UK in 2014, there were 4,421 deaths from kidney cancer. Five-year survival for kidney cancer is 56%; however, survival rates vary considerably with age. Around three-quarters of people diagnosed aged 15-49 survive their disease for 5 years or more, compared with less than a third of people diagnosed aged 80 and over[36].

[2] The International Metastatic Renal Cancer Database Consortium (IMDC) is used in metastatic disease and includes the following six prognostic risk factors: anaemia (haemoglobin <upper limit of normal [ULN]), thrombocytosis (platelets >ULN), neutrophilia (neutrophils >ULN), Karnofsky performance status (KPS) <80%, and <1 year from diagnosis to first-line targeted therapy. Favourable prognosis is defined as no prognostic factors, intermediate prognosis as 1-2 prognostic factors and poor prognosis as >3 factors44. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol* 2009;27(34):5794-9. doi: 10.1200/jco.2008.21.4809 [published Online First: 2009/10/15].

3.2 Effects of RCC on patients, carers and society

Late stage RCC has a considerable impact on HRQOL. A UK-based study demonstrated that the decline in HRQOL is significantly greater in patients with progressive disease than in patients with stable disease[39]. The consequences of advanced disease can be unpleasant and include weight loss/lethargy, fever, night sweats, dysgeusia (taste distortion), anaemia, hypercalcaemia (which may cause constipation and confusion), pain and venous thromboembolism. In patients with metastatic disease, symptoms may arise from the metastatic site e.g. lung metastases may cause airway obstruction, bleeding and dysponea. Furthermore, in patients with metastatic disease the psychosocial impact of a diagnosis with an incurable cancer with a poor prognosis is considerable[40].

Newer targeted therapies demonstrate an improvement in HRQOL over older treatments for RCC such as IFN. Clinical evidence supports a strong association between tumour response and delay in tumour progression with HRQOL benefits experienced by patients receiving the new targeted therapies[40]. Although the newer treatments have improved tolerability over older treatments, AEs of treatment also impact negatively on HRQOL[39].

Given that RCC is a relatively rare disease, there is a paucity of data on the impact of the disease on carers' QOL. At present there is no cure for patients with advanced and/or metastatic disease and the uncertainty around a diagnosis of an incurable cancer with a relatively short survival period in a loved one is likely to cause carers great concern and have a considerable impact on their QOL.

The impact of RCC on healthcare resources is considerable. In England, data from Hospital Episode Statistics (2014-2015) revealed that there were 17,309 finished consultant episodes (FCE) for C64 (Malignant neoplasm of kidney, except renal pelvis), 14,341 admissions and 63,133 FCE bed-days annually[41].

The cost of managing AE can also be considerable even with newer targeted agents[42 45 46]. A study using the US Surveillance, Epidemiology and End Results (SEER) Medicare database revealed that total cost of care over 30 days was substantially higher among patients aged ≥65 years with metastatic RCC treated with sunitinib, sorafenib, bevacizumab or pazopanib experiencing grade 3 or 4 AEs than those not experiencing AE: a mean (95% confidence interval [CI]) difference of $12,410 ($9217-$16,522). Given that 60% of patients experienced grade 3 or 4 AEs in this study, the financial impact is considerable[42].

3.3 Clinical pathway of care

The NICE pathway for renal cancer[47] sets out the clinical pathway of care. Surgery is recommended as an initial approach with systemic treatment for advanced and metastatic disease.

Prior to the launch of VEGFR-TKI more than a decade ago cytokines were the standard of care at first-line. The VEGFR-TKIs pazopanib and sunitinib have replaced cytokines and are now generally accepted, and recommended by NICE, as first-line treatment options for advanced and metastatic disease[1] [2].

Evidence provided to NICE by clinical experts in the course of several recent Technology Appraisals (axitinib, Technology Appraisal 333[3] and nivolumab Technology Appraisal 417[4]) supports this place in therapy for VEGFR-TKIs. Clinical experts in the axitinib appraisal which was issued in February 2015 suggested that <1% of patients would receive cytokines as first-line treatment[3]. Clinical opinion elicited for the nivolumab appraisal issued 21 months later in November 2016[4] reinforced this view …*The committee heard from the clinical experts that most people in the NHS with newly diagnosed advanced renal cell carcinoma would be offered one of two tyrosine kinase inhibitors; either pazopanib or sunitinib, as recommended in NICE's technology appraisal guidance…*

Bevacizumab, sorafenib and temsirolimus are not recommended by NICE as first-line treatment options[26].

NICE-approved second-line treatments post-cytokines or VEGFR-TKI include

- Axitinib for metastatic RCC. NICE only recommend axitinib as an option for treating adults with advanced RCC after failure of treatment with a first-line TKI or a cytokine[3].
- Nivolumab as an option for previously treated advanced RCC. Nivolumab satisfies the NICE end of life criteria and is used in patients with a poor prognosis[4].
- Everolimus as an option for treating advanced RCC that has progressed during or after treatment with VEGF-targeted therapy. Everolimus satisfies the NICE end of life criteria and is used in patients with a poor prognosis [7].

Sorafenib, sunitinib[26] and cabozantinib (small molecule inhibitor of the tyrosine kinases c-Met and VEGFR2)[9] are not recommended by NICE for second-line treatment

Tivozanib will be a first-line treatment option as an alternative to pazopanib and sunitinib.

3.4 Life expectancy and number of people suitable for treatment

Life expectancy for patients with advanced or metastatic disease is poor and dependent on prognostic factors; in patients with metastatic disease OS ranges from 8 months to 3.6 years dependent on risk status[38]. Clinical studies in patients treated with sunitinib or pazopanib at first line have demonstrated OS of around 2 years (26.4 months with sunitinib in patients with metastatic disease[18] and 22.9 months with pazopanib in patients with advanced or metastatic disease[20]). In the COMPARZ study which compared pazopanib with sunitinib, OS was 28.4 months and 29.3 months respectively[16].

Based on published epidemiological data and assumptions used in previous NICE STAs, we estimate that there are 3,297 patients per year in England, who would be considered eligible for treatment with first-line VEGFR-TKI. Our clinical advisors suggest that approximately 90% of these will currently be treated, equating to 2,967 patients per year (see Table 8).

Table 8: Number of patients suitable for treatment with tivozanib

	Number	**Data source**
Number of people with new kidney cancer diagnoses in England	9,023	Office for National Statistics[351]
86% of kidney cancer patients have RCC	7,760	Cancer Research[36]
44% of RCC patients have advanced or metastatic disease at presentation	3,414	National Cancer Registration and Analysis Service[48]
Of the remaining 56% who present with localised disease, 33% will relapse following surgical treatment	1,434	Cohen & McGovern[49]; cited in NICE TA169[50]
Total patients in England with advanced or metastatic RCC	4,848	3,414 + 1,434
68% of patients have an ECOG score of 0-1 and are eligible for first-line treatment with VEGFR-TKI	3,297	Elson et al[51]; cited in NICE TA169[50]
90% of eligible patients currently receive treatment with first-line VEGFR-TKI	2,967 (32.9% of all new kidney cancer cases)	Personal communication Dr Robert Jones

3.5 Relevant NICE guidance

Relevant NICE guidance is provided in Table 9.

Table 9: NICE guidance for RCC

Date	TA	Title	Guidance
2009	169	Sunitinib for the first-line treatment of advanced and/or metastatic renal cell[2] carcinoma	Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic RCC who are suitable for immunotherapy and have an ECOG performance status of 0 or 1.
2011	178	Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma[26]	Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic RCC. Sorafenib and sunitinib are not recommended as second-line treatment options for people with advanced and/or metastatic RCC.
2011	215	Pazopanib for the first-line treatment of advanced renal cell carcinoma[1]	Pazopanib is recommended as a first-line treatment option for people with advanced RCC who have not received prior cytokine therapy and have an ECOG performance status of 0 or 1 and if the manufacturer provides pazopanib with a 12.5% discount on the list price as agreed in the PAS.
2015	333	Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment[3]	Axitinib is recommended as an option for treating adults with advanced RCC after failure of treatment with a first-line TKI or a cytokine, only if the company provides axitinib with the discount agreed in the PAS.
2016	417	Nivolumab for previously treated advanced renal cell carcinoma[4]	Nivolumab is recommended as an option, as monotherapy for the treatment of advanced RCC after prior therapy in adults when the company provides nivolumab with the discount agreed in the PAS.
2017	432	Everolimus for advanced renal cell carcinoma after previous treatment[7]	Everolimus is recommended within its marketing authorisation as an option for treating advanced RCC that has progressed during or after treatment with VEGF targeted therapy, only if the company provides it with the discount agreed in the PAS.
2017	931	Cabozantinib for previously treated metastatic renal cell carcinoma[9]	Cabozantinib is not recommended within its marketing authorisation for treating advanced RCC in adults after VEGF-targeted therapy. [Note: this information is taken from the Appraisal consultation document, which is used as the source throughout this document]
RCC: Renal cell carcinoma, ECOG: Eastern Cooperative Oncology Group, PAS: Patient access scheme, VEGF: Vascular endothelial growth factor			

It should be noted that guidance for first-line sunitinib and pazopanib (TA169 and TA215) recommends first-line use in patients with an ECOG performance status of 0 or 1. Guidance for both agents states that when using ECOG performance status, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

3.6 Clinical guidance

Guidelines issued by the European Association of Urology (EAU) (2015)[38] and the European Society of Medical Oncology (ESMO) (2016)[43] have a similar approach to the NICE pathway. Surgery is recommended for RCC as an initial approach with systemic treatment for advanced and metastatic disease.

There is a focus on the targeted therapies – the VEGFR-targeted therapies (bevacizumab and VEGFR-TKIs [sunitinib, pazopanib, sorafenib, axitinib]) and mTOR inhibitors (temsirolimus and everolimus). Newer agents include nivolumab and cabozantinib.

Guidance from ESMO[43] is outlined below.

For first-line treatment:

- Bevacizumab in combination with IFN-α, sunitinib and pazopanib for patients with a good prognosis. High dose IL-2, sorafenib or bevacizumab + low dose IFN-α are recommended as alternative options.
- Temsirolimus for patients with a poor prognosis. Sunitinib, sorafenib or pazopanib are recommended as alternative options.

For second-line treatment:

- Axitinib, sorafenib and pazopanib are recommended for patients who have failed first-line cytokine therapy (e.g. IFN). Sunitinib is recommended as an alternative option.
- Nivolumab and cabozantinib are recommended for patients who have failed VEGF-targeted therapies. Axitinib, everolimus and sorafenib are recommended as alternative options.

Guidance from EAU[38] is outlined below

For first-line treatment:

- Bevacizumab in combination with IFN-α for treatment-naïve patients with low or intermediate risk advanced or metastatic RCC.
- Sunitinib and pazopanib for treatment-naïve patients with advanced or metastatic RCC. Sorafenib is not recommended by EAU for first-line treatment.
- Temsirolimus is recommended in poor risk RCC patients.

For second-line treatment:

- Axitinib for metastatic RCC. Sorafenib and pazopanib are recommended as alternatives to axitinib for patients who have failed first-line cytokine therapy (e.g. IFN).
- Everolimus is recommended for patients who have failed VEGF-targeted therapies.
- The guidelines recommend sequencing of targeted agents, but are unable to make firm recommendations on the sequence of agents due to the lack of evidence.

Of the options outlined in the European guidance, the following are approved by NICE[1-4 7 26 52].

For first-line treatment:

- Pazopanib[1] in patients with advanced RCC who have not received cytokine treatment with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Sunitinib[2] in patients with advanced or metastatic RCC who have not received cytokine treatment with an ECOG performance status of 0 or 1.

For second-line treatment:

- Axitinib for metastatic RCC. NICE only recommend axitinib as an option for treating adults with advanced RCC after failure of treatment with a first-line VEGFR-TKI or a cytokine[3].
- Nivolumab as an option for previously treated advanced RCC[4]. Nivolumab satisfies the NICE end of life criteria and is used in patients with a poor prognosis

- Everolimus as an option for treating advanced RCC that has progressed during or after treatment with VEGF-targeted therapy[7]. Everolimus satisfies the NICE end of life criteria and is used in patients with a poor prognosis

3.7 Issues relating to current clinical practice

The scope for this Technology Appraisal[53] sets out the following comparators:

In untreated disease:

- Sunitinib.
- Pazopanib.
- Immunotherapy, referred to as cytokines in this document (IFN-α, IL-2).

In previously treated disease:

- Axitinib.
- Nivolumab.
- Everolimus.
- Cabozantinib.
- Best supportive care.

The indication for tivozanib is for the treatment of adult patients with advanced RCC who are VEGFR and mTOR pathway inhibitor-naïve and are untreated or have failed prior IFN-α or IL-2 based therapy[12].

Evidence for tivozanib versus sunitinib, pazopanib and cytokines in untreated patients will be provided via a MTC and we will provide economic models for all three comparators in this submission.

We note that the treatment landscape in RCC has evolved over recent years. Prior to the launch of VEGFR-TKI more than a decade ago cytokines were the standard of care at first line. The VEGFR-TKIs pazopanib and sunitinib have replaced cytokines and are now generally accepted as first-line treatment options for advanced and metastatic disease, supported by NICE guidance[1 2].

Indeed, clinical experts in the axitinib appraisal issued in February 2015 suggested that <1% of patients would receive cytokines as first-line treatment[3]. Clinical opinion elicited for the nivolumab appraisal [4] reinforced this view …*The committee heard from the clinical experts that most people in the NHS with newly diagnosed advanced renal cell carcinoma would be*

offered one of two tyrosine kinase inhibitors; either pazopanib or sunitinib, as recommended in NICE's technology appraisal guidance…. The RECCORD registry gathered real world UK data on the use of targeted therapies in locally advanced or metastatic RCC from seven UK hospitals (five in England) from March 2009 to October 2012. Anonymised data was collected through an online registry and data was included on 415 patients[5]. Sunitinib and pazopanib accounted for 90.3% of all first-line treatments, cytokines for 1% and everolimus, sorafenib, temsirolimus for the balance. Expert opinion from the UK confirms this approach, we are aware of only one hospital in the UK (The Christie, Manchester) which routinely uses cytokines first-line in a highly selected subgroup of patients who receive high dose IL-2. We understand that around 20 patients per year receive treatment in this way (Dr Robert Jones, Personal Communication).

Therefore, we believe that sunitinib and pazopanib are the only clinically relevant comparators for tivozanib at first line, i.e. for patients with advanced RCC who are untreated and that use of sunitinib and pazopanib as comparators reflect current clinical practice.

Tivozanib will be licensed to treat patients who have received prior cytokine therapy[12]. However, there are insufficient data for independent analysis of tivozanib in pre-treated patients and the MTC cannot give reliable estimates, therefore tivozanib has not been compared with other treatments specified in the scope in previously treated disease.

Axitinib is recommended by NICE as an option for treating adults with advanced RCC after failure of treatment with a first-line VEGFR-TKI or a cytokine[3]. Nivolumab is licensed as monotherapy for the treatment of advanced RCC after prior therapy in adults[6] and is recommended by NICE in that population[4]. Theoretically, therefore tivozanib could be compared with axitinib or nivolumab post-cytokine treatment. However, we believe that axitinib and nivolumab are not relevant comparators since this pathway barely exists due to the lack of cytokine use first line in clinical practice (see above). As first line VEGFR-TKI has now been in regular use in England since March 2009, the number of cytokine-treated patients in the population who are still to progress and become eligible for targeted therapy is now so small as to be insignificant.

Everolimus is recommended by NICE for second-line treatment[7]. It is licensed for treatment of patients with advanced RCC, whose disease has progressed on or after treatment with VEGF-targeted therapy[8]. Treatment of patients previously treated with VEGFR pathway inhibitors is outside the product licence for tivozanib.

Cabozantinib is not recommended by NICE for previously treated RCC[9]. It is licensed for the treatment of advanced RCC in adults following prior VEGF-targeted therapy[10]. Treatment of patients previously treated with VEGFR pathway inhibitors is outside the product licence for tivozanib.

Best supportive care is not a relevant comparator, since if patients are eligible for tivozanib then they would also be eligible for sunitinib and pazopanib. Best supportive care is used in patients in whom targeted therapy is inappropriate. It is unlikely that there are any patients who would be considered unsuitable for sunitinib or pazopanib who would be considered suitable for tivozanib.

3.8 Equality issues

None.

4 Clinical effectiveness

- The systematic review identified one phase III RCT of tivozanib versus sorafenib in patients with metastatic RCC (TIVO-1), reported in 13 publications, plus a randomised discontinuation study of tivozanib reported in six publications.
- TIVO-1 (AV-951-09-301) was an open-label, randomised phase III trial. Patients were randomly assigned 1:1 to either tivozanib (n=260) or sorafenib (n=257) as their initial targeted therapy[11].
- TIVO-1 was a one-way planned crossover study. On progression, patients assigned to sorafenib were given the option to crossover to receive tivozanib or receive next-line treatment as recommended by their physician. Patients on tivozanib who progressed received next-line routine treatment as recommended by their physician. There was no planned crossover from tivozanib to sorafenib[11].
- Patients received treatment until disease progression, unacceptable toxicity or death. On discontinuation of treatment patients were permitted to receive further treatment. Almost two-thirds (63%) of patients in the sorafenib arm and 13% in the tivozanib arm received a next-line targeted therapy[11].
- Most patients were in late middle age, were white and male. Baseline characteristics were well balanced, except for ECOG performance score. More patients had an ECOG performance score of 0 in the sorafenib arm compared with the tivozanib arm (54% versus 45%). Most patients, 70%, had received no prior systemic treatment for metastatic disease.
- Tivozanib prolonged PFS compared with sorafenib. Median PFS, based on independent radiology review, was 11.9 months for tivozanib versus 9.1 months for sorafenib (HR 0.797; 95% CI, 0.639 to 0.993; p=0.042)[11]. Tivozanib is the only VEGFR-TKI with proven superior efficacy to an active targeted therapy in first-line treatment.
- A post-hoc analysis adjusted for baseline demographics (age, sex, race, baseline ECOG score, number of metastatic sites/organs, MSKCC prognostic group, prior treatment and time since diagnosis) and geographical region (Russia/Ukraine versus all others) resulted in a highly significant difference in PFS (HR 0.725, 95% CI 0.58-0.91, p=0.006)[13].

- Data from two phase II studies reveal a median PFS of 11.7 months[14] and 9.7 months[54].
- The MTC revealed that tivozanib has a comparable PFS to sunitinib and pazopanib, with a HR close to 1 in both the treatment-naïve and mixed (treatment-naïve and pre-treated) populations. PFS with tivozanib is significantly longer than with IFN, HR of 0.61.
- OS was not significantly different between tivozanib and sorafenib (median OS, 28.8 months with tivozanib versus 29.3 months with sorafenib; HR 1.245; 95% CI, 0.954 to 1.624, p=ns) in the primary analysis[11].
- The MTC revealed that tivozanib has a comparable OS to sunitinib (HR, 0.92) and pazopanib (HR, 0.98). OS with tivozanib is longer than with IFN (HR, 0.86).
- OS in the TIVO-1 study is difficult to interpret due to the planned one-way crossover design, which resulted in an imbalance in the access to next-line targeted therapies. The authors of the TIVO-1 publication attributed the discordant OS seen in the TIVO-1 study to a crossover effect[11]. Analysis adjusted for crossover carried out for this submission confirms this (HR of 1.021; 95% CI 0.671 to 1.553; p=0.923).
- Imbalance in access to next-line targeted therapy varied considerably by geography and was most marked in Ukraine and Russia. Pre-specified subgroups for OS included location. Regional differences in next-line therapy demonstrate that if next-line therapy is balanced as was the case in North America and Western Europe then the OS trend favours tivozanib (HR 0.846 for North America and European Union and 0.497 for North America and UK, Italy and France)[12].
- Given the results seen in North America and Western Europe, a post-hoc analysis was carried out to determine the impact of next-line therapy on OS[55]. In those patients who remained on treatment or discontinued treatment without next-line therapy 2-year survival was similar: 56% with tivozanib versus 54% with sorafenib.
- In TIVO-1 most patients remained on the full dose of treatment with tivozanib for the duration of the study. Discontinuations due to AE were relatively low in both arms: 4% versus 5%. However, significantly fewer patients had treatment interruptions due to AE (19% versus 36%, p<0.001) and dose reductions due to AE(14% versus 43%, p<0.001) in the tivozanib arm compared with the sorafenib arm[11].

- Tivozanib was well tolerated in the TIVO-1 study[11]. AEs which were more common with tivozanib compared with sorafenib included hypertension and dysphonia (altered voice sounds), whereas AEs which were more common with sorafenib included HFS (palmar-plantar erythrodysesthesia syndrome) and diarrhoea[11].

- Hypertension was controlled with medication in most patients[11]. A retrospective analysis from TIVO-1 showed significantly longer PFS in patients with treatment-induced hypertension receiving tivozanib versus those with normal blood pressure (18.3 months versus 9.1 months for diastolic blood pressure and 16.7 months versus 9 months for systolic blood pressure)[56].

- The most common on-target AEs with tivozanib (hypertension and dysphonia) decreased over time[57]. Long-term follow-up for a further 2.5 years did not reveal any new safety signals[19].

- Safety data from the two phase II studies[15 58] were consistent with the known safety profile of tivozanib and did not suggest the emergence of any new safety signals for tivozanib.

- The MTC revealed that tivozanib was less likely to result in AE, of all grades, than sunitinib or pazopanib, with the exception of hypertension. HFS was significantly less likely with tivozanib compared to sunitinib, with a trend towards benefit with tivozanib over pazopanib.

- Overall on treatment QOL was similar with tivozanib and sorafenib and maintained at a level comparable to baseline[11], but [redacted][25].

- In conclusion, tivozanib is an efficacious treatment for advanced and metastatic RCC with comparable PFS to pazopanib and sunitinib which are currently approved by NICE as first-line treatments for RCC. PFS with tivozanib is significantly improved over IFN, with a HR of 0.61. Tivozanib has a comparable OS to sunitinib (HR, 0.92) and pazopanib (HR, 0.98) and a longer OS than IFN (HR, 0.86).

- Tivozanib is well tolerated with lower rates of the AEs which RCC patients find troublesome[22] (fatigue/tiredness, diarrhoea and HFS) than pazopanib and sunitinib. This has a positive impact on the physical well being element of HRQOL. Tivozanib has lower rates of discontinuations, dose reductions and dose interruptions than pazopanib and

sunitinib, which should enable patients to remain on treatment for the duration of its benefit.

4.1 Identification and selection of relevant studies

4.1.1 Search strategy

We conducted a systematic literature review for studies relevant to the clinical effectiveness of tivozanib and other targeted therapies or immunotherapy in patients with advanced or metastatic RCC. A single search and screening process was used to identify studies relevant to the clinical effectiveness or cost-effectiveness or relevant interventions, and the quality of life and economic burden of advanced or metastatic RCC.

The following sources were searched for relevant documents:

- MEDLINE and MEDLINE-in Progress (via PubMed; http://www.ncbi.nlm.nih.gov/pubmed)
- EMBASE and EMBASE Alert (via ProQuest)
- Cochrane Library (Reviews, trials, technology assessments and economic evaluations; http://onlinelibrary.wiley.com/cochranelibrary/search/)
- Heoro.com (www.heoro.com)
- ASCO conference abstracts for 2015 and 2016 (http://meetinglibrary.asco.org/abstracts)
- ECCO abstracts for 2015 (http://www.eccocongress.org/Vienna2015/Scientific-Programme/Abstract-search)
- Clinicaltrials.gov (www.clinicaltrials.gov)
- WHO International Clinical Trials Registry Platform (ICTRP; http://apps.who.int/trialsearch/AdvSearch.aspx)
- ISRCTN Registry (BioMed Central; http://www.isrctn.com/)

The search strategy used for the combined search is reported in Appendix 2.

4.1.2 Study selection

The inclusion and exclusion criteria used to screen studies for the clinical efficacy review are reported below in Table 10. Inclusion and exclusion criteria were the same for abstract and

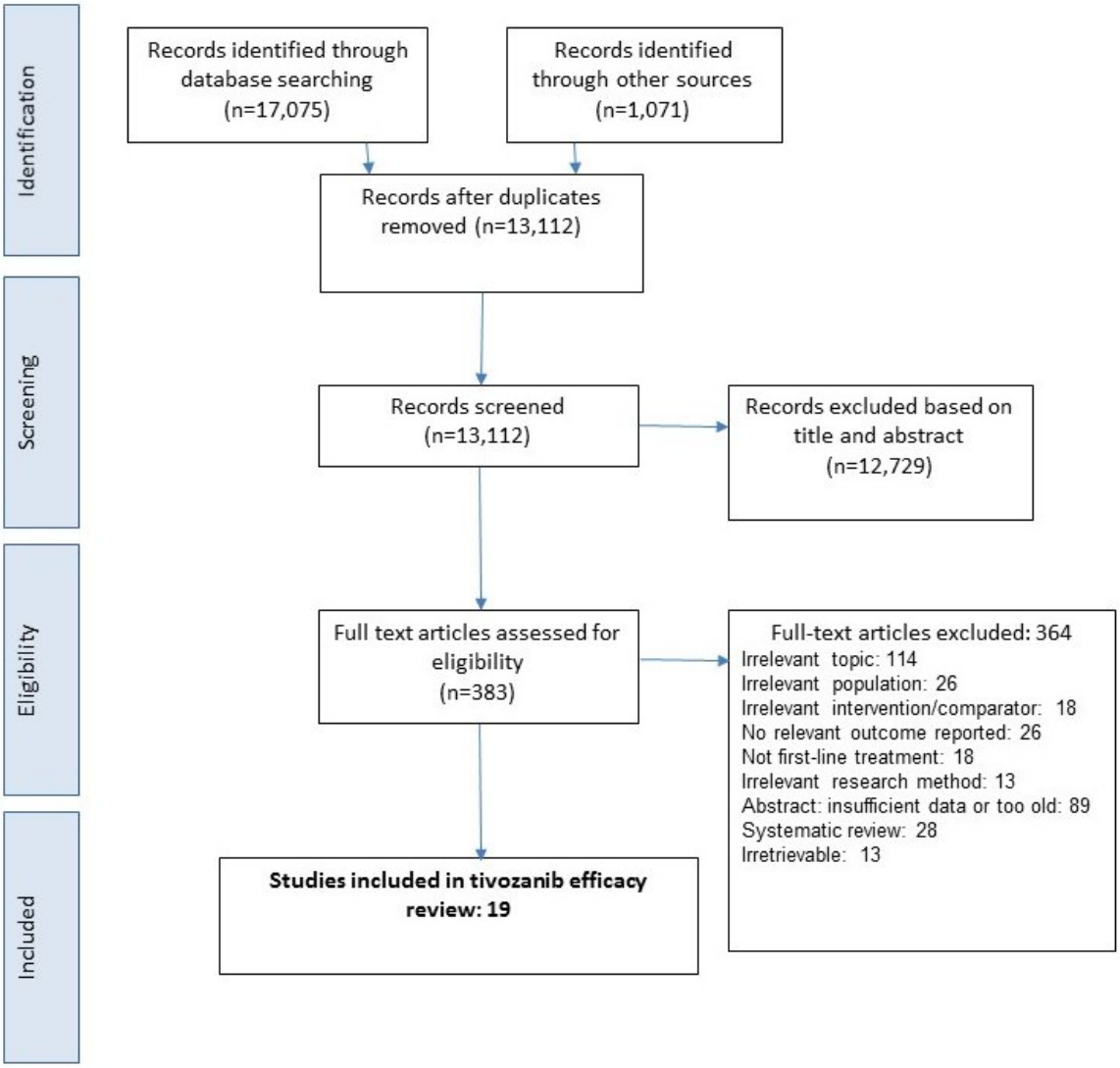
full text screening. Any study of unclear relevance from the abstract was retrieved and screened as the full text.

Details of excluded full-text articles with reasons are presented in Appendix 2.

Table 10: Eligibility criteria used in the search strategy for clinical effectiveness review

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Aged ≥ 18 years Any gender Any race Has locally advanced/advanced/metastatic/stage III/stage IV disease No prior TKI or mTOR therapy	No data reported on relevant population
Intervention	Tivozanib monotherapy (or with best supportive care)	No data reported on relevant intervention
Comparators	Axitinib monotherapy (or with best supportive care) Bevacizumab monotherapy (or with best supportive care) Everolimus monotherapy (or with best supportive care) IFN-α monotherapy (or with best supportive care) Interleukin monotherapy (or with best supportive care) Pazopanib monotherapy (or with best supportive care) Sorafenib monotherapy (or with best supportive care) Sunitinib monotherapy (or with best supportive care) Temsirolimus monotherapy (or with best supportive care) Any other targeted therapy or immunotherapy Placebo Best supportive care	No data reported on relevant comparator
Outcomes	**Efficacy**: OS PFS Time to progression Overall response rate (complete and partial) Proportion with stable disease Time to response Duration of response **Safety**: Incidence and severity of AEs Withdrawals due to AEs Deaths Serious AEs	No data reported on a relevant outcome
Study design	RCT (any blinding) Studies only available as conference abstracts will be included if they report sufficient relevant data to allow inclusion in the analysis **Systematic reviews** will be used for citation chasing only: Full text only Published from 2010 onwards Including only RCTs in a population with advanced or metastatic RCC receiving a relevant intervention	Other study design
Language restrictions	English full-text publication	Full text publication in other language
Publication dates	1980 onwards (journal articles) Last 2 years of conference abstracts	Published outside relevant dates
TKI: Tyrosine kinase inhibitor, mTOR: Mammalian target of rapamycin, IFN: Interferon, OS: Overall survival, PFS: Progression free survival, AE: Adverse event, RCT: Randomised controlled trial, RCC: Renal cell carcinoma		

Figure 1: PRISMA diagram



4.2 List of relevant randomised controlled trials

The systematic review identified one phase III RCT of tivozanib versus sorafenib in patients with advanced or metastatic RCC (TIVO-1), reported in 13 publications, plus a randomised discontinuation study of tivozanib reported in six publications.

In the discontinuation trial, all patients commenced open-label tivozanib. Participants who showed a partial response continued open-label tivozanib, those who progressed discontinued the trial and those with stable disease were then randomised to either continue with tivozinib or to placebo until disease progression, at which point they were switched back to tivozanib if they were in the placebo group, or discontinued if they were in the tivozanib group[14]. As patients in this study did not receive continuous therapy as would be the case in

normal care, it was not included further in this analysis and is described in Section 4.11 and Appendix 3.

The TIVO-1 study has reported in 13 publications, listed in Appendix 2. There is considerable duplication and the published paper[11] has been used to inform this section wherever possible, although data has also been drawn from the protocol[59] and the clinical study report (CSR)[19].

The primary study reference is Motzer RJ, Nosov D, Eisen T et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. *J Clin Oncol* 2013;31(30):3791-9.

Table 11: List of relevant RCTs

Trial number (acronym)	Population	Intervention	Comparator	Primary study reference
TIVO-1 AV-951-09-301	Patients with metastatic RCC, with a clear cell component, prior nephrectomy, measurable disease and 0 or 1 prior therapies for metastatic RCC	Tivozanib	Sorafenib	Published paper[11]

Additional post-hoc analysis of OS was presented as an abstract and poster at American Society of Clinical Oncology (ASCO) Genitourinary Symposium in 2013.

Motzer R, Eisen T, Hutson TE et al. Overall survival results from a phase III study of tivozanib hydrochloride versus sorafenib in patients with renal cell carcinoma. J Clin Oncol 2013;**31**(suppl 6):Abstract 350 and associated poster[55 60].

An extension study to Motzer et al, was also carried out in which patients on sorafenib had the option to switch to tivozanib on progression. Patients originally randomised to tivozanib received subsequent treatment post-progression according to regional standards of care. Results were presented at ASCO Genitourinary Cancers Symposium in 2013 and at ASCO 2015.

Motzer R, Nosov D, Tomczak P et al. Efficacy and safety data from patients with advanced renal cell cancer treated with tivozanib hydrochloride after progression on sorafenib. *J Clin Oncol* 2015; 31: (suppl 6; abstr 364) and associated poster[61 62].

Hutson T, Nosov D, Tomczak P et al. Tivozanib vs sorafenib targeted therapy for advanced renal cell carcinoma: Final results of a phase III trial (901) and efficacy results of a 2nd line

tivozanib extension study (902). *J Clin Oncol* 2015; 33: (suppl; abstr 4557) and associated poster[57 63].

Final results from TIVO-1 and the extension study are presented in the final CSR[19].

The primary study outcome was death or disease progression, as defined by independent central adjudicators. The study reached its pre-defined termination point (310 progression free survival [PFS] events) in December 2011, at which time centralised adjudication ceased and the dataset was unblinded. The published paper and the interim CSR contain data up to this time point (December 2011). Since that time, a number of subsidiary post-primary analyses relating to subsequent datacuts incorporating non-adjudicated outcomes, including a second CSR have carried out in order to provide additional information regarding OS and safety (Table 12). In order to retain the benefits of randomisation and centralised assessment, our submission focuses on the results from the primary analysis wherever possible.

Table 12: Data cuts for the TIVO-1 study and extension study

Publication	Data	Date
Published paper[11]	PFS for TIVO-1 (Primary analysis)	December 15 2011
CSR[64]	OS for TIVO-1	August 27 2012
	Safety data for TIVO-1	June 1 2012
CSR[19]	Post primary efficacy analysis for TIVO-1	July 10 2013
	Efficacy for extension study (patients remaining on original as randomised treatment in extension study)	June 3 2013
	Safety data for extension study	January 20 2015
PFS: Progression free survival, OS: Overall survival		

4.3 Summary of methodology of the relevant randomised controlled trials

4.3.1 Trial design

TIVO-1 (AV-951-09-301) was an open-label, randomised phase III trial. Patients were randomly assigned 1:1 to either tivozanib or sorafenib as their initial targeted therapy. Random assignment of patients was stratified by geographical region, number of prior treatments for metastatic disease and number of metastatic sites/organs involved[11]. Patients were randomised using an Interactive Voice Response/Interactive Web Response (IVR/IWR) system[59].

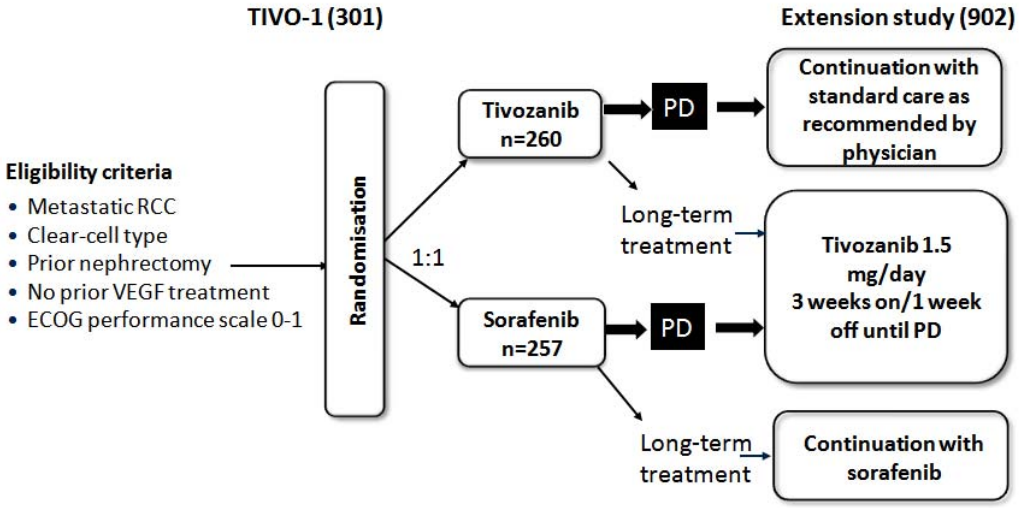
TIVO-1 was a one-way crossover study, in that patients randomly assigned to sorafenib who had Response Evaluation Criteria in Solid Tumors (RECIST)-defined progressive disease

(PD) on investigator assessment were given the option to crossover to receive tivozanib in a separate protocol (AV-951-09-902, NCT01076010) or receive next-line treatment as recommended by their physician. Patients on tivozanib did not crossover to sorafenib, but were given the option to receive routine next-line treatment as recommended by their physician.

All patients were followed for collection of subsequent cancer therapy information and OS.

An extension study (AV-951-09-902) [61 62] allowed patients long-term access to either tivozanib or sorafenib for patients who participated in TIVO-1 and experienced clinical benefit and acceptable tolerability within their randomly assigned treatment arm and allowed access to tivozanib for patients who participated in TIVO-1 and failed sorafenib treatment (see Figure 2).

Figure 2: Study design for TIVO-1 (AV-951-09-301) and the extension study (AV-951-09-902)[61]. PD: Progressive disease



4.3.2 Eligibility criteria

Eligibility criteria for TIVO-1 included the following

- Age ≥18 years.
- Histologically confirmed RCC with a clear cell component and recurrence or metastatic disease.
- Measurable disease as per RECIST.
- Prior nephrectomy.
- ECOG score 0 or 1.
- Adequate renal, hepatic or haematological function.

- Treatment naïve patients or patients with one prior systemic treatment for metastatic RCC. Prior systemic therapy given as an adjuvant following nephrectomy was counted as a prior therapy if recurrence was detected within 6 months of completing treatment.
- Patients with brain metastases if stable for at least 3 months following prior treatment.

Exclusion criteria included the following

- Prior VEGF-targeted therapies or mTOR-targeted therapies.
- Significant cardiovascular (CV) disease, including uncontrolled hypertension (blood pressure >150/100 mmHg whilst taking two or more antihypertensives), myocardial infarction and thromboembolic disorders within 6 months of study entry.

4.3.3 Location of study

This study enrolled 517 patients at 76 sites in 15 countries (Bulgaria, Canada, Chile, Czech Republic, France, Hungary, India, Italy, Poland, Romania, Russia, Serbia, UK, Ukraine, US). Four patients from two sites were enrolled from the UK (Leicester and Cambridge). Most patients (457 [88%]) were enrolled in Central or Eastern Europe[19].

4.3.4 Trial drugs and concomitant medications

Tivozanib was administered orally at 1.5 mg[3] once per day every day for 3 weeks followed by 1 week off (one cycle is 3 weeks on, 1 week off)[11]

Sorafenib was administered orally at a dose of 400 mg (two 200-mg tablets) twice per day continuously (one cycle is 4 weeks on)[11].

Patients continued to receive the study drug until disease progression, unacceptable toxicity, death or any other reason for discontinuing the study drug[11].

4.3.5 Outcomes

The primary end-point was PFS defined as the time interval between date of random assignment and the date of disease progression/death. Tumour assessments using

[3] The dose of tivozanib used in the TIVO-1 study is the licenced dose for tivozanib. Recent EMA/CHMP guidelines state that the declaration of dose in the Summary of Product Characteristics should reflect the amount of active substance (1,340 µg). The dose in the TIVO-1 study is described as a 1.5 mg capsule, which consists of 1,340 µg of tivozanib, with the balance being made up of excipients.

magnetic resonance imagining or computed tomography were made at baseline and every 8 weeks until progression. All imaging scans were evaluated by an independent radiology review, blinded to study treatment. Patients with radiological evidence of PD as assessed by the investigator had confirmation by blinded independent review within 48 hours. This independent review to confirm investigator-called PD was a separate process from the third-party review of response performed by the core imaging laboratory to assess the primary end-point. Confirmation of PD was not required if significant clinical deterioration, appearance of new lesions, or >50% increase in measurable disease per RECIST was noted by the investigator.

Secondary end-points included OS, objective response rate (ORR), safety and tolerability and HRQOL.

HRQOL was assessed with the Functional Assessment of Cancer Therapy-General (FACT-G), FACT Kidney Symptom Index–Disease-Related Symptoms (FKSI-DRS) and EuroQol-5D (EQ-5D) questionnaires. Questionnaires were administered on day 1 of each cycle and on discontinuation from the study drug[11].

4.3.6 Pre-planned subgroups

PFS was also compared between treatment arms in predefined subgroup analyses on the basis of baseline characteristics, including ECOG performance score, prior treatment for metastatic disease and Memorial Sloan-Kettering Cancer Center (MSKCC) risk group.

Pre-planned subgroups are listed below[59]:

- Age group (<65 years, ≥65 years).
- Race (white, non-white).
- Gender (male, female).
- Screening ECOG performance status (0, 1).
- Time since diagnosis (<1 year, ≥1 year).
- Geographic region (North America/Western Europe, Central/Eastern Europe, rest of the world).
- Number of prior treatments for metastatic disease (0, 1).
- Number of metastatic sites/organs involved (1, ≥2).
- Systolic blood pressure at baseline (SBP ≤140 mmHg, SBP >140 mmHg).
- Diastolic blood pressure at baseline (DBP ≤90 mmHg, DBP >90 mmHg).
- MSKCC prognostic group (favourable, intermediate, poor).

MSKCC prognostic group was derived from the following pre-treatment risk factors:

- Low Karnofsky performance status (KPS) (< 80%) (equivalent to ECOG status ≥2).
- High lactate dehydrogenase (>1.5 times upper limit of normal).
- Low serum haemoglobin (<lower limit of normal).
- High corrected serum calcium (>25.95 mmol/l [10 mg/dl).
- Absence of prior nephrectomy.

Prognostic group was favourable for patients with none of these risk factors, intermediate with 1 or 2, and poor with >3.

4.4 Statistical analysis and definition of study groups in the relevant randomised controlled trials

4.4.1 Sample size

Target enrolment was 500 patients (250 patients per arm) to observe 310 events (progression or death) yielding 90% power to detect a difference ($p<0.05$) between treatment arms with respect to PFS, assuming the median PFS for patients receiving sorafenib and tivozanib was 6.7 months and 9.7 months respectively (a projected increase of 3 months or 44.8%)[11].

Assuming the median OS for patients receiving sorafenib and tivozanib was 18 months and 24 months, respectively, approximately 300 events would be observed by the time of the final OS analysis, yielding 70% power to detect a difference ($p<0.05$) between the treatment arms with respect to OS[11].

4.4.2 Interim analyses and stopping guidelines

No formal interim analyses for the primary end-point were planned[59]. Final protocol-specified OS analysis was to be performed after completion of follow-up for all patients after all patients had died or were lost to follow-up, or when all patients in the follow-up had been on study for at least 2 years, whichever occurred first.

In the original protocol treatment was stopped for the following reasons[59]:

- Death.
- Unacceptable toxicity.
- Documented PD (RECIST-defined PD per investigator).

- Treatment failure not meeting the criteria for PD, but considered by the investigator to require removal of the patient from the study.
- Treatment interruption for >2 weeks, unless there is a clear benefit from treatment.
- Requirement for a significant surgical procedure.
- Intercurrent illness which would in the opinion of the investigator prevent completion of the study-related evaluations.
- Pregnancy.
- Non-adherence with the study or follow-up.
- Withdrawal of consent.

4.4.3 Trial population included in the primary analysis

Efficacy end points were analysed in the intent-to-treat (ITT) population, which was defined as all randomly assigned patients. PFS between treatment arms was compared on the basis of independent radiology review assessment by using a stratified log-rank test; stratification factors were the number of prior treatments (0 or 1) and the number of metastatic sites/organs involved (1 or ≥2). The distribution of PFS was estimated by using the Kaplan-Meier method. The HR and its 95% CI were determined by using the Cox proportional hazards model[11].

Missing data were treated as missing[59]. PFS data were censored on the day following the date of last tumour assessment documenting absence of PD for patients who did not have objective tumour progression and were still on study at the time of the analysis, were given anti-tumour treatment other than the study treatment or were removed from treatment follow-up prior to documentation of objective tumour progression. Patients who had no tumour assessments after randomisation had their PFS times censored on the date of randomisation, unless they died within 140 days of randomisation (i.e., after 2 or more missed assessments, where 20 weeks was chosen to be the midpoint between the second and third planned assessments during the first year on study). If PD or death occurred after more than 140 days since the last assessment (i.e., after 2 or more missed assessments), the patient was censored on the day following the date of the last assessment before the gap. If a patient had missing imaging at baseline, the patient was censored at the date of randomisation. If the patient had missing imaging during the study, they were considered treatment failures unless subsequent imaging demonstrated that they were progression free.

4.4.4 Statistical methodology for dealing with the effect of crossover

The ability to detect an effect of study treatment on OS may be influenced by subsequent anti-cancer therapies received by patients after they have discontinued study medication, this is particularly true when the study includes crossover to another active treatment. TIVO-1 included a planned one-way crossover whereby patients randomised to sorafenib were able to crossover to tivozanib on progression, whereas patients randomised to tivozanib received physician's choice on progression. Using the 2013 dataset, a total of 161 patients (63%) who progressed on sorafenib crossed over to another targeted treatment, the majority of whom (n=147, 91%) received tivozanib. This is in contrast to the tivozanib arm where only 34 patients (13%) received next-line targeted therapy (7% VEGFR-TKI and 6% mTOR inhibitors), see Table 16. Thus the true effect of tivozanib on OS is likely to be underestimated in the ITT analysis.

The objective of this analysis is to control for the potential confounding effects of crossover on OS among patients in the TIVO-1 trial. Survival outcomes, censoring and crossover in TIVO-1 is summarised in Table 13.

Table 13: Survival outcomes and crossover of patients in the TIVO-1 trial

	Tivozanib	Sorafenib	Total
N (Total patients)	260	257	517
N (Censored)	127	214	341
N (Failure – dead)	133	43	176
N (Crossover)	0	147	147

* A total of 161 patients randomised to Sorafenib crossed over to other treatments. However, 147 of these patients have crossover to Tivozanib treatment (91.3%).

Several methods have been employed for analysing OS in RCTs where OS may be confounded by crossover to an active treatment. These include censoring patients who crossover and Cox regression analysis considering crossover as a time-dependent covariate. However, these methods may be confounded by differences in between groups in time dependent factors that are correlated with crossover and survival. More recently, Inverse Probability of Censoring Weighed (IPCW) and Rank Preserving Structural Failure Time (RPSFT) methods have been employed to address this issue. Both methods are more sophisticated than simply censoring on crossover and aim to produce the results that would have been obtained had sorafenib patients not crossed over and were used to deal with the effect of crossover in the pazopanib manufacturer's submission to NICE for TA215[28 29].

In this submission, we have used the IPCW method to deal with the effect of crossover. We believe that it is the most appropriate method since the RPSFT model assumes that the treatment benefit with tivozanib is the same regardless of whether patients were originally randomised to tivozanib or crossed over to tivozanib from sorafenib at progression. This is clinically implausible since patients who crossover to tivozanib are further along the disease course and have already failed one VEGFR-TKI.

4.4.4.1 Inverse Probability of Censoring Weighed (IPCW) analysis

We used identical methodology to carry out the IPCW analysis to that used in the pazopanib manufacturer's submission to NICE for TA215[29].

The IPCW method of analysing mortality to adjust for crossover entails the following three general steps:

Step 1 Create Panel Data: For sorafenib patients, follow-up time from randomisation until crossover or end of follow-up (defined as death, withdrawal of consent or end of study, whichever occurred first) was partitioned into intervals based on the time to event. The pazopanib submission used visit time, however, we used time to event because we believe that this more accurately reflects patient outcomes. For each of these intervals, time-dependent variables that might be predictive of crossover and mortality (e.g. time since progression and time since diagnosis) were calculated.

Step 2 Calculate Stabilised Weights: Using the panel data created in Step 1, for each sorafenib patient *i* and interval (j), stabilised weights, $SW_i(j)$, were estimated. The denominator of the weights is the probability of remaining uncensored (i.e., not crossing over to tivozanib) to the end of interval (j) given baseline plus time-dependent confounders. The numerator of the weights is the probability of remaining uncensored (i.e., not crossing over to tivozanib) to the end of interval (j) given only baseline confounders. Estimates were obtained by fitting pooled logistic models with censoring (crossover) as the dependent variable.

Step 3 Run IPCW Cox Regression: Adjusted Hazard Ratio (AHR) for OS was estimated using a weighted Cox proportional hazard regression model, where patient intervals were weighted by the stabilised weights calculated in Step 2. For all patients who were randomised to tivozanib, the weight is equal to 1.0 (i.e., $SW_j = 1$). Sorafenib patients who crossed over were censored (i.e., for sorafenib patients who crossed over, intervals after crossover have a weight of zero and are therefore dropped from the model).

Each of these steps is described in greater detail below.

Step 1: Create the Panel Data

A panel data set was created with multiple intervals per patient with each interval beginning with randomisation and ending with crossover to tivozanib or trial censoring, defined as death, withdrawal of consent or end of study, whichever occurred first. For each observation, baseline personal and disease characteristics, including age, gender, MSKCC risk category, time since initial diagnosis at baseline, ECOG and the number of metastatic disease sites were calculated. Time-dependent characteristics included time since disease progression and time since diagnosis.

Patients who crossed over to tivozanib were censored at the crossover time and and were excluded from the subsequent analysis. Out of 260 patients initially randomised to the sorafenib arm, 161 patients had disease progression and 147 of these patients were IPCW-censored at the time of crossover to tivozanib after disease progression.

Among TIVO-1 patients, 29 had missing data on the time since diagnosis covariate, 14 and 15 in tivozanib and the sorafenib treatment groups, respectively. For these patients with missing information, we imputed the sample mean value in order to keep these patients in the survival analysis of tivozanib relative to sorafenib.

Step 2: Calculate Stabilised Weights

Using the panel data created in Step 1, for each Sorafenib patient *i* and interval *(j)*, an estimate of the stabilized weights $SW_i(j)$ was obtained where

$$SW(j) = \prod_{k=0}^{j} = \frac{P\left[C(k)_i \middle| C(k-1)_i, X(0)_i\right]}{P[C(k)_i | C(k-1)_i, X(0)_i, Y(k)_i]}$$

$C(k)_i$ = an indicator function representing censoring/crossover status at the end of interval *k* (1: censored or crossover, 0: uncensored)

$X(0)_i$ = an array of patients characteristics measured at baseline

$Y(k)_i$ = an array of time-dependent patients characteristics measured at or prior to the beginning of interval k

$P[C(k)_i|C(k-1)_i, X(0)_i]$ = probability of remaining uncensored at end of interval *k* given uncensored at end of interval *k-1* and conditioned on baseline characteristics $X(0)_i$

$P[C(k)_i|C(k-1)_i, X(0)_i, Y(k)_i]$ = probability of remaining uncensored at end of interval *k* given uncensored at end of interval *k-1* and conditioned on baseline characteristics $X(0)_i$, and time-dependent patient characteristics $Y(k)_i$.

To estimate the numerator of the stabilised weights we fitted a logistic regression (model 1), in which we modelled the probability of remaining uncensored at time (j) conditional on patient *i* baseline factors (age, sex, favourable/intermediate/poor MSKCC risk category, time since initial diagnosis in weeks, ECOG performance status and the number of metastatic disease sites). The dependent variable in the logistic model was a binary variable (1/0) indicating whether the patient had crossed over or not since the recorded event. We fitted this model on all patient-intervals from randomisation until crossover to tivozanib or trial censoring, defined as death, withdrawal of consent or end of study, whichever occurred first.

To estimate the denominator of the stabilised weights we fitted a logistic regression (model 2), in which we modelled the probability of remaining uncensored conditional on the same baseline factors and patient *i* time-dependent covariates at time (j): Time since progression and time since diagnostic as time dependent variables were the only time-dependent covariates. The choice of baseline and time-dependent covariates were based on prior knowledge from the literature and goodness-of-fit statistics. We fitted this second model on all patient-intervals post-disease progression, i.e., from disease progression until crossover to tivozanib or trial censoring, defined as death, withdrawal of consent, or end of study, whichever occurred first. Table 14 and Table 15 present the results of the logistic regression models 1 and 2.

Table 14: Pooled logistic regression analysis on remaining uncensored (not crossing over to tivozanib) given baseline factors in TIVO-1 trial (Sorafenib patients [n=257], all intervals [n=15,758 intervals]) (Model 1)

Covariate	OR	95% CI		p
Age (Reference: < 65 years)	1.026	0.683	1.54	0.899
Male (Reference: Female)	0.8	0.561	1.162	0.251
MSKCC score: Intermediate (Reference: Favourable)	1.35	0.962	1.92	0.081
MSKCC score: Poor (Reference: Favourable)	3.5	0.453	27.132	0.229
ECOG status: 1 (Reference: 0)	0.92	0.658	1.295	0.644
Number of metastatic disease site (Continuous variable)	1.43	1	2.043	0.045
Weeks since diagnosis (Continuous variable)	0.99	0.982	0.997	0.013
MSKCC: Memorial Sloan-Kettering Cancer Center, ECOG: Eastern Cooperative Oncology Group				

Table 15: Pooled logistic regression analysis on remaining uncensored (not crossing over to tivozanib) given baseline and time-dependent factors in TIVO-1 trial (Sorafenib patients [n=147], post-progression intervals [n=693 intervals]) (Model 2)

Covariate	OR	95% CI		p
Age (Reference: < 65 years)	1.141	0.781	1.666	0.494
Male (Reference: Female)	0.894	0.619	1.293	0.553
MSKCC score: Intermediate (Reference: Favourable)	0.914	0.66	1.266	0.592
ECOG status: 1 (Reference: 0)	0.535	0.388	0.737	<0.001
Number of metastatic disease site (Continuous variable)	1.215	0.866	1.704	0.258
Weeks since diagnosis (Continuous variable)	0.992	0.983	1.002	0.142
Weeks since progression (Continuous variable)	0.785	0.72	0.856	<0.001
Weeks since diagnosis – Time dependent (Continuous variable)	1.003	0.996	1.01	0.296
MSKCC: Memorial Sloan-Kettering Cancer Center, ECOG: Eastern Cooperative Oncology Group				

Step 3: IPCW Cox Proportional Hazards Regression (Censoring at crossover)

In the final step, a time-dependent Cox proportional hazards model was estimated using time-varying stabilised weights, as calculated in Step 2, to compare the OS between tivozanib and sorafenib. In this model, a binary variable indicating the status (0=censored; 1=death) at each person-time was used as the censoring variable and number of days since randomisation was used as the survival time variable. Patients randomised to sorafenib who crossed over to tivozanib were censored at the crossover, and post crossover time were excluded from the subsequent analysis (i.e., *SWi(j)*=0). All other person-time observations were weighted by the stabilised weights calculated in step 2. A binary indicator of randomisation arm (tivozanib relative to sorafenib) was used in the IPCW.

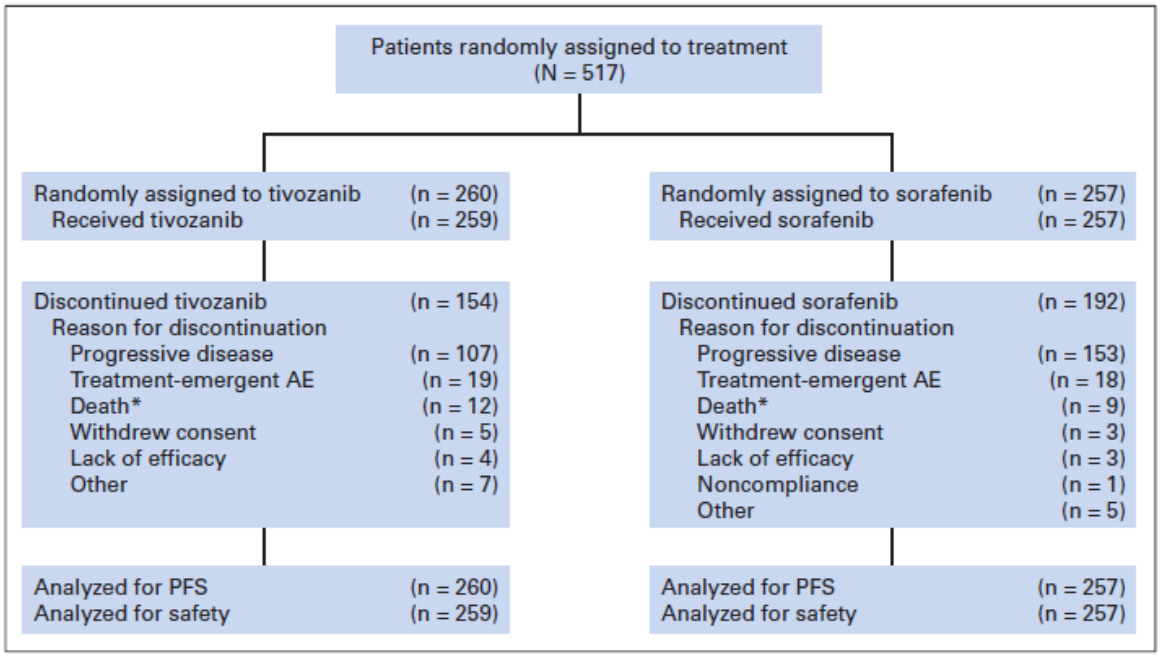
4.5 Participant flow in the relevant randomised controlled trials

Between February and August 2010, 517 patients were randomly assigned to treatment. Overall, 516 patients received treatment: 259 received tivozanib, and 257 received sorafenib. One patient was randomly assigned to tivozanib but was not dosed[11].

At the data cut off (December 15, 2011), 59% of patients in the tivozanib arm and 75% in the sorafenib arm had discontinued the study treatment, most often because of PD[11].

Figure 3 illustrates the flow of patients through the study.

Figure 3: CONSORT diagram based on data cut off date of December 15, 2011[11]



Patients were randomised to either treatment as their initial targeted therapy and patients received treatment until disease progression, unacceptable toxicity or death (Table 16). On discontinuation of treatment patients were able to receive a further line of treatment, almost two-thirds (63%) of patients in the sorafenib arm and 13% in the tivozanib arm received a next-line targeted therapy. Almost all of the patients in the sorafenib arm who received a next-line targeted agent (156 of 168, 92.8%) crossed over to tivozanib as per protocol[11].

Table 16: Summary of next-line therapy in the TIVO-1 study[11]

	Tivozanib (n=260)		Sorafenib (n=257)	
Category	**No.**	**%**	**No.**	**%**
Patients who discontinued assigned therapy	190	73	226	88
Patients with next-line therapy	68	26	168	65
Patients with next-line targeted therapy	34	13	162	63
VEGFR inhibitor	18	7	158	61
Tivozanib	0		156	61
mTOR inhibitor	16	6	4	2
Cytokines	14	5	3	1
Radiotherapy	10	4	2	1
Other	10	4	1	< 1
mTOR: mammalian target of rapamycin, VEGFR: vascular endothelial growth factor receptor				

4.5.1 Patient characteristics at baseline

Table 17: Patient characteristics at baseline in the TIVO-1 study[11]

	Tivozanib (n=260)		Sorafenib (n= 257)	
Characteristic	**No.**	**%**	**No.**	**%**
Age, years				
Median	59		59	
Range	23-83		23-85	
Sex				
Male	185	71	189	74
Female	75	29	68	26
Race/ethnicity				
White	249	96	249	97
Asian	10	4	8	3
Black	1	-1	0	0
Time from diagnosis to study entry, years				
<1	109	42	105	41
>1	137	53	137	53
Most common sites of metastasis				
Lung	212	82	204	79
Lymph nodes	182	70	166	65
Adrenal gland	78	30	57	22
Liver	67	26	49	19
Bone	61	23	52	20
No. of organs involved				
1	76	29	88	34
2	99	38	106	41
>2	85	33	63	25
ECOG performance score				
0	116	45	139	54
1	144	55	118	46
MSKCC prognostic group				
Favourable	70	27	87	34
Intermediate	173	67	160	62
Poor	17	7	10	4
Prior systemic therapy for metastatic RCC				
0	181	70	181	70
1	78	30	76	30
Prior systemic therapy by setting				
Metastatic	49	19	55	21
Adjuvant	23	9	22	9
Other	13	5	9	4

ECOG: Eastern Cooperative Oncology Group; MSKCC: Memorial Sloan-Kettering Cancer Center; RCC: Renal cell carcinoma

Most patients were in late middle age, were white and male. Baseline characteristics were well balanced between the two arms (Table 17), except for ECOG performance score. More patients had a favourable ECOG performance score of 0 in the sorafenib arm compared with the tivozanib arm (54% versus 45%, Fisher's exact test p=0.035). Most patients, 70%, had received no prior systemic treatment for metastatic disease. For the remaining 30% of previously treated patients, more than 90% had received IFN-α.

4.6 Quality assessment of the relevant randomised controlled trials

The risk of bias in the TIVO-1 trial was low indicating a good quality trial, as shown in Table 18 below.

Table 18: Quality assessment (risk of bias) results for TIVO-1

	TIVO-1 (Motzer et al. 2013)
Was randomisation carried out appropriately?	**Yes**: stratified by geographic region, number of prior treatments for metastatic disease, number of metastatic sites
Was the concealment of treatment allocation adequate?	**Yes,** randomisation was performed using an IVR/IWR (information from protocol provided as an appendix to the clinical trial publication)[59]
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes**, baseline characteristics were well balanced, with the exception of ECOG
Were the care providers, participants and outcome assessors blind to treatment allocation?	**No**: open label, independent radiological assessors of progression were blinded
Were there any unexpected imbalances in drop-outs between groups?	**No**, CONSORT diagram shows discontinuations were well balanced other than due to disease progression
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No**, all stated outcomes are reported
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes**; ITT analysis included all randomised patients, safety analysis included all patients who received one or more doses
IVR/IWR: Interactive Voice Response/Interactive Web Response, ECOG: Eastern Cooperative Oncology Group; ITT: Intention to treat	

4.7 Clinical effectiveness results of the relevant randomised controlled trials

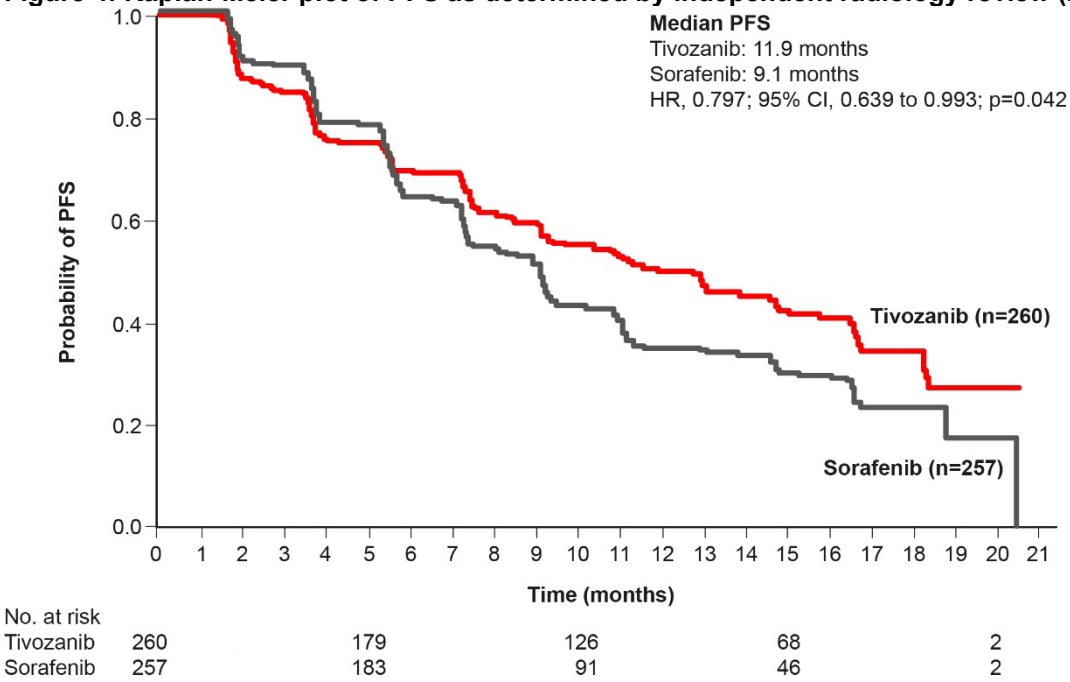
4.7.1 Primary end-point: PFS

Tivozanib prolonged PFS compared with sorafenib (Figure 4). Among the overall ITT population, 153 patients (58.8%) progressed or died while taking tivozanib versus 168 (65.4%) taking sorafenib (data cutoff was December 15, 2011)[11].

Median PFS, based on independent radiology review, was 11.9 months for tivozanib versus 9.1 months for sorafenib (HR 0.797; 95% CI, 0.639 to 0.993; p=0.042)[11].

Median PFS, per investigator review, was consistent with the primary PFS result: 14.7 months versus 9.6 months (HR 0.722; 95% CI, 0.58 to 0.899; p=0.003)[11].

Figure 4: Kaplan-Meier plot of PFS as determined by independent radiology review (ITT)[11]



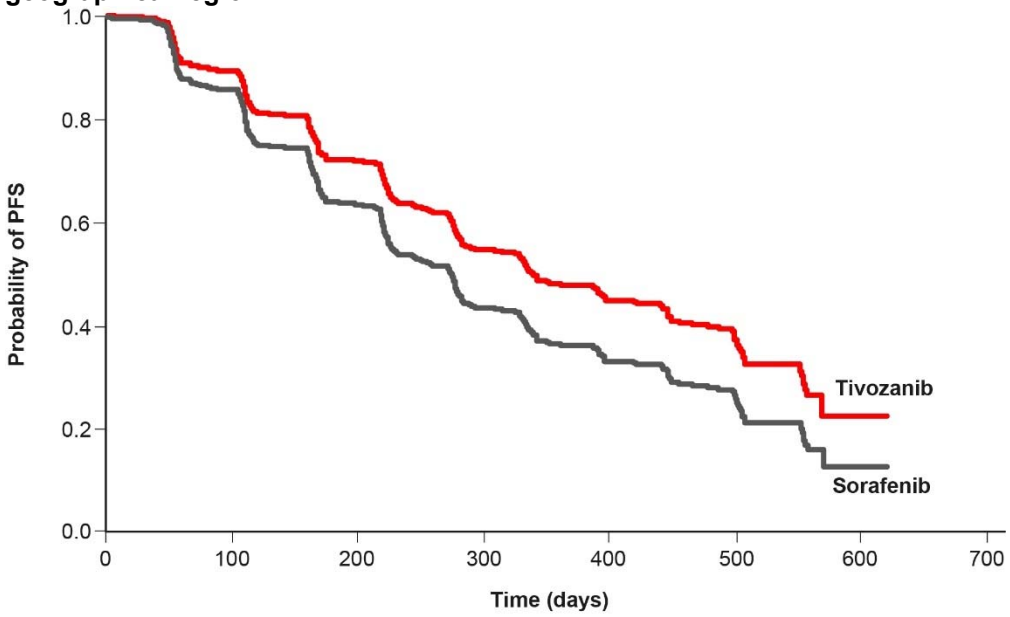
More patients had a favourable ECOG performance score of 0 in the sorafenib arm compared with the tivozanib arm (54% versus 45%, Fisher's exact test p=0.035), when adjustment was made for baseline imbalances in ECOG, PFS with tivozanib was improved over the unadjusted data for the primary end-point (HR 0.765 versus 0.785)[11].

Patients in the Ukraine and Russia had higher rates of unfavourable ECOG and MSKCC compared to the overall study population and patients with poor prognosis were more highly represented in the tivozanib arm. Consequently, these patients had higher rates of progression with tivozanib than the general population. A post-hoc analysis adjusted for baseline demographics (age, sex, race, baseline ECOG score, number of metastatic sites/organs, MSKCC prognostic group, prior treatments and time since diagnosis) and geographical region (Russia/Ukraine versus all others) resulted in a highly significant difference in PFS (HR 0.725, 95% CI 0.58-0.91, p=0.006)[13], see Figure 5 and Table 19

Table 19: Results of Cox Model Analysis for PFS as determined by IRR (ITT population) at the December 2011 analysis point[13]

Parameter (reference)	Unadjusted comparison (1)	Unadjusted comparison + geography (2)	Adjusted for covariates (3)	Covariate adjusted + geography (4)
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
Primary exploratory variables				
Treatment (Sorafenib)	0.789 (0.63-0.98) p=0.03	0.785 (0.63-0.98) p=0.03	0.731 (0.58-0.92) p=0.007	**0.725 (0.58-0.91) p=0.006**
Geography (all others)	-	0.911 (0.73-1.14)	-	0.895 (0.69-1.15)
Covariates				
Age (≥65)	-	-	1.33 (1.01-1.75)	1.35 (1.02-1.78)
Sex (female)	-	-	1.14 (0.87-1.48)	1.14 (0.87-1.48)
Race (non-white)	-	-	0.50 (0.28-0.89)	0.53 (0.30-0.95)
ECOG performance score (1)	-	-	0.77 (0.61-0.98)	0.75 (0.59-0.96)
Metastatic sites (≥2)	-	-	0.51 (0.39-0.66)	0.51 (0.39-0.67)
MSKCC (intermediate/poor)	-	-	0.70 (0.55-0.88)	0.71 (0.56-0.91)
Prior treatments (none)	-	-	1.13 (0.87-1.47)	1.14 (0.88-1.49)
Time since diagnosis (<1 year)	-	-	0.74 (0.57-0.95)	0.73 (0.56-0.94)
ECOG: Eastern Cooperative Oncology Group; MSKCC: Memorial Sloan-Kettering Cancer Center				

Figure 5: Kaplan-Meier plot of PFS analysis adjusted for baseline demographics and geographical region [13]



4.7.2 Secondary end-points

4.7.2.1 Response

ORR was significantly higher with tivozanib compared with sorafenib: 33.1% versus 23.3%, p=0.014, see Table 20

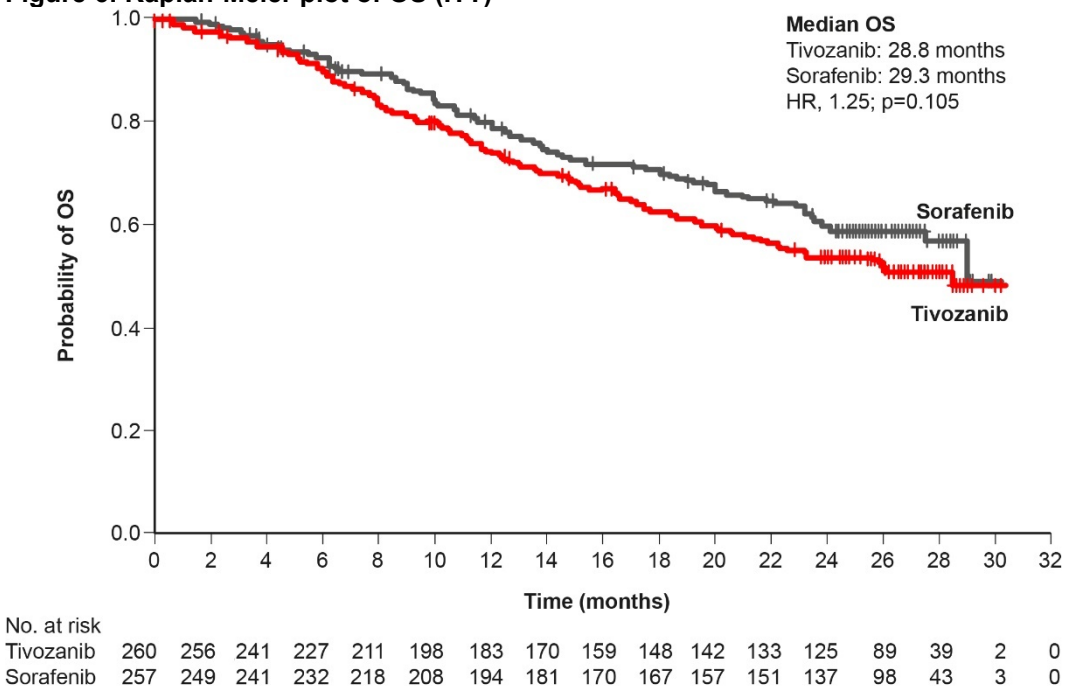
Table 20: Response in TIVO-1 (ITT population, independent radiology review)[11]

	Tivozanib (n=260)		Sorafenib (n=257)	
	n	%	n	%
CR	3	1.2	2	0.8
PR	83	31.9	58	22.6
SD	134	51.5	168	65.4
PD	34	13.1	19	7.4
Not evaluable	6	2.3	10	3.9
ORR	86	33.1	60	23.3
CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, ORR: Overall response rate				

4.7.2.2 OS

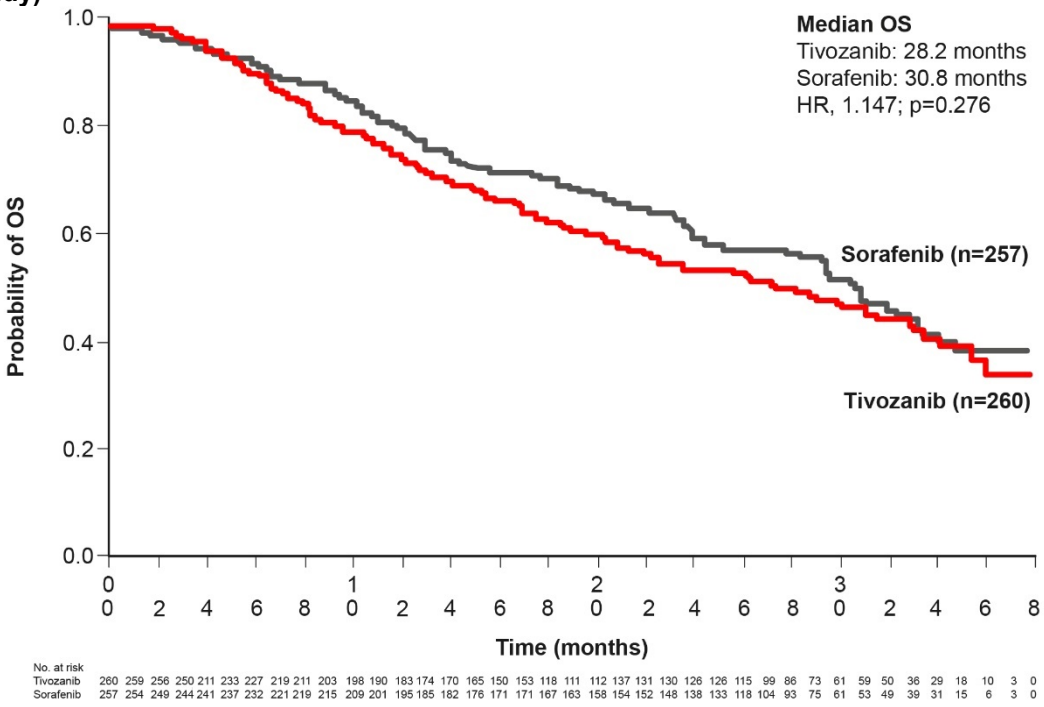
Median OS was not reached in the protocol-specified final OS analysis in the ITT population (data cut off August 27, 2012, 2 years after the last patient was enrolled). At this point there were 219 deaths (42%): 118 deaths in the tivozanib arm and 101 in the sorafenib arm. However, the final OS analysis presented in the published paper showed a trend toward longer survival with sorafenib (median OS, 29.3 versus 28.8 months; HR 1.245; 95% CI, 0.954 to 1.624), see Figure 6.

Figure 6: Kaplan-Meier plot of OS (ITT)[11]



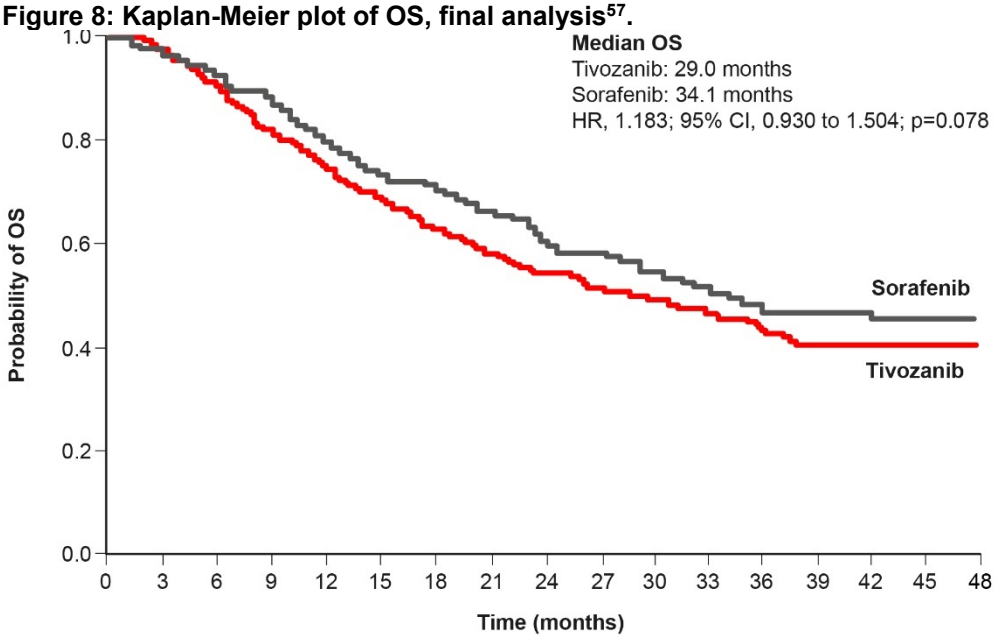
In the second CSR, data is presented from the 10 July 2013 data cut (TIVO-1 and the extension study) and is consistent with the data presented in the published paper (above). Median OS was 28.2 months for tivozanib and 30.8 months for sorafenib, HR1.147, p=0.276[19].

Figure 7: Kaplan-Meier plot of OS, analysis at 10 July 2013 data cut (TIVO-1 and the extension study)[19]



The final data cut (TIVO-1 and the extension study) presented at ASCO in 2015[57] also showed a trend towards longer survival with sorafenib. Median OS was 29.0 months for tivozanib and 34.1 months for sorafenib (HR 1.18, 95% CI, 0.930 to 1.504), see Figure 8. The extended OS in the sorafenib arm is due to a larger proportion of patients in the sorafenib arm receiving next-line targeted therapies which is consistent with other RCC studies that demonstrate that OS improves with additional lines of therapy.

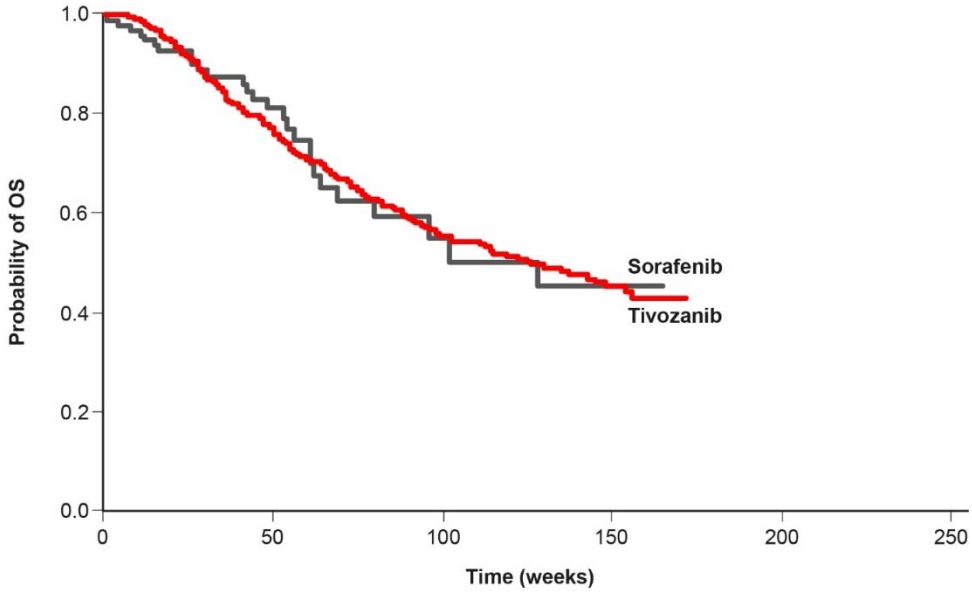
Figure 8: Kaplan-Meier plot of OS, final analysis[57].



As discussed in **Section 4.4.4.Statistical methodology for dealing with the effect of crossover** we carried out an analysis adjusted for crossover to account for the effect of planned one-way crossover from sorafenib to tivozanib.

Cox proportional regression using the IPCW-adjusted dataset revealed a HR for OS (sorafenib patients censored when crossing over to tivozanib) of 1.021; 95% CI 0.671 to 1.553; p=0.923), confirming that the discordant OS seen in the ITT analysis is a result of the one-way crossover.

Figure 9: Kaplan-Meier plot of OS, adjusted for crossover using IPCW methodolgy



4.7.2.3 HRQOL

HRQOL was maintained at a comparable level to baseline for both agents during the first 12 months of treatment, see Table 21.

Table 21: HRQOL assessments in the TIVO-1 study[11]

	FACT-G			FKSI-DRS			EQ-5D		
	Tivozanib (n=257)	Sorafenib (n=248)	p	Tivozanib (n=256)	Sorafenib (n=248)	p	Tivozanib (n=256)	Sorafenib (n=250)	p
Baseline									
Mean	77.01	77.27		29.16	29.35		0.73	0.73	
SD	14.98	15.94		4.77	5.10		0.25	0.26	
Change from baseline			0.805			0.965			0.391
LS mean change	-2.83	-3.10		-0.94	-0.93		-0.05	-0.06	
SE	1.04	1.02		0.33	0.34		0.02	0.02	
FACT-G: Functional Assessment of Cancer Therapy-General, FKSI-DRS: FACT Kidney Symptom Index–Disease-Related Symptoms ,EQ-5D: EuroQol-5D, SD: Standard deviation, LS: least squares, SE: Standard error									

HRQOL questionnaires were completed by >99% of patients at baseline, however, completion rates decreased over time and therefore data from the first 12 months (cycle 13) were considered. The least-square means for each treatment arm were estimated by using data from the first 12 months (cycle 13) of assessments by repeated-measures mixed-effects models controlling for treatment, assessment time, treatment-by-time interaction, baseline score, age, ECOG performance status, geographic region, number of metastatic sites, number of prior treatments, MSKCC prognostic factor status, time from diagnosis to study entry and any dose reduction during the study. Negative differences from baseline indicate worsened QOL or more symptoms.

Additional HRQOL assessments were evaluated using data from the TIVO-1 study[25].

[redacted]

4.8 Subgroup analysis

4.8.1 PFS

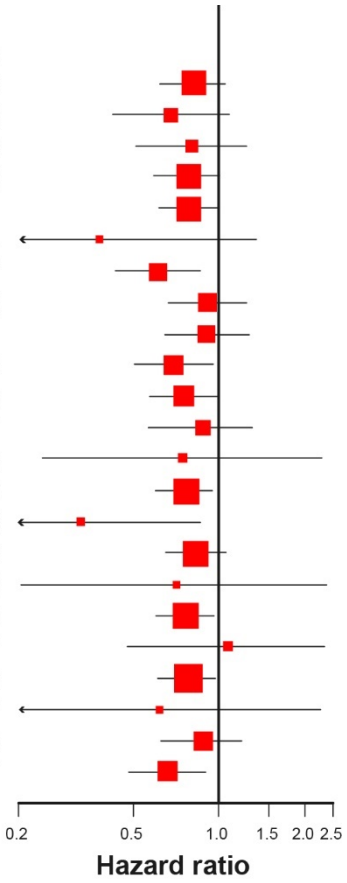
Pre-planned PFS subgroup analyses based on baseline characteristics demonstrated a consistent advantage with tivozanib, see Figure 10, with treatment effect preserved across all pre-specified subgroups.

The subgroup analyses presented in this section were pre-planned to determine whether baseline clinical characteristics or location (see Section 4.3.6.) had an impact on the efficacy of tivozanib.

In each subgroup, the p value from an unadjusted log-rank test was calculated, along with quartiles and 95% CIs of the survival distribution[59].

Figure 10: Forest plot subgroup HR (95% CI) for PFS[64]

Subgroup	Tivozanib Event/N	Sorafenib Event/N	HR
<65 years	119/195	131/193	0.818
≥65 years	34/65	37/64	0.686
Female	40/75	42/68	0.805
Male	113/185	126/189	0.782
White	146/249	161/249	0.791
Non-white	7/11	7/8	0.384
ECOG status 0	57/116	92/139	0.617
ECOG status 1	96/144	76/118	0.92
<1 year since diagnosis	71/109	71/105	0.911
≥1 year since diagnosis	73/137	84/137	0.698
No prior systemic therapy for met disease	104/181	118/181	0.756
1 prior systemic therapy for met disease	48/78	50/76	0.877
1 metastatic site	5/16	8/17	0.753
≥2 metastatic sites	148/244	160/240	0.772
North America/Western Europe	8/22	11/18	0.335
Central/Eastern Europe	140/229	149/228	0.836
Rest of World	5/9	8/11	0.706
SBP at Baseline ≤140	143/243	151/233	0.772
SBP at Baseline >140	10/17	17/24	1.067
DBP at Baseline ≤90	150/254	157/238	0.785
DBP at Baseline >90	3/6	11/19	0.627
MSKCC Intermediate	79/118	70/101	0.879
MSKCC Favourable	72/140	98/155	0.67



4.8.2 OS

OS in the TIVO-1 study is difficult to interpret due to the planned one-way crossover design, which resulted in an imbalance in the access to next-line targeted therapies. The imbalance varied considerably by geography and was most marked in Ukraine and Russia. Two analyses have been carried out to assess the impact of imbalance in access to next-line targeted therapies and are detailed below:

- Pre-specified analysis of OS by next-line therapy by region.
- Post-hoc analysis of OS by next-line therapy.

4.8.2.1 Pre-specified analysis of OS by next-line therapy by region

In the overall population patients randomised to sorafenib were more likely to receive next-line therapy on progression than patients randomised to tivozanib (65% versus 26%). Next-line therapy was targeted in almost two-thirds (63%) of patients in the sorafenib arm compared with only 13% in the tivozanib arm (see Table 16).

Pre-specified subgroups for OS included location. Regional differences in next-line therapy demonstrate that if next-line therapy is balanced, e.g. as in North America and Western Europe (UK, Italy and France) then the OS trend favours tivozanib. In the North America and Western Europe cohort, next-line treatment was more balanced in both arms compared with the overall population and the proportions of patients receiving next-line targeted therapy after discontinuation of study were closer in both arms (84.2% in sorafenib arm and 82.4% in the tivozanib arm)[12]. Median OS in North America and Western Europe (UK, Italy and France) was not reached in the tivozanib arm and was 29.5 months in the sorafenib arm, HR 0.497. These data suggest that, for the study as a whole, survival may have been improved in the sorafenib arm by the immediate availability of active second-line treatment (tivozanib in all countries) where, in many participating countries, there was no such immediate access to active second-line treatment for patients allocated first-line tivozanib.

Table 22: OS analysis of discontinued patients receiving second-line therapy[12]

	Discontinued patients on next-line therapy			**Median OS (months)**	
Region	**Tivozanib**	**Sorafenib**	**OS HR**	**Tivozanib**	**Sorafenib**
All (ITT) (n=517)	38.4%	75.7%	1.147 (p=ns)	28.2	30.8
NA & EU (n=186)	55.6%	79.5%	0.846 (p=ns)	32.9	29.5
NA & EU5 (n=40)	84.2%	82.4%	0.497 (p=ns)	NA	29.5
Russia & Ukraine (n=291)	28.4%	71.0%	1.383 (p=0.051)	26.3	32.0

ITT: Intention to treat; OS: Overall survival; HR: Hazard ratio; RCC: Renal cell carcinoma; EU: European Union
NA: North America; EU includes Bulgaria, Czech Republic, France, United Kingdom, Hungary, Italy, Poland, Romania
EU5 includes UK, Italy, and France

4.8.2.2 Post-hoc analysis of OS by next-line therapy

Given the results seen in North America and Western Europe, a post-hoc analysis was carried out to determine the impact of next-line therapy on OS[55].

Among patients who received any next-line treatment with any cancer treatment, or with VEGFR-TKI specifically, OS was improved in the sorafenib arm: 2 year survival 50% with tivozanib versus 64% with sorafenib for any cancer therapy and 55% versus 63% for next-line VEGFR-TKI therapy. This is not surprising given that almost all patients in the sorafenib

arm received tivozanib as next-line treatment (156/168, 93%) and only 10% of patients in the tivozanib arm (n=18) received next-line VEGFR-TKI therapy (see Table 23, Figure 11).

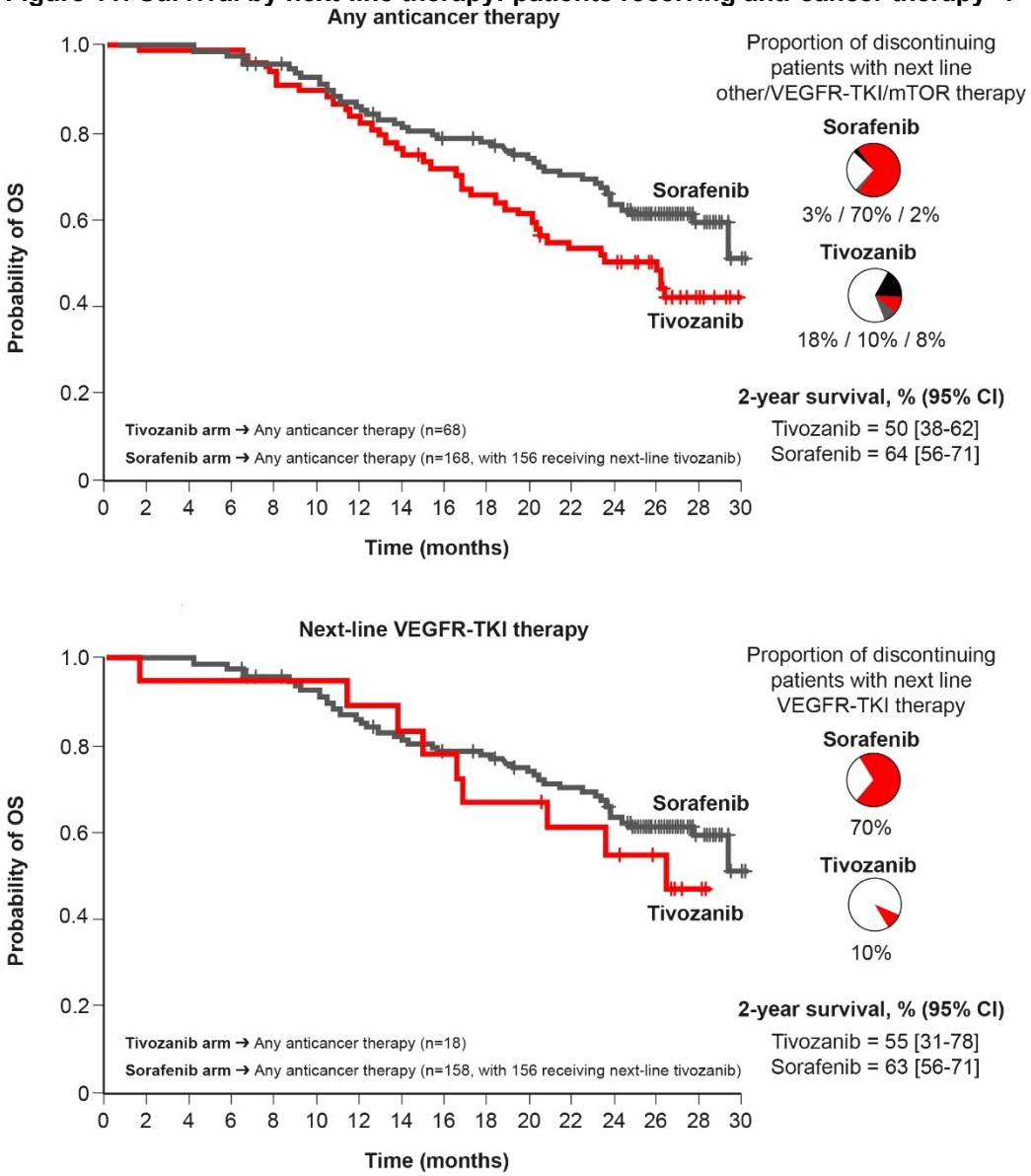
Among patients who remained on treatment or discontinued treatment without next-line therapy 2-year survival was similar: 56% versus 54% (see Table 23). In the subgroup of patients who discontinued treatment and did not receive next-line treatment median OS was similar at 12.9 months with tivozanib versus 12.3 months with sorafenib.

These data support the concept that any survival benefit seen among patients allocated sorafenib in this trial may have been, in part, due to the immediate availability of second-line treatment with tivozanib, whilst, for many patients allocated tivozanib, there was no access to immediate second-line treatment on progression.

Table 23: 2-year survival by next-line therapy[55]

	Tivozanib		Sorafenib	
	n	**2 year survival (%), 95% CI**	**n**	**2 year survival (%), 95% CI**
Any next-line anti-cancer therapy	68	50 (38-62)	168	64 (56-71)
Next-line VEGFR-TKI	18	55 (31-78)	158 (156 receiving tivozanib)	63 (56-71)
Still on study treatment or no next-line treatment	192	56 (48-63)	89	54 (43-65)
VEGFR-TKI: Vascular endothelial growth factor receptor-tyrosine kinase inhibitor				

Figure 11: Survival by next-line therapy: patients receiving anti-cancer therapy[55].



4.9 Meta-analysis

A meta-analysis was not carried out since there is inadequate data to do so.

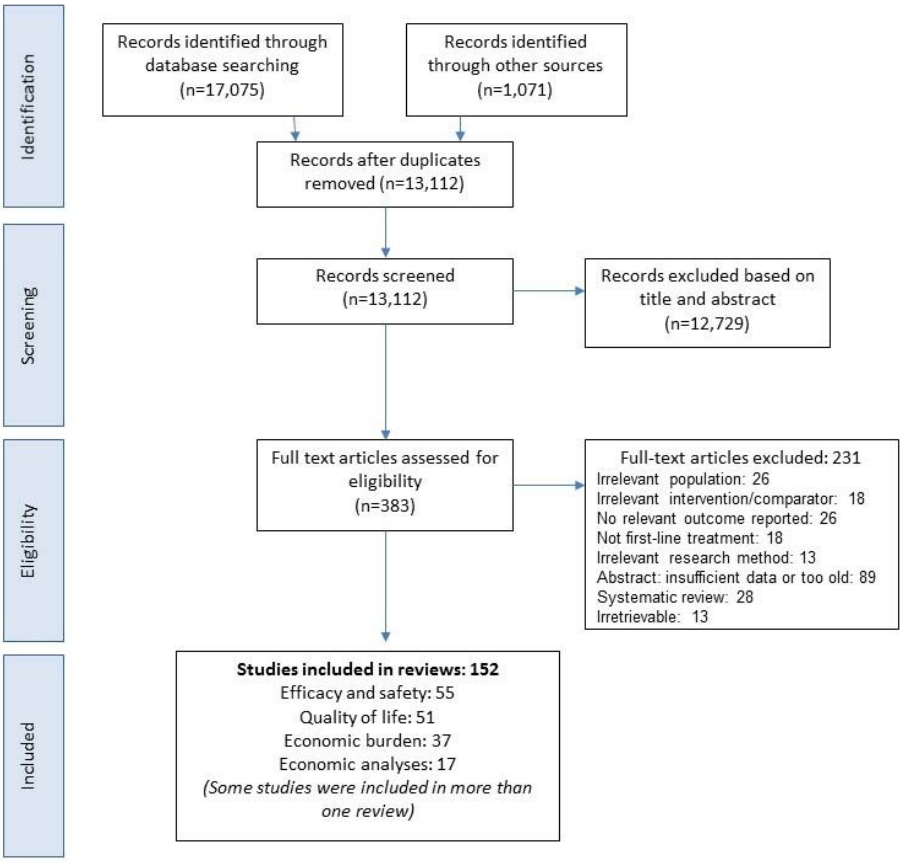
4.10 Indirect and mixed treatment comparisons

4.10.1 Search strategy

We conducted a systematic literature review for studies relevant to the clinical effectiveness of tivozanib and other targeted therapies or immunotherapy in patients with advanced/metastatic RCC as reported in Section 4.10.2 (Search strategy) and Appendix 2.

The inclusion and exclusion criteria used in the search strategy are listed in Table 10.

Figure 12: PRISMA diagram for MTC



4.10.2 Study selection

The systematic review identified 24 RCTs that reported monotherapy with one or more relevant interventions or comparators in patients with advanced and/or metastatic RCC. This included the TIVO-1 study of tivozanib versus sorafenib[11].

The scope[53] suggests that in treatment naïve patients tivozanib is compared with pazopanib, sunitinib and cytokines and that in previously treated disease tivozanib is compared with axitinib, nivolumab, everolimus, cabozantinib and best supportive care.

In this MTC we compare tivozanib with pazopanib, sunitinib and cytokines. Clinical rationale for excluding other comparators is provided in Section 3.7.

There are insufficient data for independent analysis of tivozanib in cytokine pre-treated patients and none in VEGF pre-treated patients, as this was a specific exclusion criterion for the pivotal TIVO-1 study. This means that the MTC cannot give reliable estimates and therefore we have not carried out a comparison in a pure pre-treated population. However, several studies considered a mixed population (treatment naïve and pre-treated) and wherever possible we have extracted efficacy data for the treatment naïve population.

Therefore, we have considered two populations – treatment naïve and mixed (some treatment naïve patients and some pre-treated patients).

The TIVO-1 study included patients who were either treatment naïve, or who had received only cytokines as prior systemic therapy[11]. Four other RCTs allowed participants to have received prior cytokines[17 65-67] and one study recruited participants who had only received prior cytokine therapy[68]. The remaining RCTs recruited patients who were systemic treatment naïve[16 18 69-77] or permitted prior use of chemotherapy or hormonal therapy[78 79]. It was possible to extract data for treatment naïve patients from the primary ADaM datasets for the TIVO-1 study[11] and from the published papers for Sternberg 2010[17] and SWITCH[66]. A subsequent publication of TARGET provided data on treatment naïve and pre-treated patients[80], although not for all outcomes of interest.

Two of the included studies were planned crossover studies (RECORD-3 and SWITCH)[66 76]. Data from these two studies[66 76] was not included in the network for OS since the studies pre-specified crossover to the alternative agent at progression. However, without OS data from SWITCH[66] there is no link between tivozanib and IFN. Therefore, we used OS data from TARGET[67] which compared sorafenib with placebo to enable links between tivozanib and IFN. Unfortunately, separate data is not available for OS in the treatment naïve population of TARGET and therefore we have used data from all patients (treatment naïve and pre-treated) in the treatment naïve network for OS. In TARGET, 18% of patients were treatment naïve (161/903) and PFS results were slightly improved with sorafenib in treatment naïve patients compared with the pre-treated population, although the confidence intervals overlapped. We recognise that this is a limitation of our work, however, have taken a pragmatic approach in order to include OS with IFN in the MTC.

We have included studies which compare agents outside the scope in order to make a connected network.

For the efficacy analyses, five networks were constructed leading to five different MTC. Not all the AEs were reported in every one of the selected studies; therefore, MTC for each AE is dependent on the availability of the data, which led to 20 different networks for AEs, with some AEs sharing the same network. Direct and indirect analyses were performed to investigate the comparative efficacy of tivozanib with the identified comparators for the cost effectiveness model.

Of the studies identified in our SLR the studies in bold in the table below are included in the MTC. It should be noted that not all studies are included in each MTC due to a lack of data.

Studies were excluded for the following reasons:

- Clark 2003[81] – this study reported the disease free survival (DFS) as the efficacy measure and median DFS was not reached. Neither OS nor PFS, as specified by the MTC protocol were reported.
- Dexeus 1989[82] – this study compared chemotherapy alone with chemotherapy and IFN, chemotherapy is not part of the network.
- Motzer. 2001[83] – this study is a pharmacological study investigating the pharmacodynamics and pharmacokinetics of the drugs under investigation; no efficacy measures (PFS and OS) were reported.
- Zhao 2013[84] – this study compared sorafenib and sunitinib as adjuvant treatment which is outside the scope. Furthermore, the study design was open label historically controlled comparative trial and only DFS was reported as an efficacy measure.
- Zhou 2016[85] – the full study results are yet to be published. In the published abstract, the HR for the median PFS was not reported and median OS had not been reached.

Given that we carried out a number of MTC, we have included the network diagrams for PFS and OS within the body of this submission and provided the others in Appendix 4.

Figure 13: Network for PFS in the naïve population with sunitinib as reference treatment in the network

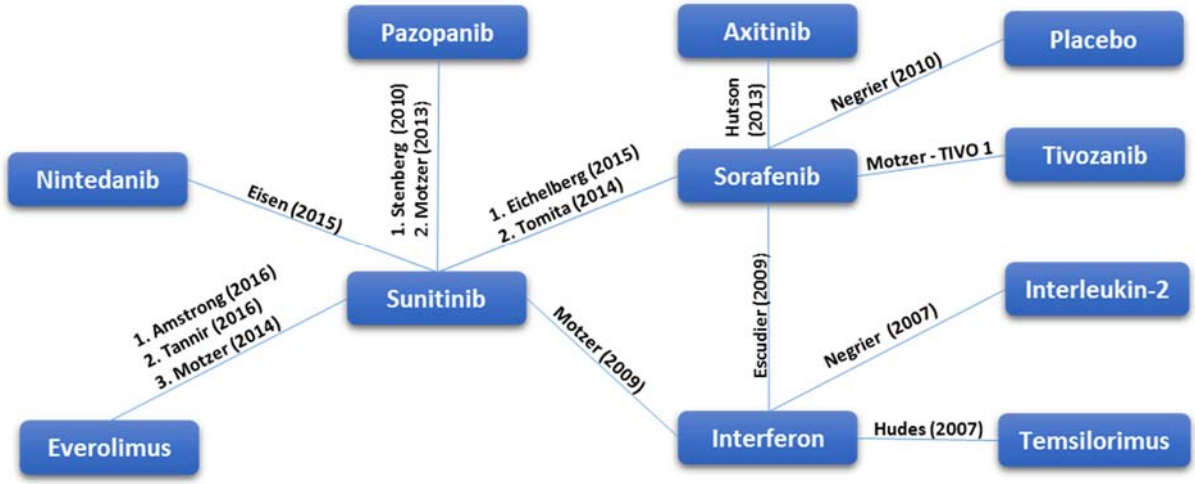


Figure 14: Network for PFS in the overall population with sunitinib as reference treatment in the network

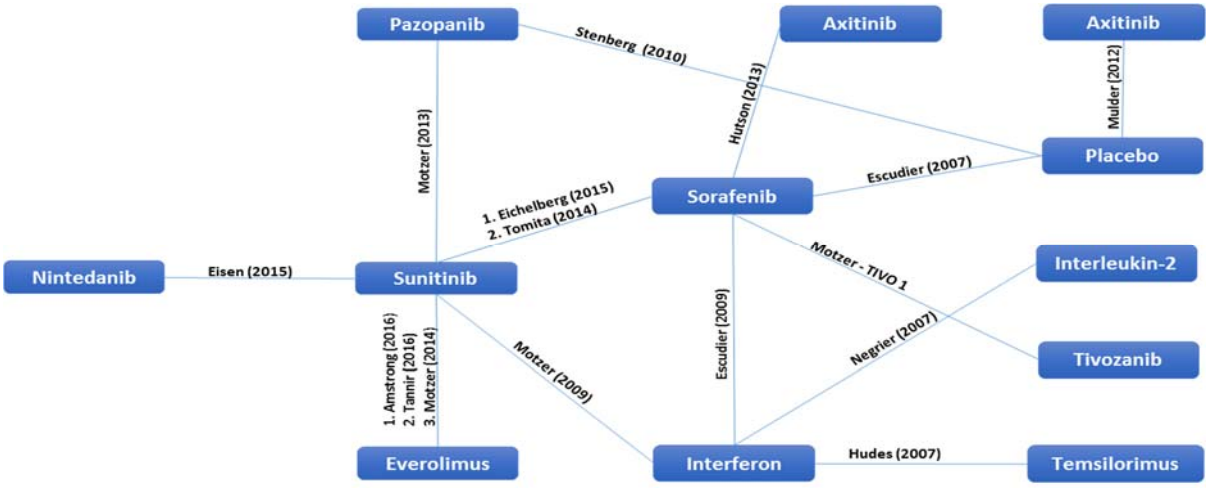


Figure 15: Network for OS in the naïve population with sunitinib as reference treatment in the network

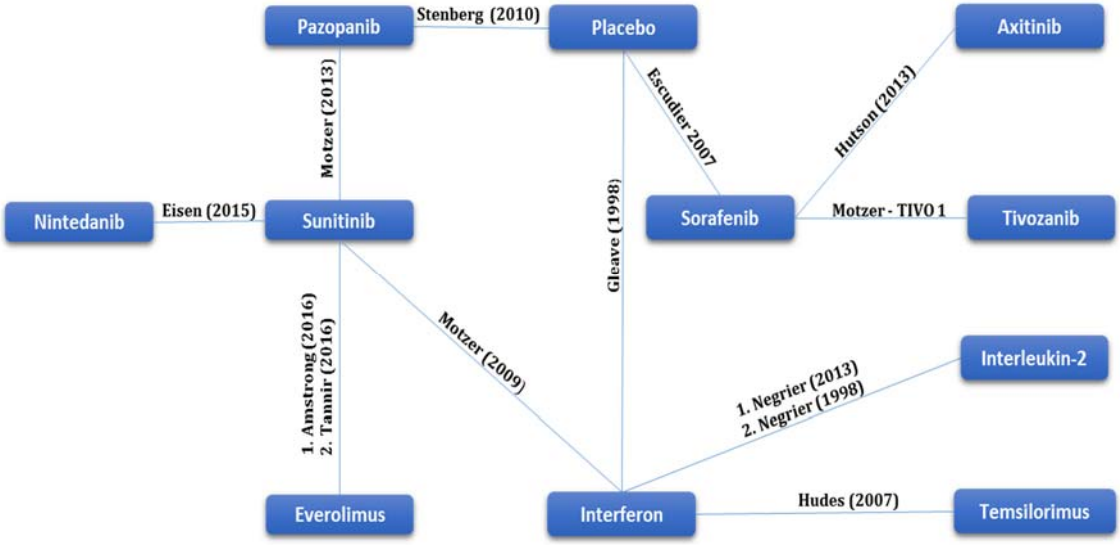


Figure 16: Network for OS in the overall population with sunitinib as reference treatment in the network

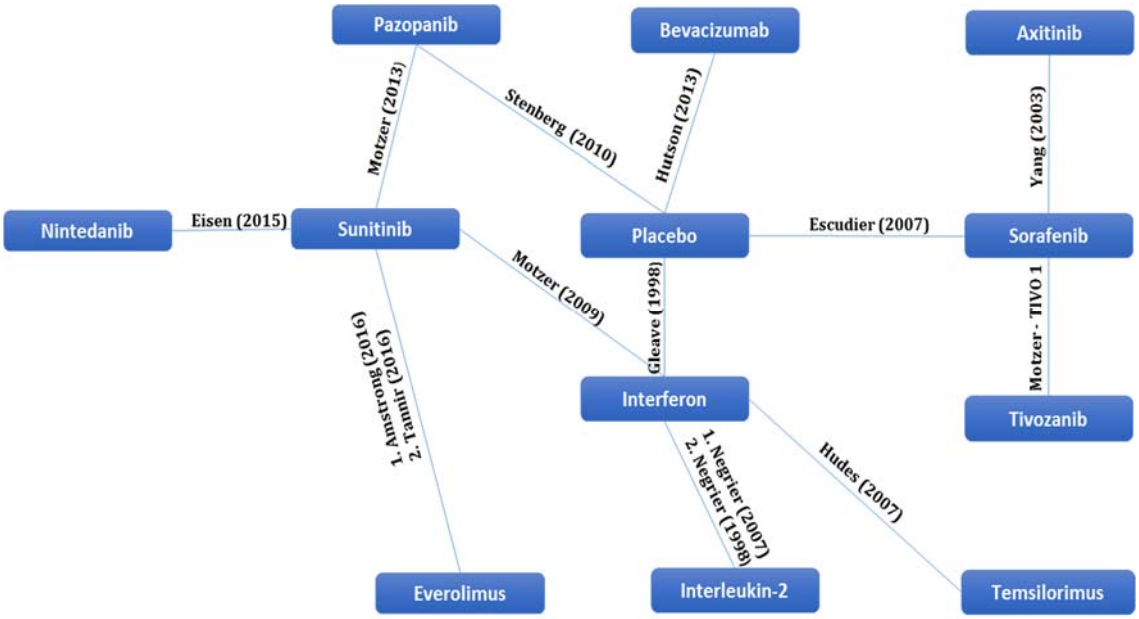


Table 24: Summary of the trials used to carry out the indirect treatment comparison

Trial number (acronym)	Tivozanib	Sorafenib	Pazopanib	Sunitinib	Nintedanib	Axitnib	Cediranib	Anlotinib	Bevacizumab	Placebo	Temsirlinus	Everolimus	IFN alpha 2a	IFN gamma-1b	Interleukin-2	Chemotherapy	IFN + chemotherapy	Treatment naïve subgroup	Primary study reference
Treatment naïve																			
ARCC											✓		✓						**Hudes et al. 2007[69]**
ASPEN				✓								✓							**Armstrong et al. 2016[70]**
COMPARZ		✓	✓																**Motzer et al. 2013[16]**
Cross-J-RCC		✓		✓															**Tomita et al. 2014[71]**
Eisen 2015				✓	✓														**Eisen et al. 2015[72]**
Escudier 2009		✓											✓						**Escudier et al. 2009[73]**
ESPN				✓								✓							**Tannir et al. 2016[74]**
Gleave 1998										✓				✓					**Gleave 1998[78]**
Hutson 2013		✓				✓													**Hutson et al. 2013[75]**
Motzer 2009				✓									✓						**Motzer et al. 2009[18]**
Negrier 1998													✓		✓				**Negrier et al. 1998[79]**
PERCY Quattro													✓	✓					**Negrier et al. 2007[77]**
RECORD-3				✓								✓							**Motzer et al. 2014[76]**
TARGET sub analysis Treatment naïve		✓								✓									**Negrier et al. 2010[80]**
Studies with a mixed population																			
Mulders 2012							✓			✓									**Mulders et al. 2012[65]**
Sternberg 2010			✓							✓								**Naïve subgroup**	**Sternberg et al. 2010[17]**
SWITCH		✓		✓														**Naïve subgroup**	**Eichelberg et al. 2015[66]**

Trial number (acronym)	Tivozanib	Sorafenib	Pazopanib	Sunitinib	Nintedanib	Axitnib	Cediranib	Anlotinib	Bevacizumab	Placebo	Temsirlinus	Everolimus	IFN alpha 2a	IFN gamma-1b	Interleukin-2	Chemotherapy	IFN + chemotherapy	Treatment naïve subgroup	Primary study reference
TARGET		✓								✓									**Escudier 2007[67]**
TIVO-1	✓	✓																**Naïve subgroup**	**Motzer et al. 2013[11]**
Studies with pre-treated patients only																			
Yang 2003									✓	✓									**Yang et al. 2003[68]**
Studies not included in the MTC																			
Clark 2003															✓				Clark et al. 2003[81]
Dexeus 1989																✓	✓		Dexeus et al. 1989[82]
Motzer 2001													✓		✓				Motzer et al. 2001[83]
Zhao 2013		✓		✓															Zhao et al. 2013[84]
Zhou 2016				✓				✓											Zhou et al. 2016[85]

4.10.3 Methods and outcomes of included studies

4.10.3.1 Outcomes

The outcomes included are those specified in the scope[53]: OS, PFS, response rates and AE. The scope also specified HRQOL, however there was insufficient data in the selected trials to consider HRQOL as an outcome.

The outcomes reported in the RCTs identified for the ITC are summarised below in Table 25, and reported in more detail in Appendix 4.

The TIVO-1 study reported OS, PFS, ORR, including CR and CR rates and number with stable disease and progressive disease, the number with grade 3 or worse AEs and withdrawals due to AEs.

Table 25: Outcomes reported and included from the relevant RCTs

Trial acronym	OS	PFS	ORR	CR	AEs
ARCC[69]	Yes	Yes	Yes		Yes
ASPEN[70]	Yes	Yes	Yes	Yes	Yes
COMPARZ[16]	Yes	Yes	Yes	Yes	Yes
Cross-J-RCC[71]		Yes	Yes		
Eisen 2015[72]	Yes	Yes	Yes	Yes	Yes
Escudier 2009[73]		Yes		Yes	
ESPN[74]	Yes	Yes	Yes		Yes
Gleave 1998[78]	Yes			Yes	Yes
Hutson 2013[75]	Yes[1]	Yes	Yes	Yes	
Motzer 2009[18]	Yes	Yes	Yes	Yes	
Mulders 2012[65]		Yes			Yes
Negrier 1998[79]	Yes		Yes	Yes	
PERCY Quattro[77]	Yes	Yes			Yes
RECORD-3[76]		Yes		Yes	
Sternberg 2010[17]	Yes	Yes	Yes	Yes	
SWITCH[66]		Yes	Yes	Yes	Yes
TARGET[67]	Yes	Yes		Yes	Yes
TIVO-1[11]	Yes	Yes	Yes	Yes	Yes
Yang 2003[68]		Yes	Yes	Yes	

1. OS data from a subsequent publication[86]
PFS: Progression free survival, ORR: Objective response rate, CR: Complete response , AE: Adverse effects

4.10.3.2 Study methodology

Details of the study methodology are shown in Table 26, with further details in Appendix 4.

Most of the studies were open label, including the TIVO-1 study, although many used an assessment board who were blinded to treatment arm to evaluate radiological data on disease progression. Four RCTs were double-blind[20 65 67 68], one was single-blind[78] and one was only available as an abstract that did not report details on blinding[71].

The majority of studies randomised patients to just one treatment, but two were planned crossover studies (RECORD-3 and SWITCH)[66 76]. Only data from the first, pre-crossover, arm has been reported here and used in the MTC for PFS, OR and selected AEs. The TIVO-1 study only allowed patients in the sorafenib arm to crossover to tivozanib after disease progression. This approach was also followed in three other RCTs, two of which allowed

patients receiving IFNα-2a to crossover to sorafenib therapy[18 73], one allowed crossover between IFNα and interleukin-2[79], and one had no planned crossover but allowed patients to switch to any active treatment after disease progression[70]. Of the remaining studies, one allowed patients to crossover from one active treatment to the other[74], two allowed patients in a placebo or observation group to crossover to active therapy on disease progression[65 67] and one allowed patients in the placebo arm to switch to pazopanib, and the pazopanib group to switch to other active treatment on disease progression[17]. Four studies did not permit crossover[69 72 75 77], however, in one of these studies, 11.8% of patients did crossover to an alternative treatment[77]. The remaining RCTs did not report details about crossover between treatment arms[16 70 71 78].

Table 26: Population and study methodology of relevant RCTs

Trial number (acronym)	Population	Intervention	Comparator	Study methodology	Primary study reference
ARCC	Stage IV/recurrent RCC, treatment naïve	IFN alpha 2a	Temsirolimus	Open label phase III RCT, assessors partly blinded	Hudes et al. 2007[69]
ASPEN	Non-clear cell metastatic RCC, treatment naïve	Sunitinib	Everolimus	Open label single phase II RCT	Armstrong et al. 2016[70]
COMPARZ	Clear cell metastatic RCC, treatment naïve	Pazopanib	Sunitinib	Open label phase III RCT, assessors partly blinded	Motzer et al. 2013[16]
Cross-J-RCC	Clear cell metastatic RCC, treatment naïve	Sunitinib	Sorafenib	RCT, abstract only	Tomita et al. 2014[71]
Eisen 2015	Clear cell unresectable/ metastatic RCC, treatment naïve	Nintedanib	Sunitinib	Open label phase II RCT	Eisen et al. 2015[72]
Escudier 2009	Clear cell stage III/IV RCC, treatment naïve	IFN alpha-2a	Sorafenib	Open label phase II RCT, crossover on progression	Escudier et al. 2009[73]
ESPN	Non-clear cell metastatic RCC, treatment naïve	Everolimus	Sunitinib	Open label phase II RCT	Tannir et al. 2016[74]
Gleave 1998	Metastatic RCC, treatment naïve	IFN gamma-1b	Placebo	Single blind RCT, assessors partly blinded	Gleave 1998[78]
Hutson 2013	Metastatic RCC, treatment naïve	Axitinib	Sorafenib	Open label phase III RCT	Hutson et al. 2013[75]
Motzer 2007	Clear cell metastatic RCC, treatment naïve	Sunitinib	IFN alpha	Open label phase III RCT, assessors partly blinded	Motzer et al. 2009[18]
Negrier 1998	Metastatic RCC, treatment naïve	Interleukin-2	IFN alpha-2a	Open label RCT, assessors partly blinded	Negrier et al. 1998[79]
PERCY Quattro	Metastatic RCC, treatment naïve	Interleukin-2	IFN alpha-2a	Open label RCT	Negrier et al. 2007[77]
RECORD-3	Metastatic RCC, treatment naïve	Everolimus	Sunitinib	Open label crossover RCT	Motzer et al. 2014[76]
Mulders 2012	Recurrent/ metastatic RCC, treatment naïve or prior cytokines	Cediranib	Placebo	Double blind phase II RCT	Mulders et al. 2012[65]
Sternberg 2010	Advanced/ metastatic RCC, treatment naïve or prior cytokine therapy	Pazopanib	Placebo	Double blind phase III RCT	Sternberg et al. 2010[17]

Trial number (acronym)	Population	Intervention	Comparator	Study methodology	Primary study reference
SWITCH	Advanced/ metastatic RCC, treatment naïve or prior cytokine therapy	Sorafenib	Sunitinib	Open label phase III crossover RCT	Eichelberg et al. 2015[66]
TARGET	Advanced RCC, subgroup with prior cytokines	Sorafenib	Placebo	Double blind phase III RCT	Escudier 2007[67]
TIVO-1	Clear cell recurrent/ metastatic RCC, treatment naïve or prior cytokines	Tivozanib	Sorafenib	Open label phase III RCT, assessors partly blinded	Motzer et al. 2013[11]
Yang 2003	Metastatic RCC, prior cytokines	Bevacizumab	Placebo	Double blind phase II RCT	Yang et al. 2003[68]

4.10.3.3 Baseline characteristics

Full details of the baseline characteristics are reported in Appendix 4.

The TIVO-1 study recruited patients with metastatic or recurrent disease[11]. Seven other RCTs included participants with a similar profile of advanced, recurrent or metastatic disease[16 17 65 66 69 72 73]. Ten of the studies only recruited patients with metastatic RCC[18 68 70 71 74-79]. One study only recruited patients with advanced disease[67].

All the studies that reported baseline gender recruited a majority of male participants. The proportion who were male ranged from 59% to 77%, with 72% of the TIVO-1 study participants being male[11]. An additional 11 RCTs had more than 70% male participants[16-18 65 67 68 70 75 77-79]. Four RCTs recruited between 60-69% male participants[69 72-74]. The remaining studies did not report the gender of participants.

The median age of participants at baseline was between 50-70 years. Participants in the TIVO-1 study had a median age between 50-60 years[11], as did participants in a further 12 RCTs[17 67-70 72 74 75 77-79 83]. Six RCTs included patients with a median age between 60 and 70 years at baseline[16 18 65 66 73 76] and the remaining studies did not report these baseline characteristics.

The TIVO-1 study was international, and more than 75% of participants were white Caucasian[11]. Seven other RCTs were international[16-18 67 69 75 76] more than 75% of participants were white in five other RCTs[17 65 70 72 74]. Seven RCTs recruited just from Europe

or North America [65 66 68 74 77-79] and one only recruited participants from Japan[71]. The geographical setting was not reported in the remaining studies.

The TIVO-1 study recruited patients with a clear cell component[11], as did nine other studies[16-18 67 68 71-73 75]. Seven RCTs either included patients with any histology, or did not report on the histology[65 66 69 76-79]. Only two studies restricted participants to those with non-clear cell RCC[70 74].

Patients in the TIVO-1 study had a good baseline performance status, with all having ECOG performance status 0 or 1, and 95% had favourable or intermediate MSKCC risk factors[11]. This pattern was seen in the majority of the other RCTs that reported this data. Fourteen RCTs included at least 90% of participants with ECOG status of 0-1 or Karnofsky performance status of 70 or higher[16-18 66-68 72-79]. Twelve RCTs included at least 75% of participants with favourable or intermediate MSKCC risk factors[16-18 65-67 70 72-76]. Only one RCT recruited participants with mainly poor performance[69]. The remaining studies did not report this data.

4.10.4 Risk of bias

The quality of the included RCTs was generally high, with the main limitation being that most were open-label and so did not try to conceal treatment allocation, or were only available as a conference abstract with few relevant details reported. Details of the quality assessment are reported below in Table 19.

One study was of poor quality, due to lack of information (Cross-J-RCC[71]) this study compared sunitinib with sorafenib and was carried out in 124 patients. The SWITCH study also compared sunitinib with sorafenib and was in a larger population (n=365). A sensitivity analysis was therefore carried out without Cross-J-RCC[71].

Table 27: Quality assessment results for parallel group RCTs

Trial acronym/reference	Randomisation appropriate	Treatment concealment adequate	Baseline comparability adequate	Researcher blinding adequate	Dropout imbalances	Outcome reporting selective	Intention to treat	Overall risk of bias
ARCC[69]	Unclear	Unclear	Yes	No	No	No	Yes	Moderate
ASPEN[70]	Yes	Yes	Yes	No	No	No	Yes	Low
COMPARZ[16]	Yes	Unclear	Yes	No	No	No	Yes	Low
Cross-J-RCC[71]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	High
Eisen 2015[72]	Yes	Yes	Yes	No	No	No	Yes	Low
Escudier 2009[73]	Yes	Unclear	Yes	No	No	No	Yes	Low
ESPN[74]	Yes	Unclear	Yes	Unclear	No	No	No	Moderate
Gleave 1998[78]	Yes	Unclear	Yes	Unclear	No	No	No	Moderate
Hutson 2013[75]	Yes	Yes	Yes	No	No	No	Yes	Low
Motzer 2009[18]	Yes	Yes	Yes	Yes	No	No	Yes	Low
Mulders 2012[65]	Yes	Yes	Yes	Yes	No	No	Yes	Low
Negrier 1998[79]	Yes	Yes	Yes	Yes	No	No	Yes	Low
PERCY Quattro[77]	Yes	Yes	Yes	No	No	No	Yes	Low
RECORD-3[76]	Yes	Unclear	Yes	No	No	No	Yes	Low
Sternberg 2010[17]	Yes	Unclear	Yes	Yes	No	No	Yes	Low
SWITCH[66]	Yes	Yes	Yes	No	No	No	Yes	Low
TARGET[67]	Yes	Unclear	Yes	Yes	No	No	Yes	Low
TIVO-1[11]	Yes	Yes	Yes	Yes	No	No	Yes	Low
Yang 2003[68]	Yes	Unclear	Yes	Yes	No	No	Yes	Low

4.10.5 Methods of analysis and presentation of results

4.10.5.1 Mixed treatment comparison methodology

MTC were conducted using a Bayesian framework, pooling both direct and indirect evidence from RCTs. The model was coded in WinBUGS software version1.4, January 2003. The Winbugs code for MTC was adapted from the code developed by the NICE Decision Support Unit (DSU)[87] and is shown in Appendix 4.

Time to event outcomes were analysed as HR, the ratio of hazard rates in two groups using the normal likelihood and the identity link. A HR of one suggests that there is no difference between tivozanib and a comparator arm, a HR greater than one indicates that the event is happening more frequently in the tivozanib arm compared with a comparator arm and a HR less than one indicates that the event is happening less frequently.

Binary outcomes were analysed as OR using the binomial likelihood and logit link. In cases where the models proved to be unstable due to zero cells, a continuity correction was applied as per the recommended methodology set out by NICE DSU (a fixed value of 0.5 is added to the numerator and 1 is added to the denominator)[87].

Each outcome measure was analysed using a fixed effects (FE) model. The choice of a FE model was based on low numbers of studies per treatment pair (not more than three studies identified per treatment pair). Anything less than four studies does not provide sufficient evidence to estimate tau (the between-study precision =1/between study variance). Each model was run with three chains and 50,000 burn-in iterations in order to limit the influence of the initial values on the simulated posterior distribution. A further 100,000 iterations were run and the sampled values were used to estimate posterior medians and 95% credible intervals (CrIs).

Convergence was assessed based on Brooks-Gelman-Rubin plot. The accuracy of the posterior estimates was determined by calculating the Monte Carlo error for each parameter (generally <5% of the sample standard deviation).

Model fit was assessed by comparing the overall residual deviance from each model with the total number of unconstrained data points (for a binomial likelihood each trial arm contributes one independent data point) to ensure these quantities were about equal[87].

Differences between treatments were considered statistically significant at the 0.05 level if the 95% CrIs around the OR or HR did not cross 1.

4.10.5.2 Efficacy results

The median HR for PFS and OS with 95% CI were those reported in the study publications. By assuming a symmetric CI around the logarithm of the median HR for PFS and OS, we back calculated the standard error (SE) from the CI. The criteria for inclusion in the MTC analysis for PFS was based on a definition of PFS, all the studies included in this analysis have a consistent definition of PFS.

In the treatment naïve population, of the 17 studies that qualified for inclusion, Gleave, 1998[78] and Negrier, 1998[79] did not report the median HR for PFS. Of the 15 studies that qualified for the MTC analysis for OS, three did not report the median HR for OS (Cross-J-RCC[71], Escudier, 2009[73], and the TARGET sub-analysis[80].

In the overall population, of the 19 studies selected for inclusion in the MTC for PFS, three did not report data for PFS (Gleave 1998[78], Negrier 1998[79] and Yang et al. 2003[68]). Of the 17 studies selected for inclusion in the MTC for OS, three did not include data for OS (Cross-J-RCC[71], Escudier 2009[73] and Mulders 2012[65]).

As discussed earlier we have provided results for the treatment naïve population and the overall mixed population. Full details of all inputs and results are shown in Appendix 4, the tables below show data for tivozanib versus sunitinib, pazopanib and IFN as per the scope.

For PFS in the treatment naïve population, the network includes 15 trials comparing 11 treatments (see Figure 13), in the overall population the network includes 16 studies and 12 treatments (see Figure 14).

Table 28: Pairwise estimates of treatment effects (HR) for PFS from MTC

	Median HR	95% CrI	
Treatment naïve population			
TIVO vs. SUN	1.051	0.761	1.452
TIVO vs. PAZ	0.995	0.702	1.410
TIVO vs. IFN	0.613	0.435	0.864
Overall (mixed) population			
TIVO vs. SUN	1.053	0.795	1.394
TIVO vs. PAZ	0.965	0.714	1.303
TIVO vs. IFN	0.620	0.456	0.843
TIVO: Tivozanib, SUN: Sunitinib; PAZ: Pazopanib, IFN: Interferon, HR: Hazard ratio			

For OS in the treatment naïve population, the network includes 13 studies comparing 11 treatments (see Figure 15), in the overall population the network includes 14 studies and 12 treatments (see Figure 16).

Table 29: Pairwise estimates of treatment effects (HR) for OS from MTC

	Median HR	95% CrI	
Treatment naïve population			
TIVO vs. SUN	0.92	0.55	1.56
TIVO vs. PAZ	0.98	0.59	1.64
TIVO vs. IFN	0.86	0.49	1.49
Overall (mixed) population			
TIVO vs. SUN	0.972	0.609	1.546
TIVO vs. PAZ	1.039	0.666	1.622
TIVO vs. IFN	0.882	0.523	1.491
TIVO: Tivozanib, SUN: Sunitinib; PAZ: Pazopanib, IFN: Interferon, HR: Hazard ratio			

OR was used for the CR analysis, OR greater than 1 suggests a favourable outcome for tivozanib and OR less than one indicates that tivozanib did less well than the comparators. For CR in the overall population, the network includes 15 trials comparing 11 treatments (network figure can be found in Appendix 4)

Table 30: Pairwise estimates of treatment effects (OR) for CR from MTC

	Median OR	95% CrI	
Overall (mixed) population			
TIVO vs. SUN	1.126	0.116	13.02
TIVO vs. PAZ	2.855	0.134	81.02
TIVO vs. IFN	3.253	0.277	46.09
TIVO: Tivozanib, SUN: Sunitinib; PAZ: Pazopanib, IFN: Interferon, HR: Hazard ratio			

4.10.5.3 Safety results

OR was used for the safety analysis.

The TIVO-1 trial was the only trial which compared tivozanib with a comparator (sorafenib) and sorafenib was the only drug connecting tivozanib to the rest of the network. Therefore, in order to carry out the MTC specific AE outcomes had to be reported in the TIVO-1 trial and also reported in at least one other trial including sorafenib as treatment arm.

AEs identified as being of particular interest based on clinical opinion (diarrhoea, nausea/vomiting, fatigue/asthenia, hypertension and HFS) and those with combined

incidence of grade 3 and 4 events ≥5% or with a combined incidence of all grades ≥20%, in any arm of any RCT of any comparator. This resulted with the list of specific AEs.

- Grade 1 and 2 AEs for naïve patients' population: Alopecia, Anaemia, Asthenia/fatigue, Diarrhoea, HFS, Hypertension, Mucositis/stomatitis, Nausea/vomiting.
- Grade 1 and 2 AEs for overall patients' population: Alopecia, Anaemia, Asthenia/fatigue, Diarrhoea, HFS, Hypertension, Mucositis/stomatitis, Nausea/vomiting, Thrombocytopenia.
- Grade 3 or higher for naïve patients' population: Anaemia, Asthenia/fatigue, Diarrhoea, HFS, Hypertension, Nausea/vomiting, Thrombocytopenia.
- Grade 3 or higher for overall patients' population: Anaemia, Asthenia/fatigue, Diarrhoea, HFS, Hypertension, Mucositis/stomatitis, Nausea/vomiting, Thrombocytopenia.

MTC was performed separately for each of the categories mentioned above. In terms of aggregate data, grade 1 and 2 AEs were only available in Armstrong (2016)[70]. Therefore, the number of patients experiencing grade 1 and 2 AEs was derived by subtracting the number of patients experiencing grade 3 and more AEs from the number of patients experiencing all grades AEs.

Given that AEs were not reported in all the selected studies, MTC for each AE was based on the availability of the data. We ended up with 20 different networks with some AEs sharing the same network.

Table 31 below shows the allocation of AEs across the networks.

Table 31: Allocation of AEs of interest across networks

	Naive		**Overall**	
Networks	**Grade 1 and 2**	**Grade 3+**	**Grade 1 and 2**	**Grade 3+**
1 (9 studies comparing 9 treatments)	Anaemia		Anaemia	
2 (12 studies comparing 10 treatments)	Asthenia/fatigue Diarrhoea Nausea/vomiting	Asthenia/fatigue		
3 (11 studies comparing 9 treatments)	HFS Hypertension	HFS	HFS	HFS
4 (6 studies comparing 6 treatments)	Alopecia		Alopecia	
5 (10 studies comparing 9 treatments)	Mucositis/stomatitis			
6 (13 studies comparing 11 treatments)			Asthenia/fatigue Diarrhoea	
7 (13 studies comparing 11 treatments)			Hypertension	
8 (13 studies comparing 11 treatments)			Nausea/vomiting	

9 (9 studies comparing 8 treatments)			Mucositis/stomatitis	
10 (7 studies comparing 7 treatments)			Thrombocytopenia	
11 (11 studies comparing 10 treatments)		Anaemia		
12 (14 studies comparing 11 treatments)		Diarrhoea Nausea/vomiting		
13 (7 studies comparing 9 treatments)		Neutropenia		
14 (11 studies comparing 10 treatments)		Thrombocytopenia		
15 (11 studies comparing 10 treatments)				Anaemia
16 (13 studies comparing 10 treatments)				Asthenia/fatigue
17 (15 studies comparing 12 treatments)				Diarrhoea Nausea/vomiting
18 (14 studies comparing 12 treatments)				Hypertension
19 (6 studies comparing 6 treatments)				Mucositis/stomatitis
20 (11 studies comparing 10 treatments)				Thrombocytopenia
HFS: Hand-foot syndrome				

Full details of all inputs and results are provided in an accompanying Excel spreadsheet ID591 company submission for tivozanib (NMA results for AEs)noACIC.xls

Table 32: Pairwise estimates of treatment effects (OR) for selected AE from MTC – naïve patients

AE	TIVO vs SUN		TIVO vs PAZ		TIVO vs IFN	
	Median	95%CrI	Median	95%CrI	Median	95%CrI
Grade 1 and 2						
Alopecia	0.614	[0.147;2.14]	0.325	[0.074;1.202]	0.865	[0.206;3.021]
Anaemia	2.328	[0.001;4147]	6.42	[0.003;1134]	3.212	[0.002;5742]
Asthenia/Fatigue	0.92	[0.473;1.793]	0.9104	[0.453;1.834]	1.09	[0.554;2.152]
Diarrhoea	0.708	[0.368;1.351]	0.558	[0.281;1.102]	4.595	[2.305;9.178]
HFS	0.221	[0.101;0.478]	0.455	[0.199;1.023]	2.79	[1.123;7.192]
Hypertension	2.356	[1.146;4.921]	1.847	[0.859;4.028]	1.456	[0.692;3.099]
Mucositis/Stomatitis	0.408	[0.149;1.123]	1.328	[0.47;3.763]	7.276	[2.488;21.56]
Nausea/Vomiting	0.521	[0.222;1.245]	0.4899	[0.204;1.203]	1.843	[0.779;4.427]
Grade 3 and over						
Anaemia	0.029	[0;43.36]	0.112	[0;158.5]	0.039	[0;59.04]
Asthenia/Fatigue	0.953	[0.245;4.014]	1.699	[0.417;7.42]	1	[0.255;4.252]
Diarrhoea	0.545	[0.097;3.144]	0.461	[0.078;2.779]	5.256	[0.78;39.25]
HFS	0.186	[0.033;0.835]	0.407	[0.069;1.935]	1.838	[0.278;11.39]
Hypertension	1.2	[0.474;3.109]	1.191	[0.447;3.255]	14.41	[3.875;63.36]
Nausea/Vomiting	0.559	[0.007;330.1]	0.694	[0.009;409.9]	2.535	[0.034;1479]
Neutropenia	//	//	0.068	[0;89.41]	//	//
Thrombocytopenia	0.237	[0.001;160.5]	1.653	[0.009;1134]	0.543	[0.003;375.9]
AE: Adverse events, TIVO: Tivozanib, SUN: Sunitinib; PAZ: Pazopanib, IFN: Interferon, HFS: Hand-foot syndrome						

Table 33: Pairwise estimates of treatment effects (OR) for selected AE from MTC – overall population

AE	TIVO vs SUN		TIVO vs PAZ		TIVO vs IFN	
	Median	95%CrI	Median	95%CrI	Median	95%CrI
Grade 1 and 2						
Alopecia	0.154	[0.558;1.758]	0.077	[0.296;0.996]	0.22	[0.797;2.53]
Anaemia	2.652	[0.4;25.43]	7.296	[1.121;68.92]	3.674	[0.537;35.63]
Asthenia/Fatigue	0.793	[0.464;1.356]	0.822	[0.474;1.43]	0.915	[0.523;1.599]
Diarrhoea	0.828	[0.476;1.432]	0.625	[0.353;1.105]	5.499	[3.014;10.08]
HFS	0.41	[0.203;0.839]	0.838	[0.399;1.79]	5.218	[2.244;12.91]
Hypertension	2.518	[1.3;4.984]	1.992	[0.999;4.058]	1.551	[0.772;3.164]
Mucositis/Stomatitis	0.553	[0.223;1.376]	1.798	[0.7;4.633]	9.83	[3.709;26.51]
Nausea/Vomiting	0.511	[0.256;1.038]	0.485	[0.24;0.997]	1.793	[0.876;3.709]
Thrombocytopenia	0.913	[0.028;34.77]	1.984	[0.06;75.98]	//	//
Grade 3 and over						
Anaemia	0.096	[0.002;1.451]	0.369	[0.009;5.028]	0.127	[0.003;2.043]
Asthenia/Fatigue	0.589	[0.234;1.484]	1.038	[0.397;2.697]	0.609	[0.238;1.554]
Diarrhoea	0.295	[0.067;1.205]	0.238	[0.053;1.002]	2.931	[0.549;16.81]
HFS	0.224	[0.056;0.86]	0.5	[0.117;2.045]	2.204	[0.442;12.02]
Hypertension	1.055	[0.452;2.477]	1.05	[0.428;2.579]	11.72	[3.582;44.92]
Mucositis/Stomatitis	0.016	[0;0.439]	0.049	[0;1.458]	//	//
Nausea/Vomiting	0.249	[0.03;1.996]	0.324	[0.039;2.602]	1.069	[0.128;8.813]
Thrombocytopenia	0.961	[0.012;566.6]	6.744	[0.081;4019]	9.623	[0.103;6079]

AE: Adverse events, TIVO: Tivozanib, SUN: Sunitinib; PAZ: Pazopanib, IFN: Interferon, HFS: Hand-foot syndrome

4.10.5.4 Sensitivity analyses

Based on the quality assessment of the studies selected for inclusion in the MTC, Cross-J-RCC[71] was categorised as having a high risk of bias. Sensitivity analysis was performed by running the MTC for PFS using naïve and overall population with Tomita 2014 excluded from the analysis. Although there is a slight improvement in favour of tivozanib compared to the comparators, there is not a significant change in the results.

Table 34: Sensitivity analysis: pairwise estimates of treatment effects (HR) for PFS from MTC excluding Cross-J-RCC

	Median HR	95% CrI	
Treatment naïve population			
TIVO vs. SUN	1.038	0.745	1.447
TIVO vs. PAZ	0.983	0.688	1.404
TIVO vs. IFN	0.607	0.428	0.861
Overall (mixed) population			
TIVO vs. SUN	1.033	0.774	1.379
TIVO vs. PAZ	0.949	0.698	1.290
TIVO vs. IFN	0.611	0.447	0.834
TIVO: Tivozanib, SUN: Sunitinib; PAZ: Pazopanib, IFN: Interferon, HR: Hazard ratio			

The posterior mean residual deviance (15.75) in this model was closed to the number of independent data points (15) which suggests a good model fit using the fixed effect model. However, Escudier 2009[73] contributes a value more than three times higher (3.61) than its expected contribution (1) to overall posterior deviance, which indicates that there is a disagreement between Escudier 2009 and the rest of the studies within the network.

A sensitivity analysis has been performed by rerunning the MTC for PFS in the naïve population with Escudier 2009 excluded from the analysis. There is a clear improvement in PFS for tivozanib compared to sunitinib and pazopanib.

Table 35: Sensitivity analysis: pairwise estimates of treatment effects (HR) for PFS from MTC excluding Escudier 2009

	Median HR	95% CrI	
Treatment naïve population			
TIVO vs. SUN	0.945	0.676	1.324
TIVO vs. PAZ	0.901	0.629	1.291
TIVO vs. IFN	0.756	0.580	0.986
Overall (mixed) population			
TIVO vs. SUN	0.948	0.708	1.271
TIVO vs. PAZ	0.882	0.647	1.202
TIVO vs. IFN	0.511	0.363	0.719
TIVO: Tivozanib, SUN: Sunitinib; PAZ: Pazopanib, IFN: Interferon, HR: Hazard ratio			

4.10.5.5 Interpretation

The MTC revealed that tivozanib has a comparable PFS to sunitinib and pazopanib, with a HR close to 1 in both the treatment naïve and mixed (treatment naïve and pre-treated populations). PFS with tivozanib is significantly longer with IFN (HR, 0.61).

Sensitivity analyses excluding a poor quality study (Cross-J-RCC[71]) and Escudier 2009[73] which contributes highly to overall posterior deviance, show an improvement with tivozanib, but this is not significant.

The MTC revealed that tivozanib has a comparable OS to sunitinib (HR, 0.92) and pazopanib (HR, 0.98). OS with tivozanib is longer than with IFN (HR, 0.86).

In terms of AE, tivozanib was less likely to result in AE, of all grades, than sunitinib and pazopanib, with the exception of hypertension and anaemia. Very small numbers of events for some AE, for example anaemia, make the results unreliable leading to high CrIs. Of the nine studies with reported AEs for anaemia, four studies including TIVO-1 were had <1% of patients with anaemia, resulting in a CrI of 0.002-5,742. HFS was significantly less likely with tivozanib compared to sunitinib and there was a clear trend towards reduced HFS with tivozanib versus pazopanib.

4.11 Non-randomised and non-controlled evidence

4.11.1 List of non-randomised and non-controlled evidence

Table 36 lists details of the non-randomised and non-controlled evidence. The discontinuation study (AV-951-07-201) has been published and the published paper[14] has been used to inform this section and Appendix 3, together with the CSR[58] where required.

Nosov DA., Esteves B, Lipatov ON et al. Antitumor activity and safety of tivozanib (AV-951) in a phase II randomized discontinuation trial in patients with renal cell carcinoma. J Clin Oncol 2012;30(14):1678-1685.

The biomarker study (AV-951-07-202) has not been published; however, data was presented at ESMO in 2014[54 88]. We have used this data, together with the CSR[15] to inform this section and Appendix 3. This study was not completed; the primary efficacy analyses of correlations between biomarkers in blood and archived tissue and PFS and objective response were never carried out.

Full methodological details are provided in Appendix 3, we provide the efficacy results below

Table 36: Non-randomised and non-controlled evidence

Study number (acronym)	Objective	Population	Intervention	Comparator	Primary study reference	Justification for inclusion
Discontinuation study Nosov, 2012 AV-951-07-201	To assess activity and safety of tivozanib in RCC	Adults with confirmed measurable recurrent or metastatic RCC or primary RCC not amenable to surgery	Tivozanib	Open label tivozanib for 16 weeks After 16 weeks patients were allocated to three arms on basis of tumour shrinkage/growth • Continue on tivozanib • Stop tivozanib • Randomised to placebo or tivozanib	Published paper [14]	Provides additional evidence for tivozanib in an open label setting and versus placebo
Biomarker study AV-951-10-202	To evaluate biomarkers and their correlation with clinical activity/treatment related toxicity in patients with RCC treated with tivozanib To estimate PFS at 6 months	Adults with unresectable locally recurrent or metastatic RCC who had undergone prior nephrectomy. Patients were treatment naïve, or had received no more than one prior systemic therapy excluding VEGF or mTOR targeted therapy	Tivozanib	None	CSR[15]	Provides additional evidence for tivozanib in an open label setting

4.11.2 Discontinuation study AV-951-07-201

4.11.2.1 Primary end-points

There were two efficacy primary end-points: ORR after 16 weeks of open label tivozanib and percentage of patients who remained progression free after 12 weeks.

The ORR after 16 weeks of open label tivozanib was 18% and all patients who responded experienced a PR, see Table 37. It should be noted that two-thirds of patients (66%) had stable disease.

Table 37: Best overall response in the phase II discontinuation study AV-951-07-201[14]

	Through 16 weeks	
	All patients (n=272)	
Response	No. of patients	%
Best overall response		
CR	0	0
PR	49	18
SD	180	66
PD	21	8
NE/ND/missing	22	8
ORR	49	18
95% CI, %	14 to 23	
CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, NE: Not evaluable, ND: Not determined, ORR: Overall response rate		

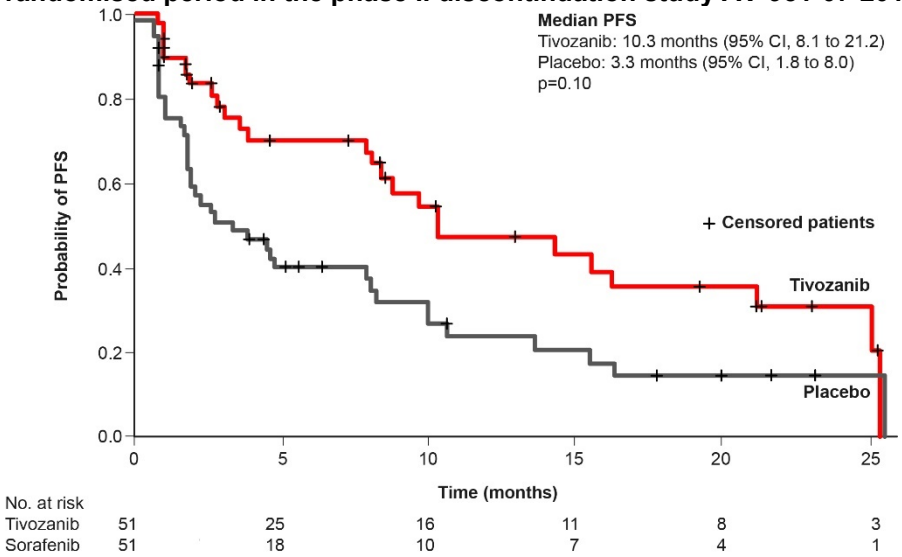
Of those patients randomised to treatment, the percentage of patients who remained progression free after 12 weeks was 49% (n=30) in the tivozanib arm versus 21% (n=12) in the placebo arm, p=0.001.

4.11.2.2 Secondary end-points

(a) PFS after treatment with tivozanib or placebo

Median PFS was significantly higher in patients randomised to tivozanib compared with those randomised to placebo: 10.3 months versus 3.3 months, p=0.01.

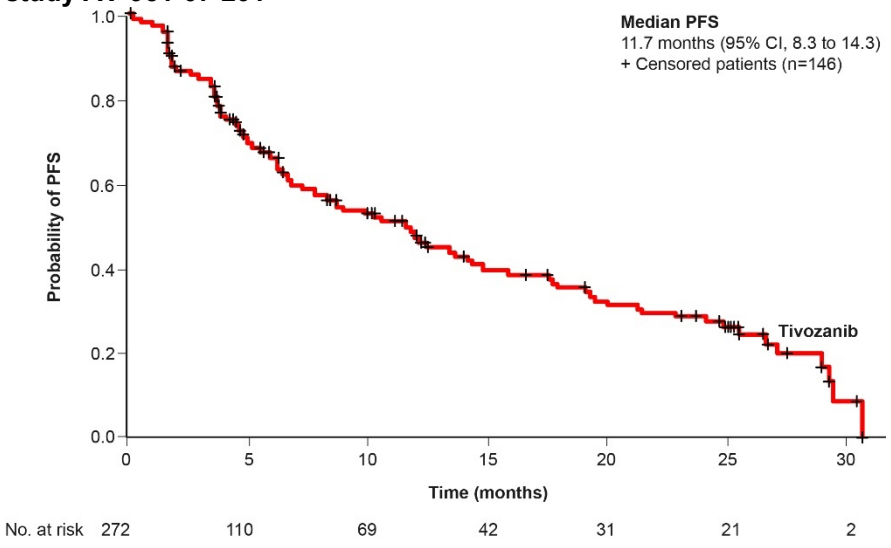
Figure 17: Kaplan-Meier plot of PFS after treatment with tivozanib or placebo in the 12-week randomised period in the phase II discontinuation study AV-951-07-201[14].



(b) Overall PFS in all treated patients

Median PFS in the whole population was 11.7 months, see Figure 18. Patients were censored at the time of random assignment to the placebo group.

Figure 18: Kaplan-Meier plot of PFS in all patients enrolled in the phase II discontinuation study AV-951-07-201[14]



4.11.2.3 Subgroups

Retrospective patient subgroups based on patient baseline characteristics revealed that patients with clear cell histology who had undergone nephrectomy demonstrated improved

outcomes compared with the overall population and patients with clear cell disease overall, see Table 38.

Table 38: Best overall response, duration of response and PFS throughout the phase II discontinuation study AV-951-07-201 according to baseline characteristics[14]

	All patients (n=272)		Clear cell RCC (n=226)		Clear-cell RCC and nephrectomy (n=176)	
Response	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**
Best overall response						
CR	1	<1	1	<1	1	1
PR	65	24	58	26	51	29
SD	164	60	134	59	103	59
PD	21	8	18	8	13	7
NE/ND/missing	21	8	15	7	8	5
ORR	66	24	50	26	52	30
95% CI, %	19 to 30		19 to 30		23 to 37	
PFS, months						
Median	11.7		12.5		14.8	
95% CI	8.3 to 14.3		9.0 to 17.7		10.3 to 19.2	
Duration of response, months						
Median	16.1		17.8		16.1	
95% CI	9.3 to 19.6		12.0 to 21.9		11.2 to 19.6	
CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, NE: Not evaluable, ND: Not determined, ORR: Overall response rate, PFS: Progression free survival						

4.11.3 Biomarker study AV-951-07-202

4.11.3.1 Primary end-point

The % of patients who remained progression free after 6 months in the ITT population was 61% overall (n=56).

4.11.3.2 Secondary end-points

(a) Objective response rate

A confirmed objective response was seen in 25% of patients (n=26) – two patients had a CR and 24 had a PR.

(b) Estimate of duration of PFS

The median KM estimate of PFS for ITT population was 25.0 weeks (9.7 months) with a 95% CI of 23.6 weeks – NE.

4.11.3.3 Subgroups

Patients with clear cell disease demonstrated improved outcomes compared to those with non clear cell disease, see Table 39.

Table 39: Best overall response and PFS throughout the phase II biomarker study AV-951-07-202 according to baseline characteristics[15]

	All patients (n=105)		Clear cell RCC (n=90)		Non clear cell (n=15)	
Response	**No. of patients**	**%**	**No. of patients**	**%**	**No. of patients**	**%**
Best overall response						
CR	2	1.9	1	1.1	1	6.7
PR	24	22.9	23	25.6	1	6.7
SD	52	49.5	42	46.7	10	66.7
PD	11	10.5	10	11.1	1	6.7
NE/ND/missing	7	6.7	6	6.7	1	6.7
ORR	26	24.8	24	26.7	2	13.3
95% CI, %	16.9 to 34.1		17.9 to 37		1.7 to 40.5	
Progression free at 6 months						
Median	56	60.9	49	62	7	53.8
95% CI	50.1 to 70.9		50.4 to 72.77		25.1 to 80.8	
CR: Complete response, PR: Partial response, SD: Stable disease, PD: Progressive disease, NE: Not evaluable, ND: Not determined, ORR: Overall response rate, PFS: Progression free survival						

Subgroup analyses did not reveal any notable differences in PFS at 6 months associated with sex, (60.0% for men and 63.6% for women), age (61.7% for patients under 65 years versus 59.4% for patients 65 years of age or older), prior therapies (56.3% in patients with prior therapies and 61.8% in those who had no prior therapies), metastatic sites/organ involvement (61.1% with metastatic sites/organ involvement = 1 and 60.8% with metastatic sites/organ involvement ≥ 2) or MSKCC status at baseline (66.7% for patients with a good prognosis and 57.7% for those with an intermediate prognosis).

4.12 Adverse reactions

Data from the June 1 2012 data cut of TIVO-1 is presented in the published paper[11]. Longer term follow-up data was presented at the ASCO annual meeting in 2015[57]. The final analysis presents data from the 20 January 2015 data cut[19].

4.12.1 Initial analysis

In the TIVO-1 study, patients had received tivozanib for 12 months and sorafenib for 9.5 months at the time of June 1 2012 data cut off. Almost all patients experienced at least one treatment emergent AE (91% in the tivozanib arm and 97% in the sorafenib arm). AE of grade 3 or above were reported by 338 patients overall (66%): 61% in the tivozanib arm and 70% in the sorafenib arm. AEs which were more common with tivozanib compared with sorafenib included hypertension and dysphonia (altered voice sounds), whereas AEs which were more common with sorafenib included HFS (palmar-plantar erythrodysesthesia syndrome) and diarrhoea[11].

Discontinuations due to AE were relatively low in both arms: 4% (n=10) versus 5% (n=14). However, significantly fewer patients had treatment interruptions and dose reductions due to AE in the tivozanib arm compared with the sorafenib arm[11]:

- Treatment interruptions: 19% (n=50) versus 36% (n=92), p<0.001
- Dose reductions: 14% (n=37) versus 43% (n=111), p<0.001

Dose reductions were most commonly due to HFS (2% versus 18%), diarrhoea (1% versus 5%) and hypertension (2% versus 4%). Skin toxicity with sorafenib and hypertension with tivozanib were managed according to specific guidelines.

The AE experienced in the TIVO-1 study are in the tables below.

Table 40: Common treatment-emergent AE (≥10% in either arm) in TIVO-1: all grades[11]

	All grades					
	Tivozanib (n=259)		Sorafenib (n=257)		RR	95% CI
Variable	**No.**	**%**	**No.**	**%**		
AE						
Hypertension	115	44	88	34	1.30	1.04-1.61
Diarrhoea	59	23	84	33	0.7	0.52-0.93
Dysphonia	55	21	12	5	4.55	2.50-8.29
Fatigue	50	19	41	16	1.21	0.83-1.76
Weight decreased	47	18	53	21	0.88	0.62-1.25
Asthenia	40	15	43	17	0.92	0.62-1.37
HFS	36	14	139	54	0.26	0.19-0.36
Back pain	35	14	21	8	1.65	0.99-2.76
Nausea	31	12	19	7	1.62	0.94-2.79
Stomatitis	29	11	23	9	1.25	0.74-2.10
Dyspnoea	29	11	22	9	1.31	0.77-2.21
Decreased appetite	27	10	24	9	1.12	0.66-1.88
Alopecia	6	2	55	21	0.11	0.05-0.25
Clinical chemistry						
Increased ALT	73	28	88	34	0.82	0.64-1.07
Increased AST	97	37	130	51	0.74	0.61-0.90
Increased amylase	104	40	135	53	0.76	0.63-0.92
Increased lipase	119	46	164	64	0.72	0.61-0.85
Hypophosphataemia	76	29	182	71	0.41	0.34-0.51
Proteinuria	186	72	187	73	0.99	0.89-1.10
Haematology						
Low haemoglobin	105	41	125	49	0.83	0.69-1.01
Neutropenia	28	11	27	11	1.03	0.62-1.70
Thrombocytopenia	47	18	31	12	1.50	0.99-2.29
AE: Adverse event, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HFS: Hand-foot syndrome						

Table 41: Common treatment-emergent AE (≥10% in either arm) in TIVO-1: grade 3[11]

	Grade 3					
	Tivozanib (n=259)		Sorafenib (n=257)		RR	95% CI
Variable	**No.**	**%**	**No.**	**%**		
AE						
Hypertension	66	25	45	18	1.46	1.04-2.04
Diarrhoea	6	2	17	7	0.35	0.14-0.87
Dysphonia	0		0	0.0		
Fatigue	14	5	9	4	1.54	0.68-3.5
Weight decreased	7	3	9	4	0.77	0.29-2.04
Asthenia	10	4	7	3	1.42	0.55-3.67
HFS	5	2	43	17	0.12	0.05-0.29
Back pain	8	3	5	2	1.59	0.53-4.79
Nausea	1	<1	1	<1	0.99	0.06-15.78
Stomatitis	1	<1	2	1	0.50	0.05-5.44
Dyspnoea	4	2	5	2	0.79	0.22-2.92
Decreased appetite	1	<1	2	1	0.50	0.05-5.44
Alopecia	0		0			
Clinical chemistry						
Increased ALT	2	1	7	3	0.28	0.06-1.35
Increased AST	5	2	8	3	0.62	0.21-1.87
Increased amylase	9	4	15	6	0.60	0.27-1.34
Increased lipase	23	9	52	20	0.44	0.28-0.69
Hypophosphataemia	11	4	67	26	0.16	0.09-0.30
Proteinuria	8	3	7	3	1.13	0.42-3.08
Haematology						
Low haemoglobin	5	2	7	3	0.71	0.23-2.20
Neutropenia	5	2	3	1	1.65	0.40-6.85
Thrombocytopenia	0		0			

AE: Adverse event, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HFS: Hand-foot syndrome

Table 42: Common treatment-emergent AE (≥10% in either arm) in TIVO-1: grade 4[11]

	Grade 4					
	Tivozanib (n=259)		**Sorafenib (n=257)**		**RR**	**95% CI**
Variable	No.	%	No.	%		
AE						
Hypertension	4	2	1	<1	3.97	0.45-35.27
Diarrhoea	0		0			
Dysphonia	0		0			
Fatigue	0		0			
Weight decreased	0		0			
Asthenia	1	<1	0			
HFS	0		0			
Back pain	0		0			
Nausea	0		0			
Stomatitis	0		0			
Dyspnoea	0		0			
Decreased appetite	0		0			
Alopecia	0		0			
Clinical chemistry						
Increased ALT	0		2	1		
Increased AST	0		2	1		
Increased amylase	3	1	2	1	1.49	0.25-8.83
Increased lipase	6	2	11	4	0.54	0.20-1.44
Hypophosphataemia	0		0			
Proteinuria	0		0			
Haematology						
Low haemoglobin	4	2	1	<1	3.97	0.45-35.27
Neutropenia	1	<1	2	1	0.50	0.005-5.44
Thrombocytopenia	1	<1	0			

AE: Adverse event, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, HFS: Hand-foot syndrome

4.12.1.1 Deaths

There were 13 deaths in the tivozanib arm and 12 in the sorafenib arm which were not due to disease progression[11]. In the tivozanib arm deaths were due to myocardial infarction (n=2), cardiac failure (n=2), hypertension (n=1), dyspnoea (n=1), cerebrovascular accident (n=1), aortic aneurysm rupture (n=1), arteriosclerosis of the coronary artery (n=1), cardiac arrest (n=1), apnoea (n=1), pulmonary embolism (n=1) and no reason specified (n=1). In the sorafenib arm deaths were due to cerebrovascular accident (n=3), cardiac failure (n=1), arteriosclerosis of the coronary artery (n=1), coronary artery insufficiency (n=1), hemorrhage (n=1), pleural effusion (n=1), jaundice (n=1), acute respiratory distress syndrome (n=1) and pulmonary embolism (n=1). One patient in the sorafenib arm had two AEs with an outcome of death within 30 days of last dose: pulmonary embolism and acute cardiac failure.

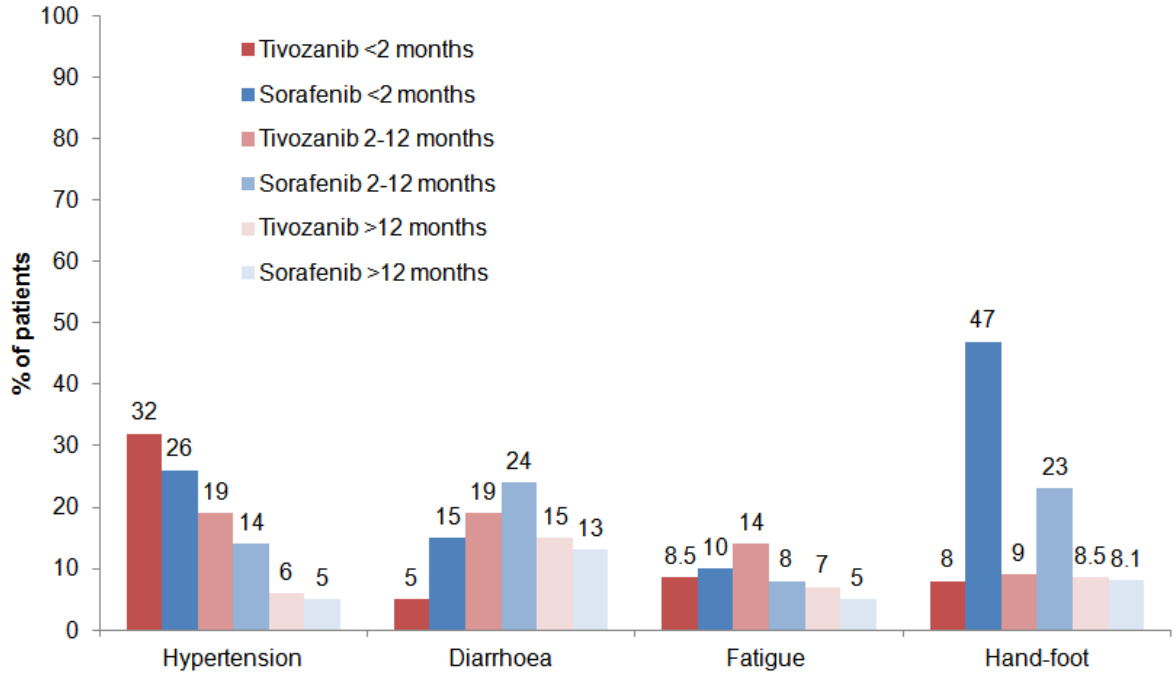
4.12.2 Long-term follow-up

Data from the October 2012 datacut revealed that most AE reduced over time, including AE of grade 3 or above[57]. Only diarrhoea and proteinuria occurred at a higher rate after >12 months of tivozanib treatment than during the first 2 months. The most common on-target AEs with tivozanib (hypertension and dysphonia) decreased over time. There were higher rates of the off-target AE HFS in the sorafenib arm than in the tivozanib arm in the first year of treatment; rates were similar after 1 year.

Table 43: Percentage of AE in first-line treatment patients over time (October 2012 datacut)[57]

	Tivozanib			Sorafenib		
	<2 months n=259	**2–12 months n=234**	**>12 months n=130**	**<2 months n=257**	**2–12 months n=226**	**>12 months n=99**
All grade AE						
Hypertension	32.0	18.8	6.2	25.7	13.7	5.1
Diarrhoea	5.4	18.8	14.6	15.2	23.9	13.1
Fatigue	8.5	14.1	6.9	9.7	8.4	5.1
HFS	7.7	9.4	8.5	47.1	23.0	8.1
Asthenia	6.9	9.8	5.4	8.2	9.7	3.0
Dysphonia	17.4	6.4	4.6	3.9	0.9	0
Decreased appetite	5.0	6.0	3.1	4.7	5.8	1.0
Dyspnoea	6.2	7.7	1.5	1.9	5.8	4.0
Peripheral oedema	1.5	1.7	2.3	0.8	3.5	0
Proteinuria	3.5	7.7	9.2	3.9	6.2	6.1
Grade 3 or 4 events						
Hypertension	20.5	7.7	3.1	13.6	4.9	4.0
Diarrhoea	0	2.1	1.5	0.8	5.8	3.0
Fatigue	1.2	3.8	1.5	1.9	2.2	0
HFS	0.4	1.7	0.8	14.0	5.3	1.0
Asthenia	2.3	1.7	0.8	1.9	0.9	0
Dysphonia	0	0	0	0	0	0
Decreased appetite	0	0.4	0	0	0.9	0
Dyspnoea	0	1.7	0.8	0	2.2	0
Peripheral oedema	0	0	0	0	0	0
Proteinuria	0.4	1.7	1.5	0.8	2.2	1.0
AE: Adverse event, HFS: Hand-foot syndrome						

Figure 19: Percentage of selected AE in first-line treatment patients over time (October 2012 datacut)[57]



4.12.3 Final analysis

The final safety analysis was published in the CSR[19] with a cut off date of 20 January 2015 and results were consistent with the data presented in the published paper (June 1 2012)[11].

Patients in the tivozanib group experienced fewer dose interruptions (n=69, 26.6%) versus sorafenib patients (n=179, 69.6%). Patients who received tivozanib had fewer dose reductions overall (n=41, 15.8%) versus sorafenib patients (n=113, 44%).

A similar number of patients experienced AEs in both arms (n=238, 91.9% with tivozanib versus n=249, 96.9% with sorafenib. However, fewer patients in the tivozanib group (n=166, 64.1%) had ≥Grade 3 AEs compared to the sorafenib group (n=181, 70.4%).

4.12.4 AE in the phase II studies

AE in the phase II studies are shown in Table 44.

Table 44: AE in the phase II studies[15 58]

AE, %	Discontinuation study AV-951-10-201		Biomarker study AV-951-10-202	
	n	%	n	%
At least one treatment-emergent AE	242	89.0	105	100.0
Most common treatment-emergent AE				
Hypertension	125	46.0	67	63.8
Fatigue	46	16.9	61	58.1
Diarrhoea	39	14.3	52	49.5
Nausea	12	4.4	52	49.5
Dysphonia	62	22.8	51	48.6
Decreased appetite	1	0.4	34	32.4
Asthenia	61	22.4	8	7.6
Dysponea	51	18.8	23	21.9
Grade 3 or above AE	135	49.6	78	74.3
Discontinuation due to AE	25	9.2	11	10.5
Dose reduction due to AE	22	8.0	11	10.5
Dose interruption due to AE	11	4.0	14	13.3
Deaths	15	5.5	2	1.2
AE: Adverse event				

There were 15 deaths in the discontinuation study (AV-951-10-201), none of the deaths was considered related to study drug by the investigators. Seven deaths were due to disease progression, the most frequently reported cause of death. Three deaths were due to CNS vascular events (two ischaemic strokes and one cardiovascular accident), three deaths were due to pulmonary events (pulmonary embolism, acute respiratory failure and pulmonary hemorrhage), and two deaths were due to cardiovascular events (hypotension and acute coronary syndrome).

There were two deaths in the biomarker study (AV-951-10-202), one cardiac arrest and one pneumonia, neither of which was related to tivozanib.

In the discontinuation study (AV-951-10-201), treatment emergent AE were grade 3 or higher in 49.6% of patients (n=135). The most common Grade 3/4 AEs were hypertension which occurred in 11.8% (n=32). asthenia in 8.5% (n=23), dysponea in 5.9% (n=16) and gamma-glutamyl transferase increased in 5.5% (n=15). Only one patient had grade 4 hypertension.

In the biomarker study (AV-951-10-202), treatment emergent AE were grade 3 or higher in 74.3% of patients (n=78), the most common grade 3 AE was hypertension which occurred in 49.5% (n=49) of patients, there were no grade 4 hypertension events.

In the discontinuation study (AV-951-10-201), AEs were responsible for discontinuation in 25 patients (9.2%), one was related to tivozanib (duodenal ulcer), two were probably related to tivozanib (hypertensive crisis and hypertension) and three were possibly related (groin pain, myocardial infarction and deep vein thrombosis. AEs were responsible for dose reduction in 22 patients (8%) and for dose interruption in 11 (4%). Hypertension was the most common cause of dose reduction (n=6, 27.2%) followed by diarrhoea (n=2, 9.1%).

In the biomarker study (AV-951-10-202), AEs were responsible for discontinuation in 11 patients (10.5%), eight of these events were serious and most occurred in the first two cycles of treatment. The events that led to study drug discontinuation for more than one patient were proteinuria and dysponea (each n=2). AEs were responsible for dose reduction in 11 patients (10.5%) and for dose interruption in 14 patients (13.3%). Fatigue was the most common cause of dose reduction (n=5, 45.4%) followed by dysponea (n=3, 27%).

Safety data were consistent with the known safety profile of tivozanib and did not suggest the emergence of any new safety signals for tivozanib.

4.12.5 Overview of the safety of the technology in relation to the decision problem

Most patients remain on the full dose of treatment with tivozanib throughout their treatment. In the TIVO-1 study, discontinuations due to AE were relatively low in both arms: 4% with tivozanib (n=10) versus 5% with (n=14) sorafenib. However, significantly fewer patients had treatment interruptions due to AE (19% versus 36%, $p<0.001$) and dose reductions due to AE (14% versus 43%, $p<0.001$) in the tivozanib arm compared with the sorafenib arm[11]: Dose reductions were most commonly due to HFS (2% versus 18%), diarrhoea (1% versus 5%) and hypertension (2% versus 4%). This pattern was continued throughout the study, in the final analysis, dose interruptions (26.6% versus 69.6%) and dose reductions (15.8% versus 44%) were lower with tivozanib than with sorafenib[19].

Discontinuations due to AE in the phase II studies were higher than those seen in the phase III study (9.2% in AV-951-10-201 and 10.5% in AV-951-10-202). Dose reductions and dose interruptions due to AE were lower than those seen in the phase III study; in AV-951-10-201

dose reductions in 8% of patients and dose interruptions in 4%, in AV-951-10-201 the figures were 10.5% and 13% respectively.

In both the phase III and phase II studies, hypertension was the most common AE with tivozanib (44% in the phase III study [TIVO-1], 46% in AV-951-10-201 and 64% in AV-951-10-202) and was controlled with medication in most patients. Grade 3 hypertension was reported by 25% of patients in TIVO-1 and grade 4 by 2%. It has been suggested that hypertension is a biomarker of efficacy for VEGFR-TKIs[23]. A retrospective analysis from TIVO-1 showed significantly longer PFS in patients with treatment-induced hypertension receiving tivozanib versus those with normal blood pressure (18.3 months versus 9.1 months for diastolic blood pressure and 16.7 months versus 9 months for systolic blood pressure)[56]. Retrospective analysis of data from four sunitinib studies (n=544) revealed similar results[23].

Table 45: Median PFS in patients with and without treatment induced hypertension in TIVO-1[56].

	Diastolic blood pressure		Systolic blood pressure	
	>90 mmHg	**≤90 mmHg**	**>140 mmHg**	**≤140 mmHg**
Patients (n)	101	158	115	144
Median PFS (months)	18.3	9.1	16.7	9.0
Hazard ratio (95% CI)	0.553 (0.39,0.78)		0.543 (0.39, 0.76)	
P value	0.001		0.001	

Diarrhoea was reported in 23% of tivozanib patients and dysphonia in 21% of tivozanib patients in TIVO-1; the majority of diarrhoea and dysphonia was mild to moderate, and there were no grade 4 events for either AE. The phase II studies did not reveal any additional safety signals and AE were comparable.

Long-term follow-up revealed that the risk of most AE reduced over time on treatment, including AE of grade 3 or above[57]. Only diarrhoea and proteinuria occurred at a higher rate after >12 months of tivozanib treatment than during the first 2 months.

4.13 Interpretation of clinical effectiveness and safety evidence

4.13.1 Clinical effectiveness

Tivozanib is an efficacious treatment for metastatic and recurrent RCC. The primary analysis of PFS data from TIVO-1 trial versus sorafenib revealed a benefit with tivozanib over sorafenib (11.9 months versus 9.1 months, HR 0.797; 95% CI, 0.639 to 0.993; p=0.042).

Baseline characteristics were well balanced between the two arms (Table 17), except for ECOG performance score; more patients had a favourable ECOG performance score of 0 in

the sorafenib arm compared with the tivozanib arm (54% versus 45%, Fisher's exact test p=0.035), this was most apparent in the Ukraine and Russia. A post-hoc analysis using Cox proportional hazards models adjusted for baseline demographics (age, sex, race, baseline ECOG score, number of metastatic sites/organs, MSKCC prognostic group, number of previous therapies, time since diagnosis) and geographical region (Russia/Ukraine versus all others) resulted in a highly significant difference in PFS (HR 0.725, 95% CI 0.58-0.91, p=0.006)[13].

Median PFS in patients receiving tivozanib during the discontinuation study (all periods, patients were censored at the time of random assignment to the placebo group) was 11.7 months[14] and median PFS in the biomarker study was 9.7 months[15].

Sorafenib is not specified as a comparator in the scope for this submission. Indirect comparisons with data from pivotal trials of other VEGFR-TKIs used as first-line treatment suggest that tivozanib may have a longer median PFS than pazopanib (8.4 months in COMPARZ versus sunitinib[16] and 9.2 months in the pivotal study versus placebo[17]) and sunitinib (9.5 months in COMPARZ[16] and 11 months in the pivotal trial versus IFN[18]). Indeed, tivozanib is the only VEGFR-TKI with superior efficacy to an active targeted therapy in first-line treatment. Comparing studies in this way is difficult, due to differences in baseline characteristics and subsequent treatment post-progression; therefore we carried out a MTC to compare tivozanib with IFN, pazopanib and sunitinib. The MTC revealed that tivozanib has a comparable PFS to sunitinib and pazopanib, with a HR close to 1 in both the treatment-naïve and mixed (treatment naïve and pre-treated) populations. PFS with tivozanib is significantly longer than with IFN with HR of 0.61.

OS was not significantly different between tivozanib and sorafenib (median OS, 28.8 months with tivozanib versus 29.3 months with sorafenib; HR 1.245; 95% CI, 0.954 to 1.624, p=ns) in the primary analysis of TIVO-1[11]. At the final 10 July 2013 data cut (TIVO-1 and the extension study) median OS was 28.2 months for tivozanib and 30.8 months for sorafenib, HR 1.147, p=ns[19]. OS was not reported in the phase II studies[14 15].

OS in the TIVO-1 study is difficult to interpret due to the planned one-way crossover design, which resulted in an imbalance in access to next-line targeted therapies. The authors of the TIVO-1 publication attributed the discordant OS seen in the TIVO-1 study to a crossover effect[11]. Indeed, analysis adjusted for crossover carried out for this submission confirms this hypothesis (HR of 1.021; 95% CI 0.671 to 1.553; p=0.923).

Pre-specified subgroups for OS included location. Regional differences in next-line therapy demonstrate that if next-line therapy is balanced, as seen in North America and Western Europe (UK, Italy and France) then the OS trend favours tivozanib[12]. Given the results seen in North America and Western Europe, a post-hoc analysis was carried out to determine the impact of next-line therapy on OS[55]. In those patients who remained on treatment or discontinued treatment without next-line therapy 2-year survival was similar: 56% with tivozanib versus 54% with sorafenib.

On indirect comparison, tivozanib has a median OS comparable to pazopanib (28.4 months in COMPARZ[16] and 22.9 months in the pivotal study versus placebo[20]) and sunitinib (29.3 months in COMPARZ[16] and 26.4 months in the pivotal trial versus IFN[18]). The MTC revealed that tivozanib has a comparable OS to sunitinib (HR, 0.92) and pazopanib (HR, 0.98) and that OS with tivozanib is longer than with IFN (HR, 0.86).

In conclusion, tivozanib is an efficacious treatment for metastatic and recurrent RCC with comparable PFS to pazopanib and sunitinib which are currently approved by NICE as first-line treatments for RCC. PFS with tivozanib is significantly improved over IFN, with a HR of 0.61. OS is comparable between tivozanib, sunitinib and pazopanib and shorter with IFN.

4.13.2 Safety

Low rates of treatment discontinuation due to AE were seen in the TIVO-1 study – 4% with tivozanib versus 5% with sorafenib[11]. Patients randomised to tivozanib experienced fewer dose reductions due to AE (19% versus 36%) and dose interruptions due to AE (14% versus 43%) than those on sorafenib.

Discontinuation rates due to AE were 9.2% in the discontinuation study[58] and 10.5% in the biomarker study[15]. Rates of dose reduction and dose interruption were 8% and 4% in the discontinuation study and 10.5% and 13.3% in the biomarker study.

The discontinuation rate with tivozanib compares favourably with that for pazopanib (24% in COMPARZ versus sunitinib[16] and 14% in the pivotal study versus placebo[17]) and sunitinib (20% in COMPARZ[16] and 19% in the pivotal trial versus IFN[18]). Dose reductions and interruptions were more common with pazopanib and sunitinib than with tivozanib, in the COMPARZ study dose reductions were 44% with pazopanib and 51% with sunitinib; dose interruptions were 44% and 49% respectively[16]. These data suggest that, by indirect comparison, tivozanib is more acceptable to patients than either sunitinib or pazopanib.

Real world evidence from a retrospective medical record review of patients receiving sunitinib for first-line treatment of RCC across Europe (41% of patients from the UK) revealed that patients with reduced dose intensity (<70%) or treatment discontinuation had significantly reduced survival times illustrating the importance of maintaining patients on the full dose[21].

In both the pivotal phase III and the phase II studies, hypertension was the most common AE with tivozanib (44% in the phase III study [TIVO-1], 46% in the discontinuation study [AV-951-10-201] and 64% in the biomarker study [AV-951-10-202]). In TIVO-1, hypertension was controlled with medication in most patients, only 2% of patients required dose reduction and <1% required dose interruption due to hypertension[11]. Data indicate that the development of hypertension with VEGF-targeted therapy is associated with improved efficacy and suggest an on-target effect[23 24].

Diarrhoea was reported in 23% of tivozanib patients and dysphonia in 21% of tivozanib patients in TIVO-1; the majority of diarrhoea and dysphonia was mild to moderate, and there were no grade 4 events for either AE. Long-term follow-up revealed that most AE reduced over time, including AE of grade 3 or above[57].The phase II studies did not reveal any additional safety signals and AE were comparable to those in TIVO-1.

The more favorable side-effect burden with tivozanib in TIVO-1 resulted [redacted][25].

Patients receiving targeted therapy for the first-line treatment of RCC perceive fatigue/tiredness, diarrhoea and HFS as the most troublesome AE[22]. In TIVO-1 rates of fatigue were 19% with tivozanib versus 16% with sorafenib, rates of diarrhoea were 23% versus 33% and rates of HFS were 14% versus 54%. Most fatigue, diarrhoea and HFS with tivozanib was mild to moderate, in contrast 17% of sorafenib patients had HFS of grade 3 or above[11]. Rates of fatigue, diarrhoea and HFS with pazopanib and sunitinib in the COMPARZ study[16] were considerably higher – fatigue 55% with pazopanib versus 63% with sunitinib, diarrhoea 63% versus 57% and HFS 29% versus 50%. Diarrhoea, fatigue and HFS were severe (grade 3 or above) in 9%, 10% and 6% of pazopanib patients and 8%, 17%, 11% of sunitinib patients, respectively.

As discussed in the efficacy section above, it is difficult to compare data across studies in this way due to differences in patients' baseline characteristics, therefore results for pazopanib and sunitinib from the MTC are presented. The MTC revealed that tivozanib was less likely to result in AE, of all grades, than sunitinib and pazopanib, with the exception of

hypertension. Table 46 shows fatigue/tiredness, diarrhoea and HFS with tivozanib versus sunitinib, pazopanib and IFN as estimated in the MTC. HFS was significantly less likely with tivozanib compared to sunitinib, with a clear trend towards benefit with tivozanib over pazopanib.

Table 46: Pairwise estimates of treatment effects (OR) for the AE which patients find most troublesome from MTC – naïve patients

AE	TIVO vs SUN		TIVO vs PAZ		TIVO vs IFN	
	Median	95%CrI	Median	95%CrI	Median	95%CrI
Grade 1 and 2						
Asthenia/Fatigue	0.92	[0.473;1.793]	0.9104	[0.453;1.834]	1.09	[0.554;2.152]
Diarrhoea	0.708	[0.368;1.351]	0.558	[0.281;1.102]	4.595	[2.305;9.178]
HFS	0.221	[0.101;0.478]	0.455	[0.199;1.023]	2.79	[1.123;7.192]
Grade 3 and over						
Asthenia/Fatigue	0.953	[0.245;4.014]	1.699	[0.417;7.42]	1	[0.255;4.252]
Diarrhoea	0.545	[0.097;3.144]	0.461	[0.078;2.779]	5.256	[0.78;39.25]
HFS	0.186	[0.033;0.835]	0.407	[0.069;1.935]	1.838	[0.278;11.39]
TIVO: Tivozanib, SUN: Sunitinib; PAZ: Pazopanib, IFN: Interferon, HFS: Hand-foot syndrome						

In conclusion, tivozanib is well tolerated with lower rates of the AE which RCC patients find troublesome (fatigue/tiredness, diarrhoea and HFS) than other VEGFR-TKIs, which has a positive impact on the physical well being element of HRQOL. There are no AE specific to tivozanib which are not observed with the other VEGFR-TKIs, or which are sufficiently more common and likely to result in a negative impact on HRQOL. This tolerability profile is reflected by the fact that tivozanib has lower rates of discontinuations, dose reductions and dose interruptions than other VEGFR-TKIs, which should enable patients to remain on treatment for the duration of its clinical benefit.

4.13.3 Strengths and limitations of the clinical evidence base

TIVO-1 was a well conducted study; there was a low risk of bias and quality assessment results (see Section 4.6) were good. The only concern was the imbalance in ECOG at baseline; post-hoc analyses using Cox proportional hazards models have been carried out to determine the impact of differences in baseline characteristics on PFS.

In the TIVO-1 study, the primary end-point was PFS, which is accepted as a valid measure of clinical benefit and was the primary end-point in the registration trials for both pazopanib[17] and sunitinib [18]. PFS has the advantage that the treatment effect is not affected by subsequent therapy; however, potential bias can be introduced if PFS is assessed by the investigator, particularly, as here, in an open-label trial. In the TIVO-1 study, tumour

assessments were made at baseline and every 8 weeks until progression, all imaging scans were evaluated by an independent radiology review board, blinded to study treatment for the primary end-point. Patients with investigator-assessed radiological evidence of PD had confirmation by blinded independent review within 48 hours. The primary PFS analysis revealed a benefit with tivozanib over sorafenib (11.9 months versus 9.1 months, HR 0.797; 95% CI, 0.639 to 0.993; p=0.042). As discussed earlier, more patients had a favourable ECOG performance score of 0 in the sorafenib arm compared with the tivozanib arm, this difference was most marked in the Ukraine and Russia. In order to adjust for differences in baseline characteristics and geographic region, a post-hoc analysis was carried out which resulted in a highly significant difference in PFS (HR 0.725, 95% CI 0.58-0.91, p=0.006)[13].

OS in TIVO-1 was complicated by planned one-way crossover in the control (sorafenib) arm on progression. As a result, overall, almost two-thirds (63%) of patients in the sorafenib arm versus only 13% in the tivozanib arm received a next-line targeted therapy, with considerable regional variation. The authors of the TIVO-1 publication attributed the discordant OS seen in the TIVO-1 study to a crossover effect[11]. Indeed, analysis adjusted for crossover carried out for this submission revealed a HR of 1.021; 95% CI 0.671 to 1.553; p=0.923, confirming the authors' hypothesis.

Imbalance in access to next-line targeted therapy varied considerably by geography and was most marked in Russia and the Ukraine. A pre-specified analysis of OS by next-line therapy by region revealed that if use of next-line therapy is balanced, for example as seen in North America and Western Europe then the OS trend favours tivozanib (HR 0.846 for North America and European Union and 0.497 for North America and UK, Italy, and France)[12].

Tumour shrinkage is measured by ORR; ORR was significantly higher with tivozanib compared with sorafenib: 33.1% versus 23.3%, p=0.014. ORR in the discontinuation study was 18%[14] and 25% in the biomarker study[15].

HRQOL was measured using a number of different scales; EQ-5D which is a standardised measure of health outcome, FACT-G which assesses the impact of cancer therapy on function and FKSI-DRS which measures symptoms related to kidney disease. Tivozanib and sorafenib maintained HRQOL at a comparable level to baseline for all three scales during the first 12 months of treatment. However, the lower side-effect burden with tivozanib in TIVO-1 resulted in a [redacted][25].

Discussion of the clinical relevance of the AE profile with tivozanib is discussed in Section 4.13.2. Overall, tivozanib had lower rates of discontinuations, dose reductions and dose

interruptions than other VEGFR-TKIs, which has clear implications for durability of treatment and, in all likelihood, efficacy. Tivozanib is well tolerated with lower rates of the AE which RCC patients find troublesome (fatigue/tiredness, diarrhoea and HFS) than other VEGFR-TKIs. Very few patients receiving tivozanib had fatigue/tiredness, diarrhoea and HFS which was grade 3 and above, most patients experienced mild to moderate symptoms which reduced over time.

The evidence-base for tivozanib is limited by a lack of direct head-to-head evidence versus the comparators in the scope. TIVO-1, the pivotal trial for tivozanib[11], is versus sorafenib which was for many countries, an acceptable standard of care when the study was initiated (first patient was dosed in 2010). However, sorafenib is not approved by NICE[26], therefore evidence for tivozanib versus sunitinib, pazopanib and cytokines in treatment naïve patents was provided via an MTC.

In TIVO-1 around 30% of patients had received one prior treatment (not VEGFR-TKI or mTOR inhibitor), therefore the patient population was mixed. The number of prior treatments for metastatic RCC was a pre-specified subgroup in the analysis (0 or 1). The HR for PFS of 0.756 in the treatment naïve population is comparable to the primary analysis of PFS in the overall population (HR 0.797; 95% CI, 0.639 to 0.993). We used data from trials in treatment naïve patients plus subgroup data reported for treatment naïve patient in trials of mixed population to inform the MTC in treatment naïve patients.

Tivozanib will be licensed to treat patients who have failed prior cytokine therapy[12]. There are insufficient data for independent analysis of tivozanib in cytokine pre-treated patients and the MTC does not give reliable estimates, therefore tivozanib has not been compared with other treatments in a pure cytokine-pretreated population. We have used data from all relevant studies identified to inform a MTC in the mixed population (treatment naïve and pre-treated). However, we believe that tivozanib would not be used in this population (see Section 3.7), since almost all patients receiving first-line treatment now receive one of the NICE-approved VEGFR-TKIs, pazopanib or sunitinib. Treatment of patients previously treated with VEGFR pathway inhibitors is outside the product licence for tivozanib, therefore everolimus and cabozantinib are not relevant comparators.

The quality of the MTC is good, sensitivity analyses carried out to exclude a poor quality study with a high risk of bias and a study contributing more than twice the expected figure to the overall posterior deviance result in an improvement for tivozanib over the comparators, but the differences are not significant. MTC have been carried out in the treatment naïve and

mixed (pre-treated and treatment naïve populations), the results do not differ significantly between the two populations. Lack of data meant that in order to include IFN in the network for treatment naïve patients we had to use data from the overall study population (treatment naïve and pre-treated patients) in TARGET[67] which compared sorafenib with placebo to enable a link between tivozanib and IFN (see Figures 15 and 16, page 81 and page 82). We recognise that this is a limitation of our work, however, and have taken a pragmatic approach in order to include OS with IFN in the MTC.

We believe that the results of the TIVO-1 study are generalisable to the UK population. TIVO-1 was carried out in Bulgaria, Canada, Chile, Czech Republic, France, Hungary, India, Italy, Poland, Romania, Russia, Serbia, UK, Ukraine and the US. Four patients from two sites were enrolled from the UK (Leicester and Cambridge). The median age of patients in TIVO-1 was 59 years; most patients were male and white and the most common metastatic sites were lung and lymph nodes. Patient characteristics in the pivotal trials for pazopanib[17] and sunitinib[27] were similar and we believe reflect the characteristics of patients with advanced RCC in the UK.

In TIVO-1, 30% of patients had received prior therapy for their RCC. None of the prior treatments were targeted therapies, since these patients were excluded from the study. It should be noted that the patients in the pivotal TIVO-1 study who were exposed to prior treatment were not assessed for treatment response before study entry; therefore we cannot be certain that they failed their initial therapy. As discussed earlier in Section 3.3, the standard of care for first-line treatment of RCC in the UK is now pazopanib or sunitinib. Prior treatment for RCC was a pre-specified subgroup, see Figure 10. There was a significant benefit with tivozanib in patients who were treatment naïve (HR 0.756), whereas the sample size in those who had received prior treatment was inadequate to show a significant difference although there was numerical benefit with tivozanib (HR 0.877). The HR of 0.756 in the treatment naïve population is comparable to the primary analysis of PFS in the overall population (HR 0.797; 95% CI, 0.639 to 0.993) suggesting that the impact of tivozanib in clinical practice is likely to be similar to, or even slightly better than, that seen in the TIVO-1 study.

The dose of tivozanib used in the TIVO-1 study is the licenced dose for tivozanib. Recent EMA/CHMP guidelines state that the declaration of dose in the Summary of Product Characteristics should reflect the amount of active substance (1,340 µg). The dose in the TIVO-1 study is described as a 1.5 mg capsule, which consists of 1,340 µg of tivozanib, with the balance being made up of excipients.

Disease assessments were carried out every 8 weeks which is more frequent than routine clinical practice in the UK, where patients are assessed every 12 weeks.

Patients with significant CV disease, including uncontrolled hypertension (blood pressure >150/100 mmHg whilst taking two or more antihypertensives), myocardial infarction and thromboembolic disorders were excluded from entry into TIVO-1. This is reflected in the Summary of Product Characteristics which recommends that blood pressure is controlled before starting treatment with tivozanib and that blood pressure is monitored during treatment. If hypertension persists then the dose of tivozanib should be reduced or interrupted and re-initiated at a lower dose once blood pressure is controlled. Discontinuation should be considered in cases of persistent severe hypertension, posterior reversible encephalopathy syndrome or other complications of hypertension. The Summary of Product Characteristics recommends that tivozanib is used with caution in patients with arterial and venous thromboembolic events[12].

Patients had to have adequate renal and hepatic function to be enrolled into TIVO-1. The Summary of Product Characteristics reflects this and recommends that tivozanib is used with caution in patients undergoing dialysis. It recommends that hepatic function is monitored before and during treatment. Tivozanib is not recommended in patients with severe hepatic impairment and should be used with caution in patients with mild/moderate hepatic impairment with close monitoring of tolerability. The dose in patients with moderate hepatotoxicity should be reduced to 1,340 µg every other day[12].

To conclude, we believe that there are no reasons why the clinical benefits of tivozanib demonstrated in TIVO-1 would not be applicable to suitable patients in the UK.

4.14 Ongoing studies

An open-label extension (roll over) study (AV-951-09-901) is ongoing at 31 sites in Russia, Ukraine, India and US. This study allows continued access to tivozanib for patients who have participated in other Phase I or II tivozanib protocols and will provide evidence on long-term safety and efficacy[89].

The TIVO-3 trial is a phase III randomised, controlled, multi-centre, open-label study to compare tivozanib to sorafenib in subjects with refractory advanced RCC and is expected to complete enrollment in June 2017. Topline data is currently expected in the first quarter of 2018. TIVO-3 is expected to enrol approximately 322 patients with recurrent RCC who have failed at least two prior regimens, including VEGFR-TKI therapy (other than sorafenib).

Eligible patients may also have received checkpoint inhibitor therapy in earlier lines of treatment. Patients will be randomised 1:1 to receive either tivozanib or sorafenib, with no crossover between arms. The primary end-point of the study is PFS. Secondary end-points include OS, ORR, safety and tolerability.

The TiNivo trial will evaluate tivozanib in combination with nivolumab in advanced RCC and was scheduled to open sites for enrollment in early March 2017. The Phase I trial will evaluate the safety of tivozanib in combination with nivolumab at escalating doses of tivozanib and, assuming favourable results, is expected to be followed by an expansion Phase 2 cohort at the established combination dose.

5 Cost effectiveness

- We used a similar approach to that used for NICE TA215 for pazopanib[1 28 29] in the same indication, extended to allow the capture of post-progression treatment costs, in line with current NICE guidance for the treatment of advanced RCC.

- For the economic model, the base case was based on the study population who had not received prior immunotherapy (70% of the total recruited patients in TIVO-1), which allows the "Untreated disease" (treatment naïve) comparator subset in the NICE Scope to be addressed. Lack of data meant that we were unable to model the "Previously treated disease" (pre-treated population).

- The analysis uses a partitioned-survival model to estimate expected clinical and economic outcomes for patients with metastatic RCC receiving treatment with tivozanib, sunitinib, pazopanib or IFN-α.

- The model quantifies transition over time through three discrete mutually exclusive health states ("Alive pre-progression", "Alive post-progression" and "Dead") and estimates proportions in each health state based on parametric survival curves fitted to clinical trial data on PFS and OS over time.

- The pivotal study for tivozanib was an active comparator study versus sorafenib, therefore, clinical efficacy data was obtained via a MTC. The derived HR versus tivozanib for each outcome and comparator were then used to inform the partitioned survival model. Using the reported Kaplan-Meier curves from the TIVO-1 study, parametric survival functions for both PFS and OS were calculated, using Weibull survival functions. Based on these outcome and treatment-specific survival curves, the proportion of patients in any of the three health states at any given time point can be estimated.

- Estimates for the relative incidence of AEs were derived from the MTC. For the purposes of the economic model, only AEs of severity grade 3 or above that had an incidence of 5% or more in any treatment arm were incorporated in the analysis, as the cost and utility impact of lesser AE grades or lower incidence, is likely to be insignificant in this clinical and financial context.

- Individual patient data from the TIVO-1 trial was used to derive estimates for utilities for both pre-progression and post-progression health states. An analysis carried out as part

of the manufacturer's submission to NICE in support of pazopanib[29] was used to assess the potential impact of AEs on utilities.

- Drug costs in the base case are the PAS price for pazopanib and sunitinib and the list price for IFN and tivozanib.
- Costs of management, follow-up and managing AE are in line with UK practice and are derived from UK sources.
- The model incorporates post-progression treatment costs based on the use of axitinib, in line with NICE guidance. Clinical advice suggests that 60% of patients who progress on a VEGFR-TKI will receive this treatment and we have modelled on this basis.
- Using the list price for tivozanib, the results of the base case show that none of the three targeted therapies is associated with an ICER versus IFN that would be below the conventionally accepted willingness to pay threshold of £30,000/QALY. Of the three, tivozanib offers the lowest ICER versus IFN (£112,050/QALY). When compared with the other targeted therapies tivozanib is cost-effective versus sunitinib (ICER of £1,500/QALY) and pazopanib (ICER dominated).
- Sensitivity and scenario analyses show that the model is highly sensitive to the estimates used for relative PFS and OS, which in turn impact on the cost of post-progression treatment – a major component of the overall cost. None of the other model inputs tested exert an effect on the results that would affect the qualitative conclusions.
- The cost-effectiveness analysis is generalisable to clinical practice in England. We have used UK data wherever possible for inputs into the model and have taken expert clinical advice from UK clinicians practising in the field.
- The model confirms that, under any reasonable set of assumptions, tivozanib cannot be considered a cost effective alternative to IFN, in line with previous health economic analyses of VEGFR-TKIs[1 2]. In current UK practice, however, few patients are treated with IFN. In this context, tivozanib is comparable to sunitinib and pazopanib in efficacy and offers a cost effective treatment alternative to sunitinib at list price.

5.1 Published cost-effectiveness studies

5.1.1 Identification of studies

The search to identify cost-effectiveness studies was conducted as part of the single search for these reviews, as reported in Section 4 and Appendix 2. The inclusion and exclusion criteria used to select relevant cost-effectiveness studies is reported below in Table 47.

Table 47: Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Aged ≥ 18 years Any gender Any race Has locally advanced/advanced/metastatic/stage III/stage IV disease	No data reported on relevant population
Intervention	Any intervention included in the efficacy review	No data reported on relevant intervention
Comparators	Any of the included interventions Placebo Best supportive care	No data reported on relevant comparator
Outcomes	Cost per life-year saved Cost per QALY gained Costs saved	No data reported on a relevant outcome
Study design	Cost-benefit analyses Cost-effectiveness analyses Cost-utility analyses Systematic reviews will be used for citation chasing only Studies only available as conference abstracts will be included if they report sufficient relevant data to inform model development or parameterisation	Other study design
Language restrictions	English only	Full text publication in other language
Publication dates	1995 onwards (journal articles) Last 2 years of conference abstracts	Published outside relevant dates
QALY: Quality adjusted life year		

5.1.2 Description of identified studies

A total of 15 cost-effectiveness studies were identified by the review, of which four (reported in five publications)[28 90-93] were relevant to England and are summarised below in Table 48. Quality assessment of the four studies can be found in Appendix 5.

All four models were cost-utility models in UK patients with advanced or metastatic RCC and had been used to inform the NICE HTA process. Two were relevant for first-line targeted therapy, the model used for the pazopanib submission to NICE that compared pazopanib with IFN, sunitinib and best supportive care[28 90] and a model comparing temsirolimus versus IFN alpha[91]. One model was a Health Technology Assessment MTA that compared bevacizumab + IFN, sorafenib, sunitinib, temsirolimus, IFN and best supportive care in

patients receiving first or second-line therapy and provided a critique of relevant manufacturers' submissions to NICE[93] and one compared second-line sorafenib with best supportive care[92]. Three of the models were based on the PenTAG Markov-type decision analytic model and adopted a societal perspective[91-93] and one was a critique of a new partitioned survival model developed by the manufacturer of pazopanib, which adopted an NHS perspective alone[28 90].

All four models had a 10-year time horizon and applied a 3.5% annual discount for costs and benefits. The three models based on the PenTAG model all used a 6-week cycle[91-93], whereas the partitioned survival model had a 1-day cycle[28 90]. All models had three health states, PFS, progressive disease and death. Efficacy data came from relevant RCTs for the interventions[17 67 69] and a systematic review and ITC for the MTA[93]. Data on resource use was largely based on expert opinion in all models and utility values were taken from the pazopanib RCT[17] or the manufacturer submission for sunitinib plus additional published literature[91-93].

The pazopanib model, which had a 1-day cycle length, assumed that treatment would stop immediately on disease progression, which is unlikely to be the case in the real world and would underestimate the cost of treatment, so could bias the results in favour of the more expensive treatment[28 90]. The sorafenib model included a reduction in the cost of sorafenib and assumed 100% compliance[92], whereas the temsirolimus model assumed that compliance would be less than 100%[91]. All models were limited by sparse clinical efficacy data and uncertainty about the costs of care in the UK, the most appropriate utility values for the health states and handling of data about crossovers in the RCTs.

All four evaluations conducted deterministic sensitivity analyses, which varied assumptions on dose intensity, efficacy, costs and utility values. Three models also conducted probabilistic sensitivity analyses [28 90-92].

The results of the economic evaluations are reported below in Table 48. All concluded that the new technology was unlikely to be cost-effective at a willingness to pay threshold of £30,000 without a discount in the cost of the technology, such as via a PAS.

Table 48: Summary list of published cost-effectiveness studies

Study	**Pazopanib STA, Kilonzo** [28 90]	**Hoyle 2010a[92]**	**Hoyle 2010b[91]**	**Thompson Coon 2010[93]**
Year	2007/08	2007/08	NR	NR
Summary of model	Cost-utility model	Cost-utility model	Cost-utility model	Cost-utility model

	Partitioned survival model in Visual Basic: calculates % of patients in each treatment arm at any given time using parametric survival curves fitted to empirical OS and PFS data over time; 1 day cycle length	Markov-type decision analytic model in MS Excel, Weibull curves fitted to PFS and OS Kaplan-Meier curves to predict survival, 6-week cycle	Markov decision-analytic model in MS Excel using area under the curve to model disease progression; Weibull curves fitted to PFS and OS Kaplan-Meier data from RCT; 2nd line treatments not explicitly modelled; 6-week cycle	Markov-style decision-analytic model in MS Excel; Weibull curve survival analysis for each baseline comparator using PFS and OS Kaplan-Meier curves from most appropriate RCT; 6-week cycles
Patient population	Advanced and/or metastatic RCC, patients receiving 1st line therapy	Advanced or metastatic RCC, patients receiving 2nd line therapy	Advanced/ metastatic RCC, patients receiving 1st line therapy	Advanced and/or metastatic RCC, patients receiving 1st or 2nd line therapy
QALYs	**Base case:** Pazopanib: 1.966 IFN: 1.249 Sunitinib: 1.898 BSC: 0.987	Sorafenib: 1.18 BSC: 0.91	**Base case:** Temsirolimus: 0.77 IFN alpha: 0.53	Bevacizumab + IFN: 1.45 Sorafenib: 1.15 Sunitinib: 1.62 Temsirolimus: 0.77 IFN: 1.19 BSC: 0.91
Costs	**Base case:** Pazopanib: £40,441; after 12.5% discount £36,301 IFN: £8,379 Sunitinib: £36,179 BSC: £4,085	Sorafenib: £23,860 BSC: £3,797	**Base case:** Temsirolimus: £28,849 IFN alpha: £6,519	Bevacizumab + IFN: £53,873 Sorafenib: £27,797 Sunitinib: £39,623 Temsirolimus: £25,794 IFN: £8,438 BSC: £3,797
ICER/ QALY gained	**Base case:** IFN ICER vs baseline £16,395; incremental analysis £16,396 Sunitinib: ICER vs baseline £35,231; incremental analysis £42,832 Pazopanib: ICER vs baseline £37,126; incremental analysis £62,414 **After 12.5% discount for PAZ** IFN: ICER vs baseline £16,395; incremental analysis £16,395 Sunitinib: ICER vs baseline £35,231;	**Base case:** Cost/QALY £75,398 At willingness to pay £30,000/QALY threshold, 0% chance that sorafenib is cost-effective. ICER from sensitivity analyses ranged from £47,440 to £86,734	**Base case:** Cost/QALY £94,632 At willingness to pay threshold of £30,000, close to 0% probability that temsirolimus is cost-effective vs IFN-alpha Sensitivity analyses have ICERs ranging from £56,589 to £254,146 Clear cell subgroup: ICER £150,721/QALY Prior nephrectomy subgroup: ICER £154,752/QALY	**ICER SUN v IFN:** £58,647/LYG; £71,462/QALY Sensitivity analyses: ICER range £36,587 to £263,363 Bevacizumab + IFN: total costs £53,873; LYG 1.96; QALYs 1.45 **ICER BEV+IFN vs IFN**: £133,952/LYG; £171,301/QALY Sensitivity analyses: ICER range from £49,190 to £868,881 IFN in poor prognosis: total costs £6,519; LYG 1.07; QALYs 0.53

	incremental analysis extendedly dominated by pazopanib Pazopanib: ICER vs baseline £32,898; incremental analysis £38,925 In most cases, deterministic sensitivity analyses indicate that pazopanib is cost-effective vs sunitinib at threshold of £20,000-30,000/QALY Below cost/QALY threshold of £15,000, BSC is most cost-effective Between £15,000-£35,000/QALY threshold, IFN is most cost-effective Between £35,000-£50,000/QALY, pazopanib likely to be cost-effective **Committee decision:** ICER £33,000/QALY for pazopanib v BSC, £38,900 vs IFN-alpha, £1,790 vs sunitinib, after 12.5% discount for pazopanib under patient access scheme.		No nephrectomy subgroup: ICER £74,369/QALY	Temsirolimus: total costs £25,794; LYG 1.52; QALYs 0.77 **ICER TEM vs IFN**: £42,902/LYG; £81,687/QALY Sensitivity analyses: ICER range £49,359 to £217,243 **ICER SOR vs BSC:** £78,960/LYG; £102,484/QALY Sensitivity analyses range £55,585 to £368,830
QALYs: Quality-adjusted life years, ICER: Incremental cost-effectiveness ratio				

5.2 De novo analysis

5.2.1 Patient population

Tivozanib has a licence for the treatment of adult patients with advanced RCC, who have not been previously treated with targeted therapy (VEGF inhibitor or mTOR inhibitor) but who may have previously received immunotherapy (IFN-α or interleukins). This is consistent with the inclusion criteria for the pivotal TIVO-1 study.

For this economic model, the base case will be based on the study population who had not received prior immunotherapy (70% of the total recruited patients), which allows the "Untreated disease" or treatment naïve comparator subset in the NICE Scope to be addressed. No separate analysis of efficacy is available from the study for the group of

patients who had previously received immunotherapy – a similar limitation applies to comparator studies included in the MTC described in Section 4.11 above, which forms the basis for the comparator group in the economic model. There are no completed studies assessing the use of tivozanib in patients previously treated with targeted therapy. For these reasons, the “Previously treated disease” comparator subset in the NICE Scope has not been addressed in this submission.

5.2.2 Model structure

The analysis uses a partitioned-survival model to estimate expected clinical and economic outcomes for patients with metastatic RCC receiving treatment with tivozanib, sunitinib, pazopanib or IFN-α. The approach is similar to a Markov cohort model, in that it quantifies transition over time through three discrete mutually exclusive health states (“Alive pre-progression”, “Alive post-progression” and “Dead”). Unlike a pure Markov approach, which uses explicit transition probabilities for each change in health state, the partitioned survival approach estimates proportions in each health state based on parametric survival curves fitted to clinical trial data on PFS and OS over time.

In the model, patients are assumed to be in the “Alive pre-progression” state until disease progression or death (if it occurs before progression). In the “Alive pre-progression state” all patients are assumed to be treated with the primary treatment under evaluation (tivozanib, sunitinib, pazopanib or IFN-α). Following disease progression, primary treatment is discontinued and patients transition to the “Alive post-progression” state until death. While in the “Alive post-progression” state, all patients are assumed to be treated with axitinib, in accordance with NICE guidance TA333[3], although only costs of care associated with this treatment are captured – the risk of progression to death being determined by the OS survival curve associated with the relevant primary treatment, rather than that of axitinib. This reflects the fact that in both the TIVO-1 study and the comparator studies, treatment following progression with alternative targeted therapy was the normal strategy and is thus already captured in the relevant study OS survival curves.

The approach adopted is analogous to that used for NICE TA215 for pazopanib[1] in the same indication, extended to allow the capture of post-progression treatment costs, in line with current NICE guidance for the treatment of advanced RCC.

Figure 20: Model schematic

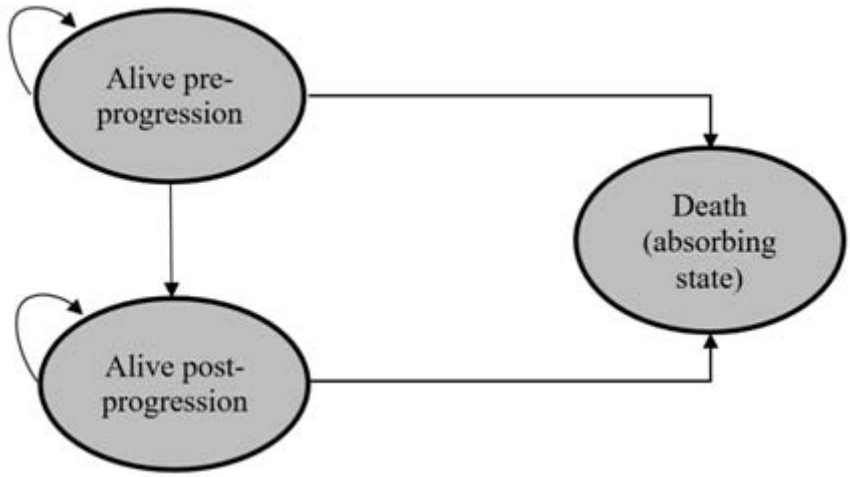


Table 49: Features of the de novo analysis

Factor	Chosen values	Justification
Time horizon	10 years	Parametric projection of the OS curve for tivozanib in the TIVO-1 study suggests that >98% of patients would be dead after 10 years. This projection is consistent with clinician advice that few patients would survive longer than this. For this reason, a 10 year time horizon approximates a lifetime projection.
Were health effects measured in QALYs; if not, what was used?	1 week	This cycle length allows differences in cost for the treatment regimens to be compared
Discount of 3.5% for utilities and costs	Yes	As per reference case
Perspective (NHS/PSS)	Yes	As per reference case
PSS: Personal social services, QALYs: Quality-adjusted life years		

5.2.3 Intervention technology and comparators

Intervention and comparators are modelled using licensed dose regimens for this indication and patient population. Doses and indications are in line with previous NICE guidance[1 2].

Table 50: Dosage regimen for comparators[94]

Treatment	Dosage regimen
Tivozanib (oral)	1,340 µg daily for 3 weeks followed by 1 week without treatment
Sunitinib (oral)	50 mg daily for 4 weeks followed by 2 weeks without treatment
Pazopanib (oral)	800 mg daily, continuously administered
IFN-α (subcutaneous)	3 MU three times weekly for 1 week 6 MU three times weekly for the second week 9 MU three times weekly thereafter

5.3 Clinical parameters and variables

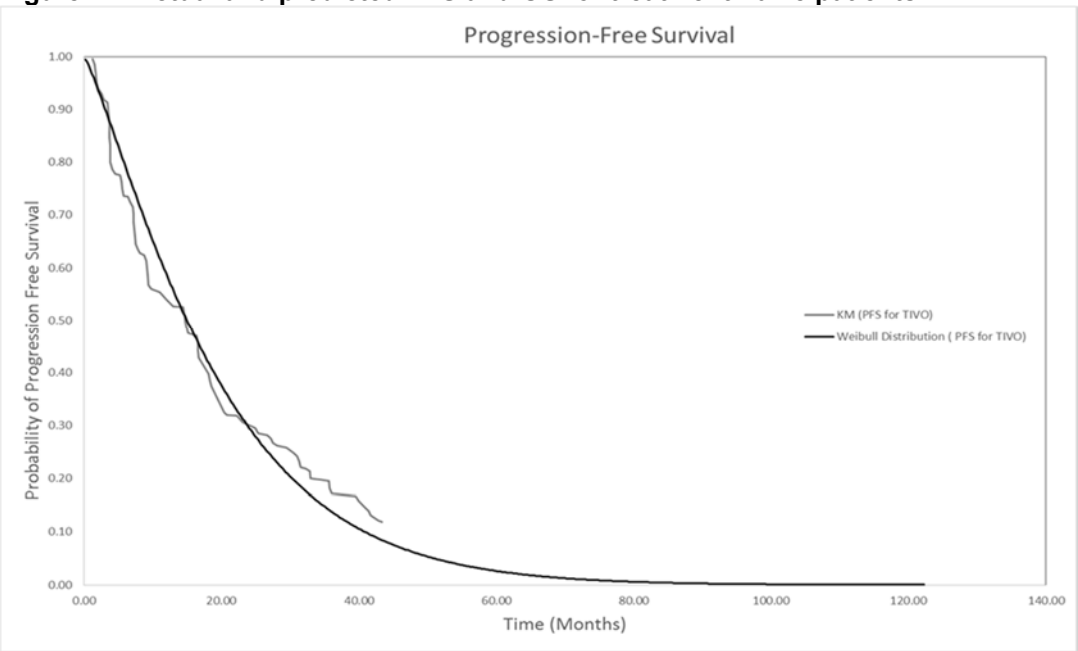
5.3.1 Incorporation of clinical data into model

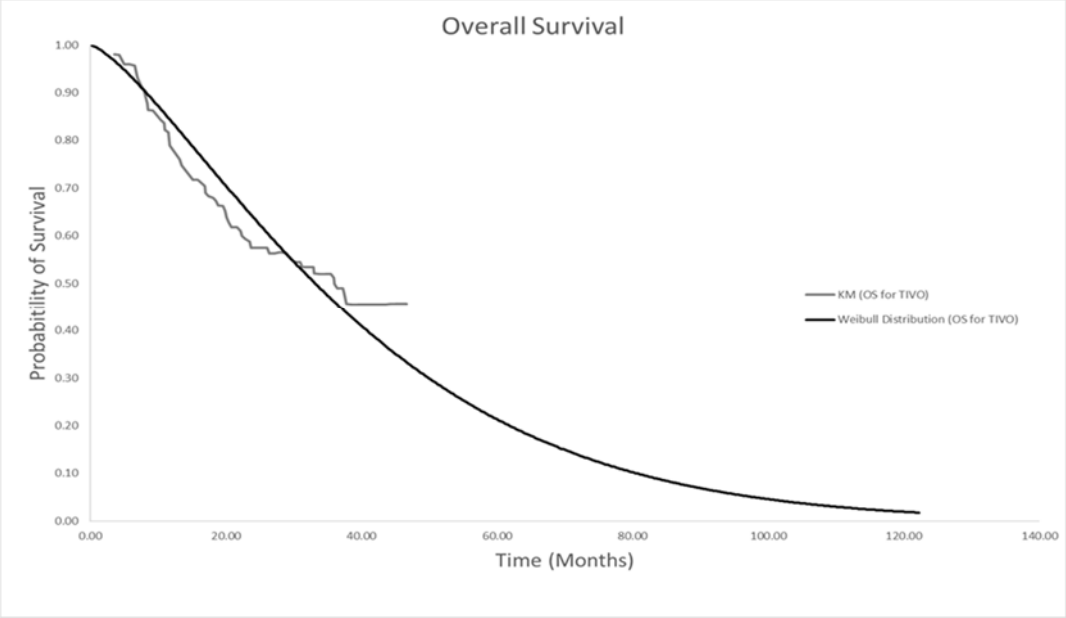
5.3.1.1 Clinical efficacy

The pivotal study for tivozanib was an active comparator study versus sorafenib. Although a reasonable choice at the time the study was designed, sorafenib is now rarely used in UK clinical practice and consequently is of limited value as a point of comparison for this economic model. Consequently, as described in Section 4.11, a MTC was carried out, in order to estimate the relative efficacy, expressed as PFS and OS, of tivozanib versus sunitinib, pazopanib and IFN-α. The derived HR versus tivozanib for each outcome and comparator were then used to inform the partitioned survival model, as described below.

Using the reported Kaplan-Meier curves from the TIVO-1 study, parametric survival functions for both PFS and OS were calculated, using Weibull survival functions. The Weibull approach is widely adopted for this type of analysis, as it sufficiently flexible to allow for changes in event rates over time[95]. Figure 21 below compares the actual Kaplan-Meier survival curves for tivozanib-treated patients with the predicted curves based on the derived Weibull functions.

Figure 21: Actual and predicted PFS and OS for treatment-naïve patients





Using this approach, at any given time point within the simulation, the proportion of the tivozanib-treated cohort modelled, expected to have experienced either progression or death can be calculated using the appropriate Weibull parameters:

$$Ln(P_{tivo}) = - (t^{\gamma} * \lambda) \quad (1)$$

Where:

- P_{tivo} = probability of modelled outcome in tivozanib arm at chosen timepoint;
- t = timepoint (days after treatment start);
- γ = Weibull shape parameter;
- λ = Weibull scale parameter.

Similar survival probability curves for the three comparator groups are then constructed by applying the appropriate hazard ratio derived from the ITC to formula 1. Thus:

$$Ln(P_{comp}) = - (t^{\gamma} * \lambda) \ / HR_{comp} \quad (2)$$

Where:

- P_{comp} = probability of modelled outcome in comparator arm at chosen timepoint;
- HR_{comp} = Hazard ratio for tivozanib vs comparator for modelled outcome from MTC.

The resulting survival curves for PFS and OS are shown in Figure 22 and Figure 23.

Figure 22: Predicted PFS survival curves used in the economic model

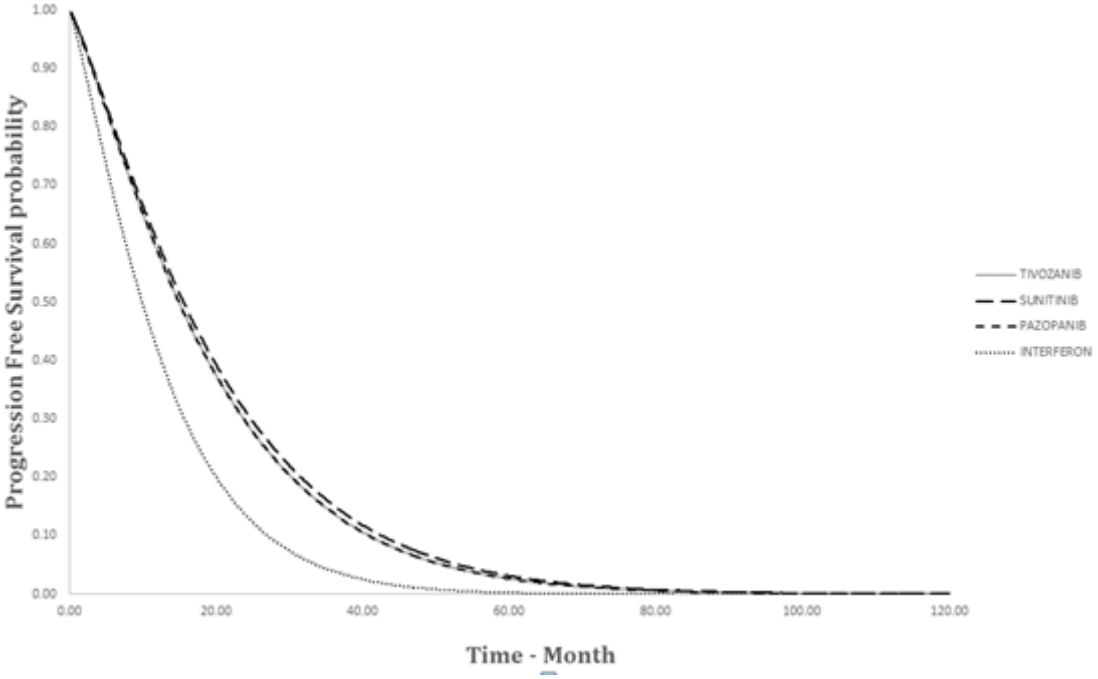
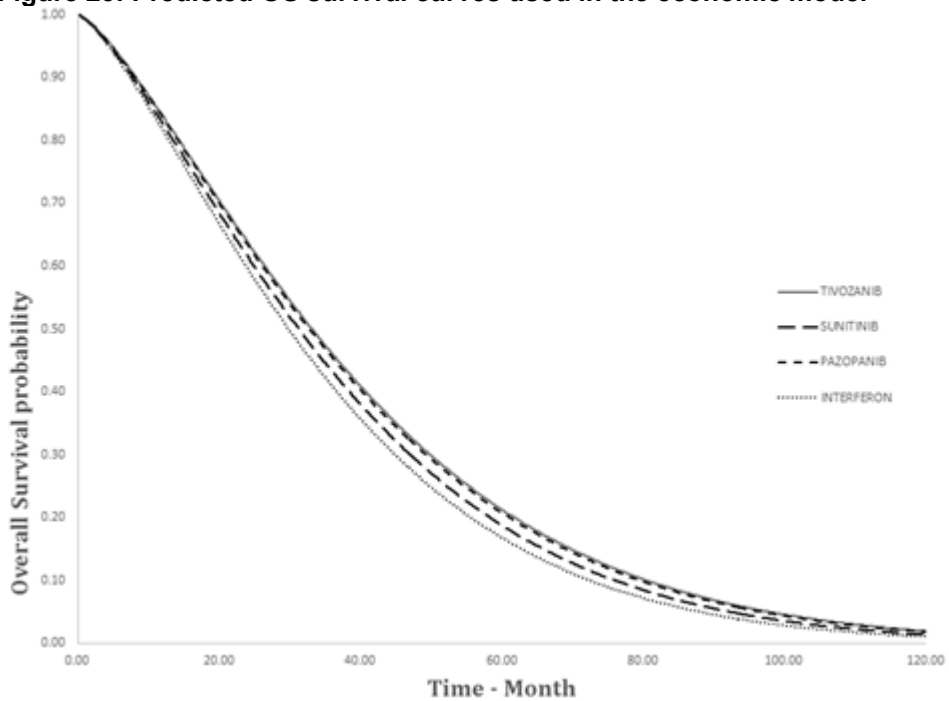


Figure 23: Predicted OS survival curves used in the economic model



Based on these outcome and treatment-specific survival curves, the proportion of patients in any of the three health states at any given time point can be estimated.

- Pre-progression state = Estimated PFS
- Post-progression state = Estimated OS – Estimated PFS

- Death = 1 – Estimated OS

The mean amount of time spent in each health state is then calculated by analyzing the area under each curve (see Figure 24) – effectively a summation of all the point comparisons.

Figure 24: Interaction of OS, PFS and PPS curves in the estimation of mean time spent in each health state (example using tivozanib curves)

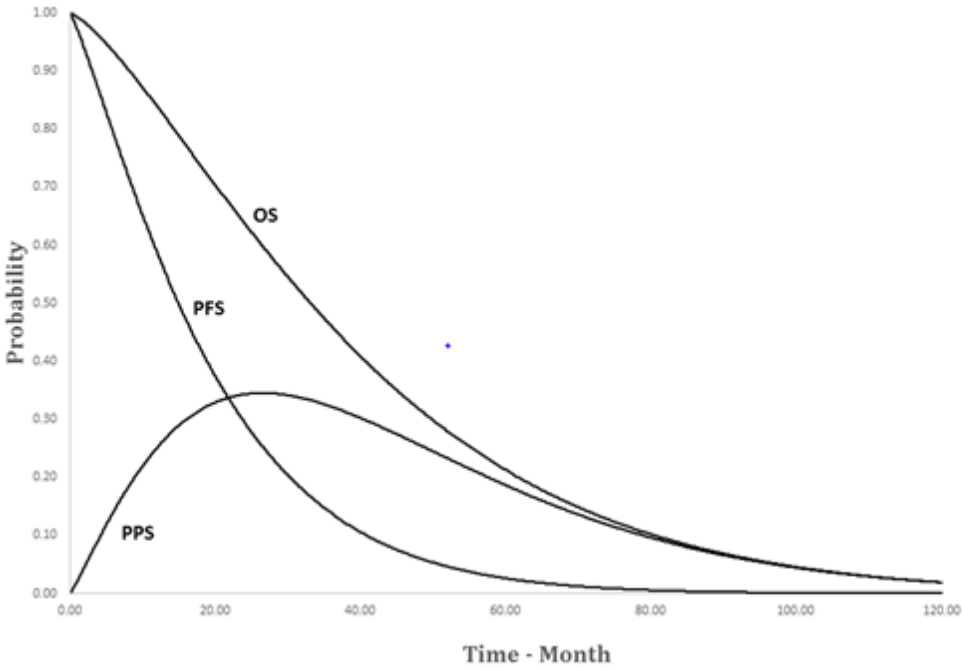


Table 51 summarises the effectiveness estimates used in the economic model.

Table 51: Summary of effectiveness estimates used in the economic model

Treatment	Parameter	PFS		OS		Source
		Mean	95%CrI	Mean	95%CrI	
Tivozinib (Weibull parameters)	γ (shape parameter)	1.1945	-	1.3523	-	TIVO-1 [11]
	λ (scale parameter)	0.0005	-	0.0001	-	
Sunitinib	HR (tivozanib vs sunitinib)	1.05	0.68 – 1.32	0.92	0.55 – 1.56	MTC
Pazopanib	HR (tivozanib vs pazopanib)	1.00	0.63 – 1.29	0.98	0.59 – 1.64	MTC
IFN	HR (tivozanib vs IFN)	0.61	0.58 – 0.99	0.87	0.51 – 1.47	MTC
PFS: Progression free survival, OS: Overall survival, HR: Hazard ratio, MTC: Mixed treatment comparison						

5.3.1.2 Adverse events

Estimates for the relative incidence of AEs were derived from the MTC, details and results of which are presented in Section 4.11. For the purposes of the economic model, only AEs of

severity grade 3 or above that had an incidence of 5% or more in any treatment arm were incorporated in the analysis, as the cost and utility impact of lesser AE grades or lower incidence, is likely to be insignificant in this clinical and financial context.

For each grade 3+ AE under consideration, the incidence of each in tivozanib treatment was first identified from the TIVO-1 study. The OR for each pairwise comparison versus tivozanib, drawn from the MTC, was then applied to this baseline incidence figure, in order to estimate the expected incidence in each of the comparator groups. Four adverse events were seen in >5% of patients in at least one treatment arm. The results of this process are summarised in Table 52 and Table 53 below.

As data for the timing of AEs was lacking for the comparator treatments in the MTC, for the model the conservative assumption was made that all AEs would occur during the first cycle of treatment.

Table 52: Pair-wise estimates of treatment effects (OR) for grade +3 AEs derived from MTC

AE	Tivozanib vs Sunitinib		Tivozanib vs Pazopanib		Tivozanib vs IFN	
	Median	95% CrI	Median	95% CrI	Median	95% CrI
Anaemia	0.03	0.00 -47.69	0.11	0.00 - 176	0.04	0.00 - 64.43
Asthenia/Fatigue	0.95	0.25 - 4.014	1.70	0.42 - 7.42	1.00	0.26 - 4.252
HFS	0.19	0.03 - 0.835	0.41	0.07 - 1.935	1.84	0.28 - 11.39
Hypertension	1.15	0.46 - 2.951	1.14	0.43 - 3.091	12.80	3.69 - 51.91
AE: Adverse event, IFN: Interferon, HFS: Hand-foot syndrome						

Table 53: Estimates of incidence of grade 3+ AE rates in each treatment arm

AE	Tivozanib		Sunitinib		Pazopanib		IFN	
	Median	95% CI	Median	95% CI	Median	95% CI	Median	95% CI
Anaemia	0.04	0.016 – 0.064	0.60	0.538 – 0.658	0.28	0.267 – 0.297	0.53	0.469 – 0.590
Asthenia/ Fatigue	0.10	0.064 – 0.137	0.10	0.067 – 0.142	0.06	0.052 – 0.071	0.10	0.063 – 0.137
HFS	0.02	0.003 – 0.037	0.10	0.063 – 0.135	0.05	0.021 – 0.074	0.01	0.000 – 0.024
Hypertension	0.27	0.216 – 0.324	0.24	0.191 – 0.296	0.24	0.185 – 0.305	0.03	0.008 – 0.048
AE: Adverse event, IFN: Interferon, HFS: Hand-foot syndrome								

5.4 Measurement and valuation of health effects

5.4.1 Health-related quality-of-life data from clinical trials

In the TIVO-1 study, all patients were asked to complete the EQ-5D-3L questionnaire on the first day of each treatment cycle. This was continued as long as the patient participated in

the study, regardless of whether they remained on randomised treatment or experienced progressive disease. The detailed results of these EQ-5D-derived utilities have not been published but, using the individual patient data from the trial, we were able to derive estimates for utilities for both pre-progression and post-progression health states.

Pre-progression: Baseline EQ-5D derived indices were available for 516 patients in the study. Mean utility was 0.726 (95%CI: 0.705 to 0.748).

Post-progression: For 275 patients who experienced progression on treatment, subsequent EQ-5D results were available. The estimate for post-progression utility was derived from the results from the first treatment cycle following the diagnosis of progression. Mean utility at this point was 0.649 (95%CI: 0.612 to 0.686).

These results are comparable with those cited in the literature and used in previous cost utility analyses, as documented in Section 5.4.3 below.

5.4.2 Mapping

No mapping was required, as EQ-5D was used in the original trial

5.4.3 Health-related quality-of-life studies

The search to identify studies reporting QOL and utilities was conducted as part of the single search for these reviews, as reported in Section 4 and Appendix 2. The inclusion and exclusion criteria used to select relevant QOL studies is reported below in Table 54.

Table 54: Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Aged ≥ 18 years Any gender Any race Has locally advanced/advanced/metastatic/stage III/stage IV disease	No data reported on relevant population
Intervention	Any intervention included in the efficacy review Surgery if reports follow-up of more than 3 months Radiotherapy if reports follow-up of more than 3 months Placebo Best supportive care No intervention	No data reported on relevant intervention
Comparators	Any of the included interventions No comparator	No data reported on relevant comparator
Outcomes	Utility values Other quality of life measures	No data reported on a relevant outcome
Study design	Randomised controlled trials Observational studies Systematic reviews will be used for citation chasing only Studies only available as conference abstracts will be included if they report sufficient relevant data to allow analysis	Other study design
Language restrictions	English only	Full text publication in other language
Publication dates	1995 onwards (journal articles) Last 2 years of conference abstracts	Published outside relevant dates

The systematic review identified 58 studies that were relevant to the reference case of patients with advanced or metastatic RCC who were either treatment naïve or receiving second-line therapy after prior cytokines. Of these, 15 reported utility values. These 15 studies are summarised below in Table 55 and Table 56.

Out of the 15 relevant studies identified, 13 reported utility results based on the EQ-5D. Baseline progression free utility ranged from 0.62 to 0.80, with the bulk of the results falling in the range 0.71 to 0.76. This is consistent with the estimate derived from the TIVO-1 study, which was 0.73.

Two of the identified studies provided data of use in estimating post-progression utility. Cella et al (2012)[96] estimated a utility value of 0.68 for progressive disease, while Zbrozek et al estimated a value of 0.59[97]. A third publication, which drew on unpublished data[98], presented an estimate for utility of 0.63 in patients on second-line treatment following progression on first-line treatment with either sunitinib or IFN-alpha. These results are also consistent with the result of 0.65, derived from TIVO-1.

Table 55: Population and methods for relevant studies reporting utility values in patients receiving first-line therapy for advanced/ metastatic RCC

Study	Population	Recruitment	Interventions	Sample size	Response rates	Consistency with reference case
Castellano 2009[99]	MRCC, France, Germany, Italy, Spain, UK, Poland; mean age 60-61 yrs; 72% male (Motzer 2007 trial)	RCT participants	IFNα Sunitinib	304 (European subgroup)	>94% at baseline; EQ-5D response rates were 94.2 to 100% throughout study	High (study included in ITC)
Cella 2008[100]	MRCC, US, Europe, Canada, Australia, Russia, Brazil; median 59-62 yr; 71% male (Motzer 2007 trial)	RCT participants	IFNα Sunitinib	750	95%	High (study included in ITC)
Cella 2010[101]	MRCC, US, Europe, Canada, Australia, Russia, Brazil; median 59-62 yr; 71% male (Motzer 2007 trial)	RCT participants	IFNα Sunitinib	750 total; 347 from US; 274 from Europe	92% completed at least 1 assessment; 88-97% competed all questionnaires	High (study included in ITC)
Cella 2012[96]	Advanced/ mRCC receiving 1st-2nd line therapy, US, Canada, Italy; mean 59 yr; 70% male (Sternberg 2010 trial)	RCT participants	Pazopanib Placebo	435	99% at baseline, 88-96% completed assessments to week 48	Moderate (study included in ITC; includes 2nd line)
Cohen 2012[102]	MRCC, newly diagnosed, US; mean 59 yrs; 77% male	Patients attending cancer centre	Not specified	217	NR	Moderate (treatment unclear)
De Groot 2014[103]	MRCC, Netherlands; mean 63yr; 77% male	Dutch RCC registry	Not specified	100	NR	Moderate (treatment unclear)
Escudier 2009[104]	MRCC, 2nd line after cytokines, US, Europe; median 59 yrs; 82% male	RCT participants	Sunitinib regimen comparisons	107	>95%	High
Goebell 2014[105]	MRCC, 64% receiving 1st line therapy, Germany; median 70 yrs; 72% male (FAMOUS study)	Patients recruited by clinicians to German RCC registry	Sunitinib (51%), sorafenib (15%), temsirolimus (16%), bevacizumab+IFN (11%), everolimus (5%), IFNα (1%)	98	59% of patients returned questionnaire	High
Hagiwara 2016[106]	MRCC, 1st line therapy, setting, age, gender NR (COMPARZ trial)	RCT participants	Pazopanib Sunitinib	NR	NR	High (study included in ITC)

Study	Population	Recruitment	Interventions	Sample size	Response rates	Consistency with reference case
Hutson 2013[75]	Metastatic RCC, receiving 1st line therapy; International; median 58 yrs; 72% male (Hutson 2013 study)	RCT participants: details NR	Axitinib Sorafenib	288	>95% at baseline and during therapy, 60% at end of study	High (study included in ITC)
Litwin 1997[107]	Advanced RCC 1st line, US; mean 58 yrs; 100% male	Patients who had received treatment at cancer centre	Infiltrating lymphocytes + Interleukin-2	25	80%	Moderate (not all treatments relevant)
Motzer 2013[11]	Recurrent/ mRCC, 1st line or after cytokines; International median 59yrs; 72% male (TIVO-1 trial)	RCT participants	Tivozanib Sorafenib	517	>99% at baseline, <50% after 13th cycle	High (TIVO-1 trial)
Sternberg 2010[17]	Advanced/ mRCC, 1st line or after cytokines; US; median 59-60 yrs; 71% male (Sternberg 2010 trial)	RCT participants	Pazopanib Placebo	435	>90% fo all assessments	High (study included in ITC)
Yang 2010[108]	Advanced/ recurrent RCC, 1st line therapy, setting NR; mean 59 yrs; 68% male (ARCC trial)	RCT participants	IFNα Temsirolimus	270 subgroup	NR	High (study included in ITC)
Zbrozek 2010[97]	Advanced/ recurrent RCC, 1st line therapy, setting NR; mean 59 yrs; 69% male (ARCC trial)	RCT participants	IFNα Temsirolimus	626	96% at baseline 260 reported values at disease progression, 230 after grade 3-4 adverse event, 278 during progression-free and toxicity-free survival	High (study included in ITC)

Table 56: Utility values reported in relevant studies

Study	Health states and appropriateness	Adverse events	Elicitation, validation, mapping	Results, uncertainty	Appropriateness for cost-utility model
Castellano 2009[99]	Baseline only: PFS	NR	Values correlated with FKSI, FKSI-DRS and FACT-G	**EQ-5D index**: sunitinib 0.72 (0.24); IFN 0.74 (0.25); difference -0.02, p=0.41 **EQ-VAS**: sunitinib 68.57 (18.39); IFN 65.95 (19.32); difference 2.63, p=0.23	Moderate: values not reported for all health states
Cella 2008[100]	Baseline and end of treatment; PFS and mixed health states	NR	NR	**EQ-5D index** Baseline, mean (SD): sunitinib 0.76 (0.23) IFN 0.76 (0.23) End of treatment (Least squares mean): sunitinib 0.762 IFN 0.725 **EQ-VAS** Baseline, mean (SD): sunitinib 73.8 (18.5) IFN 71.43 (19.51) End of treatment (Least squares mean): sunitinib 73.4 IFN 68.7	Moderate: values not reported for all health states
Cella 2010[101]	Baseline and end of treatment; PFS and mixed health states	NR	NR	Mean scores of all post-baseline observations in European group **EQ-5D Index:** sunitinib 0.72 IFN 0.71 **EQ-VAS:** sunitinib 72.55 IFN 67.22	Moderate: values not reported for all health states
Cella 2012[96]	Baseline and end of treatment; PFS and mixed health states; Change in EQ-5D and EQ-5D VAS scores from baseline reported for CR/PR, SD, PD	NR	NR	**EQ-5D Index values**, mean (SD) Baseline: placebo 0.73 (0.24); pazopanib 0.72 (0.25) *Change from baseline with complete/partial response (CR/P)* Placebo: 0.03 (0.11) Pazopanib: -0.01 (0.15) *Change from baseline in stable disease (SD)* Placebo: 0.01 (0.17) Pazopanib: -0.05 (0.25) *Change from baseline in progressive disease (PD)* Placebo: -0.15 (0.32) Pazopanib: -0.14 (0.26) **EQ-5D VAS values**, mean (SD)	High: values can be determined for all health states

Study	Health states and appropriateness	Adverse events	Elicitation, validation, mapping	Results, uncertainty	Appropriateness for cost-utility model
				Baseline: placebo 65.9 (23.84); pazopanib 64.6 (23.69) *Change from baseline in CR/PR* Placebo: 6.3 (20.7) Pazopanib: 1.6 (23.1) *Change from baseline in SD* Placebo: 3.6 (23.8) Pazopanib: 2.5 (21.3) *Change from baseline in PD* Placebo: -9.6 (18.4) Pazopanib: -7.7 (21.1)	
Cohen 2012[102]	Baseline only: PFS	NR	NR	**SF-36 values at baseline**: SF-36 MCS: mean 52.1 (SD9.9) SF-36 PCS: mean 34.7 (SD 11.9)	Moderate: values not reported for all health states
De Groot 2014[103]	Baseline and end of treatment; PFS and mixed health states	NR	NR	**EQ-5D values at diagnosis**: 0.73 (95%CI 0.64 to 0.82) EQ-5D values after 2-6 months: 0.75 (0.66 to 0.84)	Moderate: values not reported for all health states
Escudier 2009[104]	Baseline and end of treatment; PFS and mixed health states	NR	NR	**EQ-5D values**, median Baseline: 0.8 for both treatment arms; no significant change over up to 29 cycles of therapy **EQ-VAS scores**, median Baseline: 70 for both treatment arms; no significant change over up to 29 cycles of therapy	Moderate: values not reported for all health states
Goebell 2014[105]	Baseline only: PFS	Fatigue	NR	**EQ-5D values** Patients with fatigue: 0.76 (SD 0.23) Patients without fatigue 0.89 (SD 0.12)	Moderate: values not reported for all health states
Hagiwara 2016[106]	Progression-free survival	NR	NR	**Regression model-derived EQ-5D utility values during PFS**, mean (95%CI): Pazopanib: 0.709 (0.67 to 0.75) Sunitinib: 0.683 (0.64 to 0.73) **Published estimates of EQ-5D utility values during PFS**, mean (95%CI): Pazopanib: 0.739 (0.73 to 0.75) Sunitinib: 0.708 (0.70 to 0.72)	High

Study	Health states and appropriateness	Adverse events	Elicitation, validation, mapping	Results, uncertainty	Appropriateness for cost-utility model
Hutson 2013[75]	Baseline and end of treatment; PFS and mixed health states	NR	NR	**EQ-5D values,** mean (SD) Axitinib: baseline 0.71 (0.25); end of treatment 0.64 (0.27) Sorafenib: baseline 0.71 (0.27); end of treatment 0.59 (0.29)	Moderate: values not reported for all health states
Litwin 1997[107]	End of treatment, mixed health states	NR	NR	**RAND-36 mean scores** (95% confidence interval) in all mRCC patients (100=best, 0=worst): Physical function: 65 (53-76) Social function: 69 (58-80) Bodily pain: 70 (58-81) Emotional well-being: 74 (66-82) Energy/fatigue: 47 (37-57) General health perceptions: 52 (42-62) Physical role limitations: 36 (16-57) Emotional role limitations: 53 (32-75) **RAND-36 scores by number of comorbidities in mRCC patients (4 patients had no comorbidities, 5 had one, 6 had 2, 5 had 3 or more)** Physical function: None: 76; 1: 75; 2: 70; 3+: 39 Social function: None: 78; 1: 83; 2: 65; 3+: 53 Bodily pain: None: 60; 1: 86; 2: 75; 3+: 54 Emotional well-being: None: 77; 1: 88; 2: 71; 3+: 59 Energy/fatigue: None: 55; 1: 55; 2: 51; 3+: 28 General health perceptions: None: 63; 1: 55; 2: 58; 3+: 32 Physical role limitations: None: 44; 1: 50; 2: 38; 3+: 15 Emotional role limitations: None: 50; 1: 100; 2: 39; 3+: 27	Moderate: values not reported for all health states
Motzer 2013[11]	Baseline and end of treatment; PFS and mixed health states	NR	NR	**EQ-5D:** Baseline: Tivozanib 0.73, SD 0.25; Sorafenib 0.73, SD 0.26 Change from baseline, LS mean: Tivozanib -0.05, SE 0.02; Sorafenib -0.06, SE 0.02, p=0.391	High
Sternberg 2010[17]	During treatment; mixed health states	NR	NR	**EQ-5D Index** (values less than 0 = advantage for placebo; minimal clinically important difference= 0.08) Baseline values NR Week 6: 0.01 (-0.04 to 0.05), p=0.84 Week 12: -0.04 (-0.09 to 0.01), p=0.08 Week 18: -0.02 (-0.08 to 0.04), p=0.5 Week 24: -0.03 (-0.09 to 0.04), p=0.44	Moderate: values not reported for all health states

Study	Health states and appropriateness	Adverse events	Elicitation, validation, mapping	Results, uncertainty	Appropriateness for cost-utility model
				Week 48: 0.03 (-0.03 to 0.1), p=0.33 **EQ-VAS** (values less than 0 = advantage for placebo; minimal clinically important difference= 7) Baseline values NR Week 6: 1.85 (-2.41 to 6.12), p=0.39 Week 12: 0.06 (-4.79 to 4.91), p=0.98 Week 18: -0.08 (-5.04 to 4.89), p=0.98 Week 24: -0.15 (-4.83 to 4.53), p=0.95 Week 48: -1.97 (-9.02 to 5.09), p=0.58	
Yang 2010[108]	Baseline and end of treatment; PFS and mixed health states	NR	NR	**Baseline values, mean (SD)**: EQ-5D: 0.62 (0.24) EQ-VAS: 64.03 (17.17) **Least square mean on-treatment values**, up to week 32, mean (SE): EQ-5D: IFN 0.492 (0.031); temsirolimus 0.590 (0.026), p for difference=0.0022 EQ-VAS: IFN 58.83 (1.83); temsirolimus 63.33 (1.56), p=0.0168	Moderate: values not reported for all health states
Zbrozek 2010[97]	TOX: serious toxicity TwiST: no progression or toxicity REL: progressive disease	Specific adverse events NR	Q-TwiST calculated by multiplying health state utility by time in that state	**Baseline EQ-5D values** (median) IFNα: 0.656; Temsirolimus 0.689 **EQ-5D values by health state** (median) TOX: 0.585; TWiST: 0.689; REL: 0.587	High

5.4.4 Adverse reactions

Adverse reactions are considered to be an important driver of on-treatment QOL in these patients and may also influence dose-reduction requirements. Because the administration of EQ-5D questionnaires in the TIVO-1 study was keyed to treatment cycles, rather than clinical events, it has not been possible to analyse the impact of individual AEs on QOL. However, an analysis carried out as part of the manufacturer's submission to NICE in support of pazopanib[29] demonstrates the potential impact of AEs on utility, see Table 57.

Table 57: EQ-5D utility values for patients with and without AEs[29]

AE	Unadjusted								Adjusted Difference
	With Event			Without Event			Difference		
	N	Mean	SE	N	Mean	SE	Mean	SE	
Anaemia	23	0.58	(0.01)	1,488	0.70	(0.01)	-0.12	(0.01)	-0.17
Bleeding	9	0.61	(0.12)	1,502	0.70	(0.01)	-0.09	(0.12)	-0.03
Diarrhoea grades 3+	nr	nr	nr	nr	nr	nr	nr	nr	-0.02
Diarrhoea all grades	293	0.76	(0.01)	1,218	0.69	(0.01)	0.07	(0.01)	-0.10
Fatigue/asthenia grades 1-2	nr	nr	nr	nr	nr	nr	nr	nr	-0.19
Fatigue/asthenia Grade 3+	207	0.59	(0.02)	1,304	0.72	(0.01)	-0.13	(0.02)	nr
Fatigue/asthenia All Grades	nr	nr	nr	nr	nr	nr	nr	nr	nr
Fever	4	0.62	(0.09)	1,507	0.70	(0.01)	-0.08	(0.10)	0.00
Flu-like symptoms	4	0.71	(0.07)	1,507	0.70	(0.01)	0.01	(0.07)	-0.34
HFS	51	0.76	(0.03)	1,460	0.70	(0.01)	0.06	(0.03)	-0.05
Hypertension	248	0.72	(0.02)	1,263	0.70	(0.01)	0.02	(0.02)	-0.07
Low white blood cells	44	0.73	(0.04)	1,467	0.70	(0.01)	0.03	(0.04)	nr
Mucositis/stomatitis	26	0.65	(0.05)	1,485	0.70	(0.01)	-0.05	(0.05)	-0.02
Nausea/vomiting	168	0.65	(0.02)	1,343	0.71	(0.01)	-0.06	(0.02)	-0.09
Non-HFS rash	42	0.79	(0.04)	1,469	0.70	(0.01)	0.10	(0.04)	-0.01
Thrombocytopenia	61	0.71	(0.03)	1,450	0.70	(0.01)	0.01	(0.04)	nr
AE: Adverse event, HFS: Hand-foot syndrome, SE: Standard error									

5.4.5 Health-related quality-of-life data used in cost-effectiveness analysis

The utility values chosen for the two health states are both derived from the TIVO-1 study[11], which is the primary source for all the clinical inputs in this model. The approach used to derive the estimates is consistent with the NICE reference case and yields results in the centre of the ranges identified by the literature search.

For the four qualifying AEs captured in the model, we were unable to directly source these data from TIVO-1. Instead, the utility decrements associated with each AE in a previously published cost effectiveness analysis of pazopanib based on study VEG105192[109] have been used, with each decrement being applied to the pre-treatment (and consequently AE-free) utility estimate derived from TIVO-1. This approach is justified on the grounds that pazopanib is one of the comparators in the economic analysis and the study from which the utility estimates have been derived was carried out in a broadly similar population to that recruited for TIVO-1.

In order to ensure consistency, the mean durations of AEs (required to estimate the decrement in QALYs) were also estimated using data from VEG105192 and are reported in Table 58. SEs for the duration of AEs were not reported and were therefore assumed to be equal to 0.25 multiplied by the mean.

Table 58: Estimates of mean duration (days) of key grade 3 AEs

Duration of AEs	Mean days	95% CI
Anaemia	37.5	19.1 – 55.9
Fatigue	56.9	29.0 – 84.8
HFS	60.5	30.9 – 90.2
Hypertension	40.2	20.5 – 59.9
AE: Adverse event, HFS: Hand-foot syndrome		

Table 59 is a summary of the utility values used in the cost-effectiveness analysis.

Table 59: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (Section and page number)	Justification
Health states				
Pre-progression	0.726 (0.011)	0.705; 0.748	5.4.1 (Page 133)	Directly derived from study being modelled. Consistent with literature
Post-progression	0.649 (0.019)	0.612; 0.686	5.4.1 (Page 133)	
Adverse reactions (all grade 3+)				
Anaemia	0.61 (0.020)	0.525; 0.765	5.4.4 (Page 141)	In the absence of AE-specific data from the TIVO-1 study, the values chosen are derived from a clinical trial of pazopanib (VEG105192)[109], carried out in a similar patient group.
Asthenia/Fatigue	0.60 (0.026)	0.517; 0.777	5.4.4 (Page 141)	
HFS	0.68 (0.006)	0.638; 0.738	5.4.4 (Page 141)	
Hypertension	0.66 (0.007)	0.600; 0.740	5.4.4 (Page 141)	

5.5 Cost and healthcare resource use identification, measurement and valuation

5.5.1 Resource identification, measurement and valuation studies

The search to identify costs studies was conducted as part of the single search for these reviews, as reported in Section 4 and Appendix 2. The inclusion and exclusion criteria used to select relevant costs studies is reported below in Table 60 and the results of the five identified studies[16 46 110-112] in Table 61

Table 60: Eligibility criteria used in the search strategy

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Aged ≥ 18 years Any gender Any race Has locally advanced/advanced/metastatic/stage III/stage IV disease	No data reported on relevant population
Intervention	Any intervention included in the efficacy review Best supportive care No intervention	No data reported on relevant intervention
Comparators	Any of the included interventions No comparator	No data reported on relevant comparator
Outcomes	Direct costs Indirect and informal costs Resource use	No data reported on a relevant outcome
Study design	Randomised controlled trials Observational studies Database studies Systematic reviews will be used for citation chasing only Studies only available as conference abstracts will be included if they report sufficient relevant data to inform model development or parameterisation	Other study design
Language restrictions	English only	Full text publication in other language
Publication dates	2000 onwards (journal articles) Last 2 years of conference abstracts	Published outside relevant dates

Table 61: Summary of relevant studies reporting costs or resource use

Study	Hansen et al. 2015[110]	Hill et al. 2016[111]	James et al. 2009[112]	Mickisch et al. 2010[46]	Motzer et al. 2013[16]
Country	Europe, Asia, Australia, North America	International	UK	UK, Germany, France, Italy	North America, Europe, Australia, Asia
Date	US$, 2013	US$ 2014-15	GBP 2008	NR	NR
Population	Advanced or metastatic RCC, 1110 patients receiving 1st line pazopanib or sunitinib, Karnofsky performance status 70% or more; mean age 61yrs (COMPARZ trial)	Theoretical cohort of patients with cancer, including those receiving sorafenib for RCC	Patients attending tertiary cancer centre with mRCC and applying for sorafenib or sunitinib funding as first (33%) or second-line (51%); median age 56-63 yrs, 75% male	Hypothetical cohort of patients with metastatic RCC, receiving 1st line therapy with bevacizumab + IFN or sunitinib	Advanced or metastatic RCC, 1110 patients with clear cell histology, receiving 1st line therapy with pazopanib or sunitinib (COMPARZ trial)
Applicability to England	Moderate	Moderate	High	High	Moderate
Cost valuations	Resource use from COMPARZ trial; total healthcare costs; unit costs of managing grade 3+ AEs	Sorafenib product costs	Mean cost of inpatient episodes	Costs per adverse event, grade 3-4 (grade 2) in UK	Medical resource use over first 6 months of treatment
Costs for use in economic analysis	**Average total health care resource use, mean unadjusted costs by component** Providers: pazopanib $963; sunitinib $1,007, Diagnosis: pazopanib $161; sunitinib $235 Hospitalisations: pazopanib $426; sunitinib $1,198 Procedures: pazopanib $601; sunitinib $713 **Unit costs of managing grade 3-4 adverse events (mean)** Hypertension: $190.51; Fatigue: $131.14; Diarrhoea: $174.29; Palmar-plantar erythrodysesthesia: $112.04;		£2,246 total costs for funded patients vs £2,332 for unfunded patients. Mean 19 outpatient episodes for unfunded vs 22 episodes for funded patients	**Cost per adverse event grade 3-4 (grade 2), all Euros** Anaemia: 2494 (112) Anorexia: 70 (70) Arterial thromboembolism: 2494 (112) Bleeding: 637 (637) Chills: 42 (42) Reduced cardiac ejection fraction: 1123 (1123) Depression: 224 (224) Diarrhoea: 3207 (112) Dry skin: 0 (112) Dyspnoea: 42 (42) Epistaxis: 1084 (112) Fatigue/ aesthenia: 372 (372) GI perforation: 5929 (112) Hair colour changes: 70 (70) HFS: 2589 (112) Headache: 274 (274)	**Cumulative mean (SD) medical resource use per patient per month over first 6 months for study participants** Non-study medical visits: pazopanib 0.726 (1.472); sunitinib 0.779 (1.690) Telephone consultations: pazopanib 0.279 (0.718); sunitinib 0.312 (0.656) Number of days in hospital: pazopanib 0.402 (2.273); sunitinib 0.562 (2.187) Emergency department visits: pazopanib 0.037 (0.156); sunitinib 0.067 (0.195)

Study	Hansen et al. 2015[110]	Hill et al. 2016[111]	James et al. 2009[112]	Mickisch et al. 2010[46]	Motzer et al. 2013[16]
	Headache: $250.61; Nausea/vomiting: $174.55; Arthralgia: $127.16; Dyspnoea: $235.61; Asthenia: $131.60; Anorexia: $138.45; Mucositis: $171.42; Dehydration: $195.79; Syncope: $203.84; Pleural effusion: $229.81			Heart failure: 3293 (112) Hypertension: 21 (21) Influenza-like syndrome: 42 (42) Leucopenia: 1792 (112) Lymphopenia: 1792 (1792) Mucosal inflammation: 495 (495) Myalgia: 274 (274) Nausea: 2803 (112) Neutropenia: 1792 (70) Pain in extremity: 274 (274) Proteinuria: 3929 (112) Pyrexia: 42 (42) Rash: 148 (148) Skin discolouration: 70 (70) Stomatitis: 495 (88) Thrombocytopenia: 3372 (112) VTE: 2246 (112) Vomiting: 2803 (112) Wound healing complications: 148 (148)	
Technology costs	Study drug: pazopanib $69,417; sunitinib $74,433, Non-study drug: pazopanib $9,118; sunitinib $9.091	Sorafenib - product costs API/tablet: 200 mg Tablets/month: 112 API price/kg: $3000 API cost/tablet: $0.60 Add costs of excipients, formulation: $0.62 Add costs of tableting: $0.66 Cost per month: $73.83 Add cost of bottle, packaging, shipping, duties: $74.18 Add 50% mark-up: $111.27 Target price: $1,450/patient/yr Lowest available price of sorafenib in UK: $58,027			

5.5.2 Intervention and comparators' costs and resource use

Table 62 below shows the treatment acquisition costs for tivozanib and the three comparators. Because the treatment regimens differ, these costs have also been expressed as a mean cost per week, taking into account treatment-free periods, where applicable. In the case of sunitinib and pazopanib, PAS have been agreed with NICE and consequently these are the costs used in the base case model. For sunitinib the PAS allows for free treatment in the first cycle, with list price charged thereafter[2]. For pazopanib, a straight discount of 12.5% is applied to the list price[1].

For IFN-α treatment, in week 1 the dose of 3 MU requires the use of a 6 MU prefilled syringe, with the unused portion being discarded. It was assumed that 75% of injections would be self-administered, with the remainder given by a district nurse. This is in line with the assumptions made in previous NICE STAs for pazopanib and sunitinib[1 2]. The cost per district nurse face-to-face contact is taken as £37.98[113].

Table 62: Drug acquisition prices

Treatment	Dose regimen	PAS discount	List price	Mean cost per week no PAS
Tivozanib	1,340 µg daily for 3 weeks followed by 1 week rest	None	[redacted]	[redacted]
IFN (Roferon-A)	3 MU 3x weekly for 1 week; 6 MU 3x weekly for second week; 9 MU 3x weekly thereafter	None	6 MU prefilled injection: £14.20 9 MU prefilled injection: £21.29[94]	First 4 weeks: £53.24 Thereafter: £63.87
Treatment	**Dose regimen**	**PAS discount**	**List price**	**Mean cost per week including PAS**
Sunitinib	50 mg daily for 2 weeks followed by 2 weeks rest	No charge for first cycle. List price thereafter	50 mg caps x 28: £3,138.80[94]	First 6 weeks: nil Thereafter: £523.13
Pazopanib	800 mg daily administered continuously	12.5% discount on all doses	400 mg tabs x 30: £1,121[94]	£457.74

5.5.3 Health-state unit costs and resource use

When patients start treatment it is assumed that they will require a first consultant appointment with a medical oncologist. Thereafter, it is assumed that they will be followed up in outpatients on a monthly basis and undergo a CT scan once every 3 months. This is in keeping with the approach adopted in previous NICE STAs for pazopanib and sunitinib[1 2].

In the previous STAs, once treatment had failed there was no alternative treatment option, hence it was assumed for costing purposes that patients reverted to GP-led palliative care. This situation has now changed, with a range of VEGFR-TKI inhibitors and mTOR inhibitors

now being licensed as second-line targeted therapies. For the purposes of this model, we have assumed that 60% patients in the post-progression health state will be treated with axitinib, in line with clinical advice and the recommendations in TA333[3], with the remaining 40% receiving supportive care only. For axitinib-treated patients, we have assumed that the ongoing monitoring requirement will remain the same as in the pre-progression health state. For patients on supportive care, we have assumed that a monthly follow-up appointment will be provided, but no further CT scans.

For the purposes of sensitivity analysis, the SE of all cost estimates was assumed to be 25% of the mean value.

Table 63: Assumed cost of monitoring in pre-progression and post-progression health states

Health state	Service	Unit cost	Reference
Pre-progression	Consultant led medical oncology outpatients		
	First visit	£197	NHS Reference Costs 2015/6[113] HRG WF01B: service code 370 Medical Oncology
	Subsequent visit (monthly)	£163	NHS Reference Costs 2015/6 HRG WF01A: service code 370 Medical Oncology[113]
	CT scan (3 monthly)	£115	NHS Reference Costs 2015/6[113] Currency code RD25Z CT scan 3 areas without contrast
Post-progression	Subsequent visit (monthly)	£163	NHS Reference Costs 2015/6[113] HRG WF01A: service code 370 Medical Oncology
	CT scan (3 monthly)	£115	NHS Reference Costs 2015/6[113] Currency code RD25Z CT scan 3 areas without contrast

5.5.4 Adverse reaction unit costs and resource use

Four AEs of interest (Grade 3 or above affecting 5% of patients in at least one treatment arm) were identified. Estimated costs for each are shown in Table 64 below. The standard errors of the costs were assumed to be 25% of the mean estimates. We took advice from a UK clinician on the resource use to manage AEs (Dr Robert Jones, Personal Correspondence).

Table 64: Assumed service requirement for managing grade 3+ AEs

AE	Service	Proportion of patients	Unit cost	Reference

Anaemia	Day case transfusion	50%	£306	NHS reference costs 2015/6[113] Weighted mean of HRG SA04G-SA04L
	Short stay transfusion	50%	£509	
	Mean expected cost:		£407.50	
Fatigue	Additional outpatient attendance	50%	£163	NHS Reference Costs 2015/6[113] HRG WF01A: service code 370 Medical Oncology
	Mean expected cost		£81.50	
HFS	Additional outpatient attendance	60%	£163	NHS Reference Costs 2015/6[113] HRG WF01A: service code 370 Medical Oncology
	Short stay admission	30%	£526	NHS reference costs 2015/6[113] Weighted mean of HRG SA04G-SA04L
	Mean expected cost		£255.60	
Hypertension	GP attendance x3	100%	£109	PSSRU Costs of health and social care 2016[114]
	Treatment with antihypertensive	100%	£28	Assumes treatment with Ramipril 5 mg + bendroflumethiazide 2.5 mg for 1 year[94]
	Mean expected cost		£137	
AE: Adverse event, HFS: Hand-foot syndrome				

5.5.5 Miscellaneous unit costs and resource use

Of the patients who transition to the post-progression health state 60% are treated with axitinib. Although a PAS exists for axitinib within the NHS, its terms are confidential, so the undiscounted list price has been applied.

Table 65: Miscellaneous costs

Treatment	Dose regimen	PAS discount	List price	Mean cost per week including PAS
Axitinib	5 mg daily administered continuously	Discount applied but details confidential, so list price used in the model	5 mg tabs x 56: £3,517	£879.25

5.6 Summary of base-case de novo analysis inputs and assumptions

5.6.1 Summary of base-case de novo analysis inputs

Table 66: Summary of variables applied in the economic model

Variable	Value (reference to appropriate table or figure in submission)	Measurement of uncertainty and distribution used in OWSA: CI (distribution)	Distribution used in PSA	Reference to section in submission
Efficacy outcomes				
PFS (tivozanib)	Time-specific - derived from Weibull curve. Datum point against which other PFS HRs (see below) are applied			5.3.5.1
PFS (tivozanib vs sunitinib)	HR = 1.05	0.76 – 1.45 (95%CrI from Bayesian model)	Gamma	
PFS (tivozanib vs pazopanib)	HR = 1.00	0.70 – 1.41 (95%CrI from Bayesian model)	Gamma	
PFS (tivozanib vs IFN)	HR = 0.61	0.44 – 0.87 (95%CrI from Bayesian model)	Gamma	
OS (tivozanib)	Time-specific - derived from Weibull curve. Datum point against which other PFS HRs (see below) are applied			
OS (tivozanib vs sunitinib)	HR = 0.92	0.55 – 1.56 (95%CrI from Bayesian model)	Gamma	
OS (tivozanib vs pazopanib)	HR = 0.98	0.59 – 1.64 (95%CrI from Bayesian model)	Gamma	
OS (tivozanib vs IFN)	HR = 0.87	0.51 – 1.47 (95%CrI from Bayesian model)	Gamma	
AE (grade 3+)				
Tivozanib	Median probability	95% CI		
Anaemia	0.040	0.016 – 0.064 (normal)	Beta	5.3.5.2
Fatigue	0.100	0.064 – 0.137 (normal)	Beta	
HFS	0.020	0.003 – 0.037 (normal)	Beta	
Hypertension	0.270	0.216 – 0.324 (normal)	Beta	
Sunitinib				
Anaemia	0.598	0.538 – 0.658 (normal)	Beta	
Fatigue	0.104	0.067 – 0.142 (normal)	Beta	
HFS	0.099	0.063 – 0.135 (normal)	Beta	
Hypertension	0.244	0.191 – 0.296 (normal)	Beta	
Pazopanib				
Anaemia	0.282	0.267 – 0.297 (normal)	Beta	
Fatigue	0.061	0.052 – 0.071 (normal)	Beta	
HFS	0.048	0.021 – 0.074 (normal)	Beta	
Hypertension	0.245	0.185 – 0.305 (normal)	Beta	
IFN				
Anaemia	0.530	0.469 – 0.590 (normal)	Beta	
Fatigue	0.100	0.064 – 0.137 (normal)	Beta	
HFS	0.011	0.000 – 0.024 (normal)	Beta	
Hypertension	0.028	0.008 – 0.048 (normal)	Beta	
Duration of AEs	Mean days			
Anaemia	37.5	19.1 – 55.9 (normal)	Gamma	5.4.5
Fatigue	56.9	29.0 – 84.8 (normal)	Gamma	
HFS	60.5	30.9 – 90.2 (normal)	Gamma	
Hypertension	40.2	20.5 – 59.9 (normal)	Gamma	
Utilities				
Health states	Mean	95% CI		

Pre-progression state	0.726	0.705 – 0.748 (normal)	Beta	5.4.1
Post progression state	0.649	0.612 – 0.686 (normal)	Beta	
Adverse events: utility calculated as specific decrement on pre-progression utility				
Anaemia	0.606	0.525 – 0.765 (normal)	Beta	5.4.4
Fatigue	0.596	0.517 – 0.777 (normal)	Beta	
HFS	0.676	0.638 – 0.738 (normal)	Beta	
Hypertension	0.656	0.600 – 0.740 (normal)	Beta	
Costs				
Drug costs: expressed as mean cost per week including any PAS				
Tivozanib (list price)	[redacted]	-		5.5.1
Sunitinib (cycle 1)	£0.00	-		
Sunitinib (cycle 2+)	£523.13	-		
Pazopanib	£457.73	-		
IFN (month 1)	£53.24	-		
IFN(month 2+)	£63.87	-		
Axitinib (post-progression)	£879.25	-		5.5.5
AE costs				
Anaemia	£407.50	£207.83 - £607.18 (normal)	Gamma	5.5.4
Fatigue	£81.50	£41.57 - £121.44 (normal)	Gamma	
HFS	£255.60	£130.36- £380.84 (normal)	Gamma	
Hypertension	£137.00	£69.88 - £204.13 (normal)	Gamma	
Treatment + monitoring costs				
Pre-progression monitoring	£201.33 per month	£102.68 – £280.46 (normal)	Gamma	5.5.3
Post-progression monitoring	£201.33 per month	£102.68 – £280.46 (normal)	Gamma	
AE: Adverse event, IFN: Interferon, HFS: Hand-foot syndrome, PFS: Progression free survival, OS: Overall survival, HR: Hazard ratio				

5.6.2 Assumptions

Table 67 lists the assumptions made in the economic model together with justifications for each assumption.

Table 67: Assumptions and justifications in the economic model

Assumption	Justification
All treatments are administered until disease progression or death	As specified in market authorisations for treatments modelled
Following progression, all patients are considered to be treated with axitinib for purposes of cost accumulation, although OS probability is based on study data for the primary randomised data	NICE recommends the use of axitinib in patients who have progressed on targeted therapy[3]. Although there may be subsequent changes in therapy following new progression in the post-progression period, there are insufficient data to model the likely treatment flow. Consequently, patients are assumed to stay on axitinib until death

PFS and OS can reasonably modelled by applying MTC-derived HR values to a parameterised version of the tivozanib PFS and OS Kaplan-Meier survival curves, modelled using a Weibull distribution	The Weibull approach is widely adopted in economic analyses of oncology therapy. In thecase of this analysis we have shown that the Weibull approximation is a good fit to the primary Kaplan-Meier curves. Use of an MTC in circumstances where direct comparative studies are lacking is also well established in cost-utility model used for NICE STAs
Utility values for the pre-progression and post-progression health states are derived from analysis of EQ-5D results from the TIVO-1 study. It is assumed that these values are applicable to patients treated with any of the four therapies evaluated	The estimates obtained from the TIVO-1 study are compatible with published utilities based on other similar studies. Given the nature of the disease and interventions, there is no reason t believe that there will be between-treatments differences in these utilities
Utility decrements and durations for AEs were derived from a previously published study of pazopanib used in the same indication as the current model[109]. It is assumed that these values are applicable to the TIVO-1 based model.	In the absence of TIVO-1 derived utility estimates, this is a reasonable compromise that may be expected to be applicable to all treatments evaluated. The values adopted have previously been used for the NICE STA for pazopanib[1].
The cost and utility impact of AEs of grade 1 or 2 were not considered to add to the understanding of the relative cost effectiveness and were not included in the model	The cost and QALY impact of grade 3 AEs is a minor contributor to the overall result, due to low costs and relatively short duration of exposure. It is anticipated that lesser AEs, although more numerous, would be associated with such low costs, utility decrements and duration that their inclusion would add complexity without contributing significantly to the understanding of relative cost effectiveness. This is in keeping with standard practice in economic models used to support NICE MTAs
It was assumed that a 10 year lifetime horizon will approximate to a lifetime horizon	Based on the Weibull-derived OS curves, 98-99% of patients will have died by the end of 10 years, with little difference between treatment arms – an observation that matches clinical experience. Extension to longer periods is unlikely to give improved estimates of ICERs, given the small numbers of patients involved and the mitigating effects of discounting.
OS: Overall survival; PFS: Progression free survival; MTC: Mixed treatment comparison; HR: Hazard ratio; STA: Single technology appraisal; AE: Adverse event; QALY: Quality adjusted life year; ICER: Incremental cost-effectiveness ratio	

5.7 Base case results

5.7.1 Base case incremental cost effectiveness analysis results

Results are presented for the base case result for a population of patients with no previous treatment with either immunotherapy or targeted therapy using tivozanib at list price (see Table 71). Costs used for the comparators reflect established PAS prices for sunitinib and pazopanib and list price for IFN.

In the base case (tivozanib at list price) none of the three targeted therapies is associated with an ICER versus IFN that would be below the conventionally accepted willingness to pay threshold of £30,000/QALY (see Table 71). Of the three, tivozanib offers the lowest ICER versus IFN (£112,050/QALY). When compared with the other targeted therapies, at list price

tivozanib is cost-effective versus sunitinib (ICER of £1,500/QALY) and pazopanib (ICER dominated), see Table 69 and Table 70.

Table 68: Base-case results: pairwise comparisons – tivozanib versus IFN

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£84,351	2.085	
IFN	£59,585	1.864	
Increment (TIVO - IFN)	£24,767	0.221	£112,050
TIVO: Tivozanib, IFN: Interferon, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio.			

Table 69: Base-case results: pairwise comparisons – tivozanib versus sunitinib

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£84,351	2.085	
SUN	£84,199	1.983	
Increment (TIVO - SUN)	£152	0.101	£1,500
TIVO: Tivozanib, SUN: Sunitinib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 70: Base-case results: pairwise comparisons – tivozanib versus pazopanib

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£84,351	2.085	
PAZO	£85,094	2.063	
Increment (TIVO - PAZ)	-£742	0.022	Dominated
TIVO: Tivozanib, PAZ: Pazopanib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 71: Base-case results (list price for tivozanib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus IFN (QALYs)	ICER (£) incremental (QALYs)
Tivozanib at list price								
IFN	£59,585	2.756	1.864					
Sunitinib	£84,199	2.876	1.983	£24,615	0.120	0.120	£205,840	£205,840
Tivozanib	**£84,351**	**3.028**	**2.085**	**£24,767**	**0.272**	**0.221**	**£112,050**	**£1,500**
Pazopanib	£85,094	2.997	2.063	£25,509	0.241	0.199	£128,228	£11,272
ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALYs: Quality-adjusted life years; IFN: Interferon								

5.7.2 Clinical outcomes from the model

In the TIVO-1 study, the median PFS for treatment naïve patients was 12.7 months, compared with 14.9 months for the model. Median OS in TIVO-1 (all patients) was 28.2 months, compared with 33.4 months in the model. The slight overestimate for both survival curves is not unexpected. The reflects that requirement for the Weibull modelled curve to be extended out to 10 years in each case, which tended to make the gradient of the curve in the early stages of the time period slightly shallower than that seen in the actual study.

For the comparator treatments, data from multiple studies was pooled in the MTC to arrive at an estimated curve, relative to that of tivozanib. This approach precludes direct comparison with the survival curves in the parent studies for the comparator studies. The MTC approach adopted, however, ensures that the relative performance of the four treatments will accurately reflect differences in the contributing evidence base.

5.7.3 Disaggregated results of the base case incremental cost effectiveness analysis

5.7.3.1 Versus IFN

Table 72: Summary of QALY gain by health state (tivozanib versus IFN)

Health state	QALY tivozanib	QALY IFN	Increment	Absolute increment	% absolute increment
Pre-progression (no AEs)	1.071	0.687	0.384	0.384	70.2%
Pre-progression (with AEs)	0.034	0.046	0.012	0.012	2.2%
Post-progression	0.981	1.131	0.151	0.151	27.6%
Total	2.085	1.864	0.547	0.547	100.0%

QALY: Quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 73: Summary of costs by health state (tivozanib versus IFN)

Health state	Cost tivozanib	Cost IFN	Increment	Absolute increment	% absolute increment
At list price					
Pre-progression	£38,805	£7,122	£31,683	£31,683	82.1%
Post-progression	£45,546	£52,462	-£6,916	£6,916	17.9%
Total	£84,351	£59,585	£24,767	£38,599	100.0%

QALY: Quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 74: Summary of predicted resource use by category of cost – tivozanib versus IFN

Item	Cost tivozanib	Cost IFN	Increment	Absolute increment	% absolute increment
At list price					
Medication cost (pre-progression)	£34,659	£4,134	£30,525	£30,525	78.4%
Medication cost (post-progression)	£41,498	£47,873	-£6,375	£6,375	16.4%
Total medication cost	£76,157	£52,007			94.8%
Management cost (pre-progression)	£3,988	£2,666	£1,322	£1,322	3.4%
Management cost (post-progression)	£4,049	£4,589	-£541	£541	1.4%
AE cost	£158	£322	-£164	£164	0.4%
Total	£84,351	£59,585	£24,767	£38,927	100.0%

AE: Adverse event

5.7.3.2 Versus sunitinib

Table 75: Summary of QALY gain by health state (tivozanib versus sunitinib)

Health state	QALY tivozanib	QALY sunitinib	Increment	Absolute increment	% absolute increment
Pre-progression (no AEs)	1.071	1.065	0.005	0.005	2.9%
Pre-progression (with AEs)	0.034	0.076	-0.042	0.042	22.8%
Post-progression	0.981	0.842	0.138	0.138	74.4%
Total	2.085	1.983	0.101	0.186	100.0%

QALY: Quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 76: Summary of costs by health state (tivozanib versus sunitinib)

Health state	Cost tivozanib	Cost sunitinib	Increment	Absolute increment	% absolute increment
At list price					
Pre-progression	£38,805	£45,094	-£6,289	£6,289	49.4%
Post-progression	£45,546	£39,106	£6,441	£6,441	50.6%
Total	£84,351	£84,199	£152	£12,729	100.0%

QALY: Quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 77: Summary of predicted resource use by category of cost – tivozanib versus sunitinib

Item	Cost tivozanib	Cost sunitinib	Increment	Absolute increment	% absolute increment
At list price					
Medication cost (pre-progression)	£34,659	£36,263	-£1,604	£1,604	61.9%
Medication cost (post-progression)	£41,498	£40,657	£840	£840	32.4%
Total medication cost	£76,157	£76,921			94.3%
Management cost (pre-progression)	£3,988	£3,988	£0	£0	0.0%
Management cost (post-progression)	£4,049	£3,963	£85	£85	3.3%
AE cost	£158	£222	-£64	£64	2.5%
Total	£84,351	£85,094	-£742	£2,593	100.0%

AE: Adverse event

5.7.3.3 Versus pazopanib

Table 78: Summary of QALY gain by health state (tivozanib versus pazopanib)

Health state	QALY tivozanib	QALY pazopanib	Increment	Absolute increment	% absolute increment
Pre-progression (no AEs)	1.071	1.056	0.015	0.015	31.6%
Pre-progression (with AEs)	0.034	0.047	-0.013	0.013	26.9%
Post-progression	0.981	0.961	0.020	0.020	41.5%
Total	2.085	2.063	0.022	0.048	100.0%

QALY: Quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 79: Summary of costs by health state (tivozanib versus pazopanib)

Health state	Cost tivozanib	Cost pazopanib	Increment	Absolute increment	% absolute increment
At list price					
Pre-progression	£38,805	£40,473	-£1,668	£1,668	64.3%
Post-progression	£45,546	£44,621	£926	£926	35.7%
Total	£84,351	£85,094	-£742	£2,593	100.0%

QALY: Quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table 80: Summary of predicted resource use by category of cost – tivozanib versus pazopanib

Item	Cost tivozanib	Cost pazopanib	Increment	Absolute increment	% absolute increment
At list price					
Medication cost (pre-progression)	£34,659	£40,539	-£5,881	£5,881	46.2%
Medication cost (post-progression)	£41,498	£35,639	£5,859	£5,859	46.0%
Total medication cost	£76,157	£76,178			92.2%
Management cost (pre-progression)	£3,988	£4,147	-£160	£160	1.3%
Management cost (post-progression)	£4,049	£3,467	£582	£582	4.6%
AE cost	£158	£407	-£248	£248	2.0%
Total	£84,351	£84,199	£152	£12,729	100.0%

AE: Adverse event

5.8 Sensitivity analyses

5.8.1 Probabilistic sensitivity analysis

For the purposes of the PSA, all variables listed in Section 5.6.1, with the exception of the costs of IFN, tivozanib, sunitinib, pazopanib and axitinib, were tested across the stated ranges, using the distributions named in Table 66. IFN, tivozanib, sunitinib, pazopanib costs were excluded on the grounds that these are fixed NHS prices, not subject to parameter uncertainty. Although the price of post-progression treatment with axitinib is similarly fixed, it is subject to a confidential PAS and the proportion of patients receiving this treatment is also uncertain. These assumptions are tested in a specific scenario analysis in Section 5.8.3. Separate PSAs were carried out for each of the pairwise comparisons, together with a three way cost effectiveness acceptability curve. All PSA simulations were run 1,000 times to generate estimated ICERs.

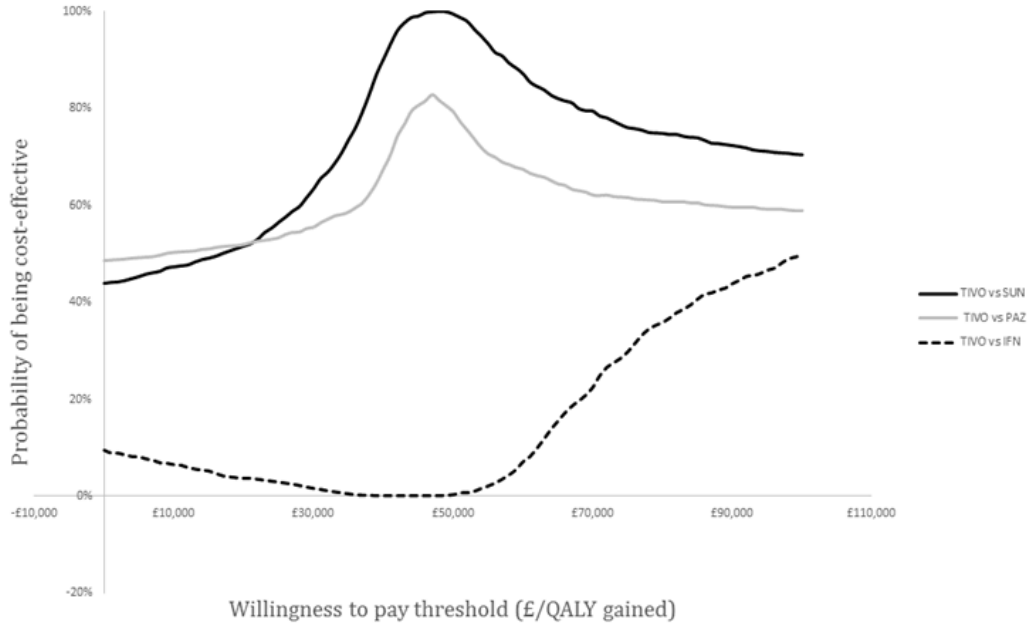
5.8.1.1 Results of PSA

The probability of tivozanib being cost effectiveness at a willingness to pay (WTP) threshold of £30,000 per QALY is documented in Table 81 below. Cost effectiveness acceptability curve (CEAC) for all three comparisons are shown below in Figure 25 with the individual scatter plots for each comparison shown in Figure 26 to Figure 28.

Table 81: PSA results – probability of being cost effective at a WTP threshold of £30,000 per QALY

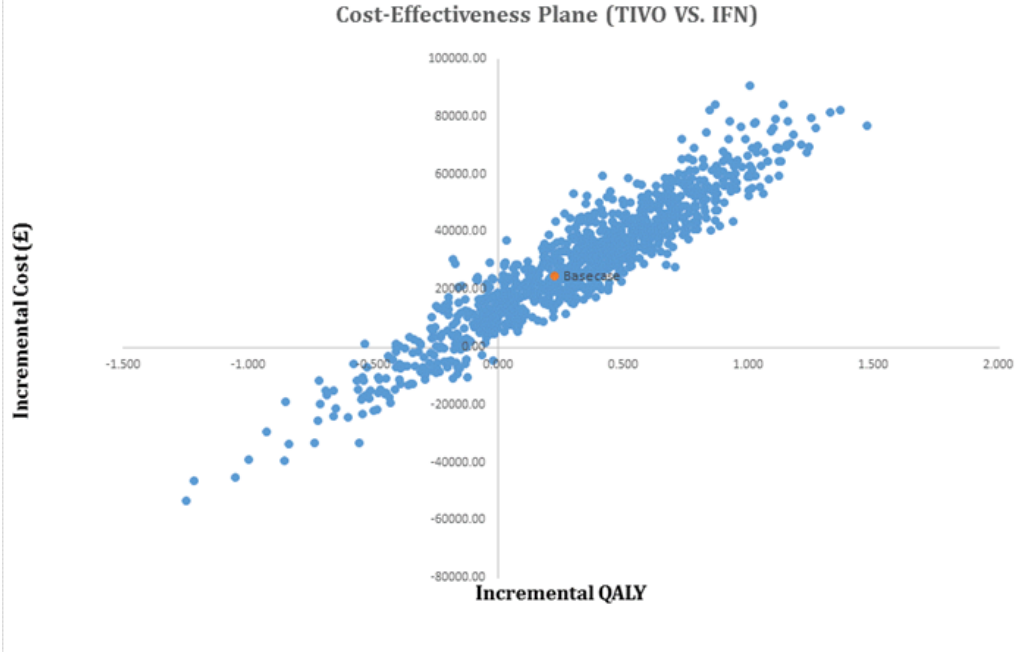
	Tivozanib list price
Versus IFN	5%
Versus sunitinib	59%
Versus pazopanib	52%

Figure 25: Cost effectiveness acceptability curve (tivozanib at list price)



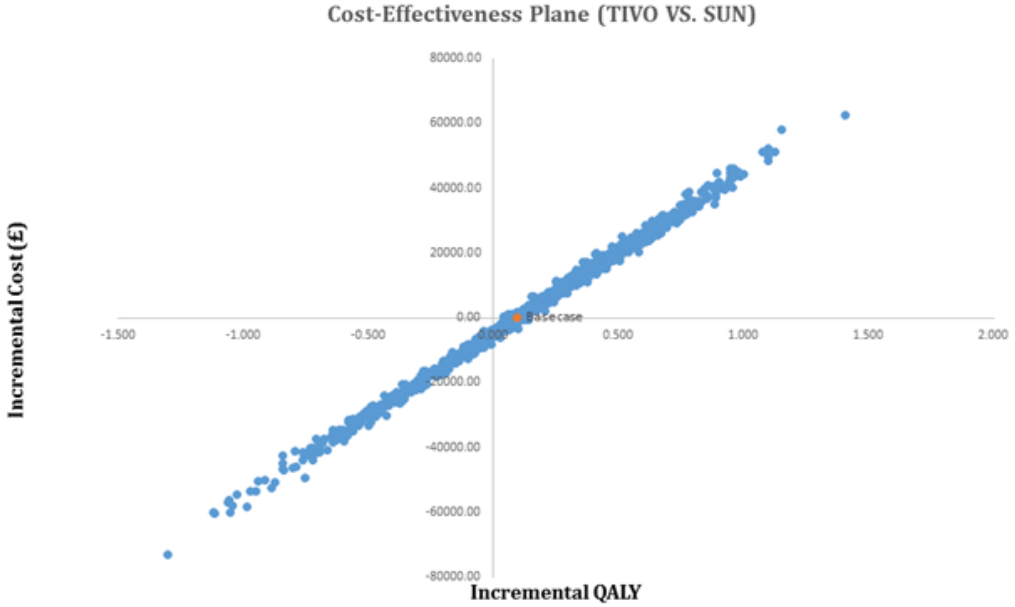
(a) Versus IFN

Figure 26: Cost effectiveness scatter plot: tivozanib versus IFN (tivozanib at list price)



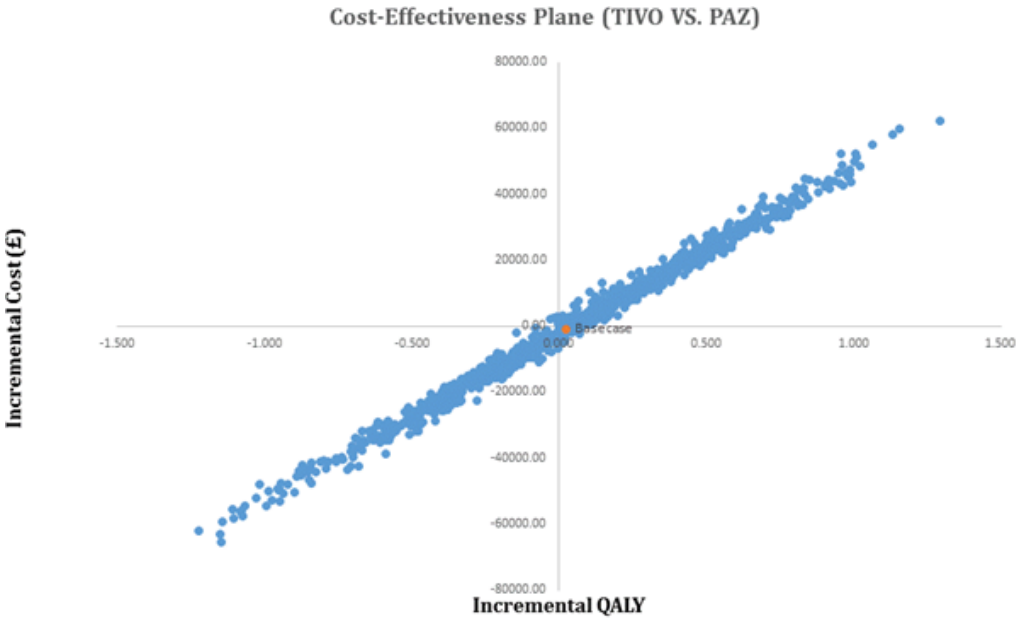
(b) Versus sunitinib

Figure 27: Cost effectiveness scatter plot: tivozanib versus sunitinib (tivozanib at list price)



(c) Versus pazopanib

Figure 28: Cost effectiveness scatter plot: tivozanib versus pazopanib (tivozanib at list price)



5.8.2 Deterministic sensitivity analysis

For the purposes of the deterministic sensitivity analyses (DSA) , all variables listed in Section 5.6.1, with the exception of the costs of IFN, tivozanib, sunitinib, pazopanib and axitinib, were tested across the stated ranges. IFN, tivozanib, sunitinib, pazopanib costs were excluded on the grounds that these are fixed NHS prices and not subject to parameter uncertainty. Although the axitinib price is similarly fixed, it is subject to a confidential PAS and the proportion of patients receiving this treatment is also uncertain. These assumptions are tested in a specific scenario analysis in Section 5.8.3.

Given that the costs of AEs are small and the duration of their utility impact is limited, it was not anticipated that these would exert a significant effect on the ICERs. However, they were included for the sake of completeness.

DSA were carried out separately for the comparisons of tivozanib with IFN, sunitinib and pazopanib.

The full results are presented in Table 82 to Table 84 below, including all variables for completeness. The ten parameters associated with the greatest ICER spread were also graphed as tornado diagrams, see Figure 29 to Figure 31.

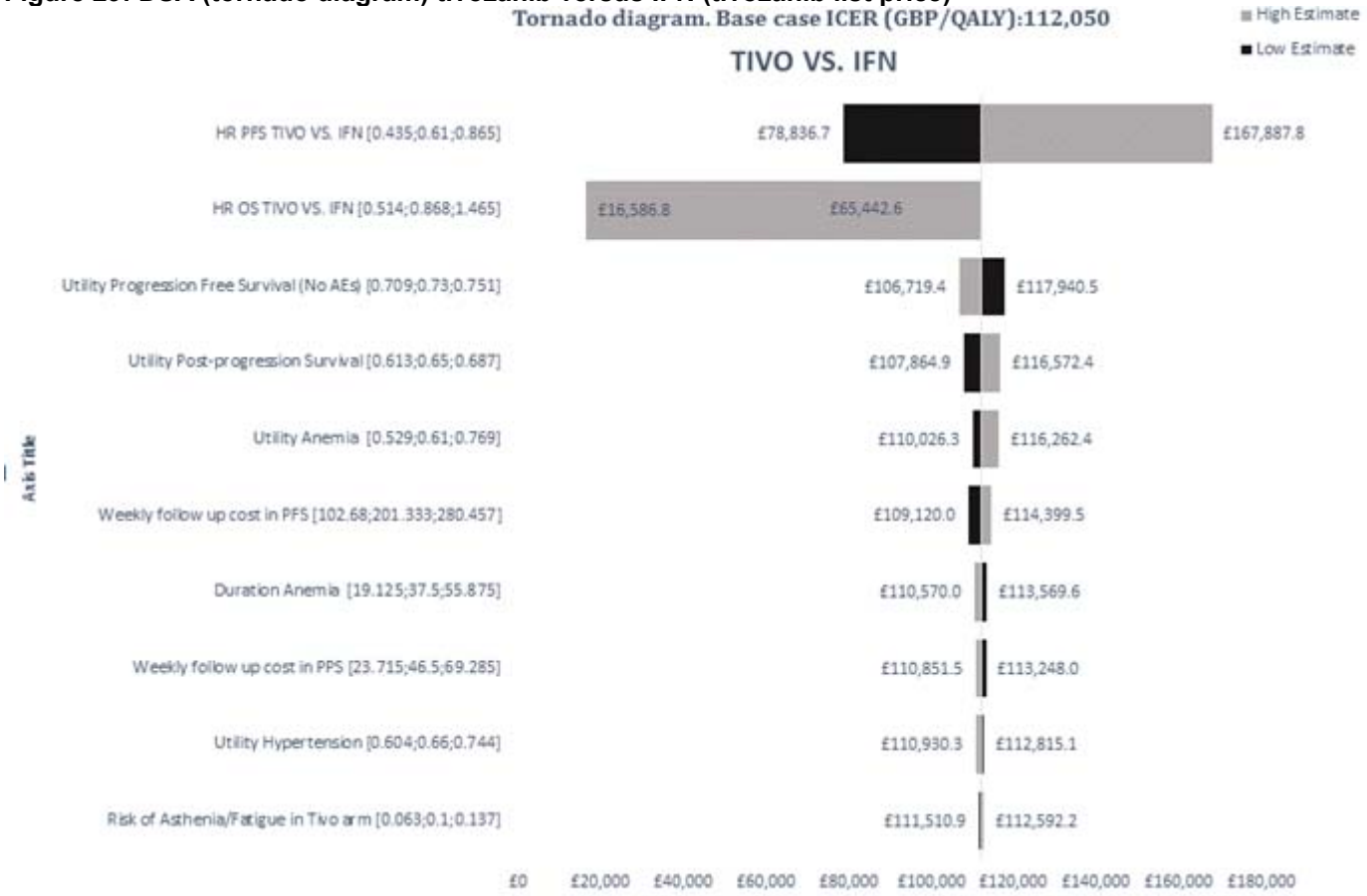
5.8.2.1 Versus IFN

Table 82: Deterministic analysis - tivozanib (list price) versus IFN

				Low estimate				High estimate				
Variable	Lower	Base Case	Upper	Inc LYs	Inc QALYs	Inc Cost	ICER	Inc LYs	Inc QALYs	Inc Cost	ICER	Spread
HR PFS TIVO vs. IFN	0.435	0.610	0.865	0.272	0.241	£18,988	£78,837	0.272	0.194	£32,604	£167,888	£89,051
HR OS TIVO vs IFN	0.514	0.868	1.465	1.108	0.764	£50,018	£65,443	-0.808	-0.481	-£7,977	£16,587	£48,856
Utility PFS (No AEs)	0.709	0.730	0.751	0.272	0.210	£24,767	£117,940	0.272	0.232	£24,767	£106,719	£11,221
Utility PPS	0.613	0.650	0.687	0.272	0.230	£24,767	£107,865	0.272	0.212	£24,767	£116,572	£8,707
Utility Anaemia	0.529	0.610	0.769	0.272	0.225	£24,767	£110,026	0.272	0.213	£24,767	£116,262	£6,236
Weekly follow up cost in PFS	102.680	201.333	280.457	0.272	0.221	£24,119	£109,120	0.272	0.221	£25,286	£114,399	£5,279
Duration Anaemia	19.125	37.500	55.875	0.272	0.218	£24,767	£113,570	0.272	0.224	£24,767	£110,570	£3,000
Weekly follow up cost in PPS	23.715	46.500	69.285	0.272	0.221	£25,032	£113,248	0.272	0.221	£24,502	£110,851	£2,397
Utility Hypertension	0.604	0.660	0.744	0.272	0.220	£24,767	£112,815	0.272	0.223	£24,767	£110,930	£1,885
Risk of Asthenia/Fatigue in TIVO arm	0.063	0.100	0.137	0.272	0.222	£24,730	£111,511	0.272	0.220	£24,803	£112,592	£1,081
Risk of Asthenia/Fatigue in IFN arm	0.063	0.100	0.137	0.272	0.220	£24,803	£112,592	0.272	0.222	£24,730	£111,511	£1,081
Risk of Anaemia in IFN arm	0.469	0.530	0.590	0.272	0.220	£24,791	£112,543	0.272	0.222	£24,742	£111,559	£984
Duration Hypertension	20.502	40.200	59.898	0.272	0.222	£24,767	£111,588	0.272	0.220	£24,767	£112,515	£927
AE cost for Anaemia	207.825	407.500	607.175	0.272	0.221	£24,864	£112,492	0.272	0.221	£24,669	£111,607	£885
Risk of Hypertension in TIVO arm	0.216	0.270	0.324	0.272	0.221	£24,759	£111,805	0.272	0.221	£24,774	£112,295	£490
Risk of Anaemia in Tivo arm	0.016	0.040	0.064	0.272	0.221	£24,757	£111,857	0.272	0.221	£24,776	£112,243	£386
Risk of HFS in TIVO arm	0.003	0.020	0.037	0.272	0.221	£24,762	£111,958	0.272	0.221	£24,771	£112,141	£183
Risk of Hypertension in IFN arm	0.008	0.028	0.048	0.272	0.221	£24,769	£112,141	0.272	0.221	£24,764	£111,959	£182
AE cost for Hypertension	69.870	137.000	204.130	0.272	0.221	£24,750	£111,976	0.272	0.221	£24,783	£112,123	£147
Risk of HFS in IFN arm	0.000	0.011	0.024	0.272	0.221	£24,770	£112,109	0.272	0.221	£24,763	£111,982	£127
Utility HFS	0.642	0.680	0.742	0.272	0.221	£24,767	£112,079	0.272	0.221	£24,767	£112,003	£76
Duration HFS	30.855	60.500	90.145	0.272	0.221	£24,767	£112,031	0.272	0.221	£24,767	£112,068	£37
AE cost for HFS	130.356	255.600	380.844	0.272	0.221	£24,766	£112,045	0.272	0.221	£24,768	£112,055	£10
Duration Asthenia/Fatigue	29.019	56.900	84.781	0.272	0.221	£24,767	£112,050	0.272	0.221	£24,767	£112,050	£0
AE cost for Fatigue/Asthenia	41.565	81.500	121.435	0.272	0.221	£24,767	£112,050	0.272	0.221	£24,767	£112,050	£0
Utility Asthenia/Fatigue	0.521	0.600	0.781	0.272	0.221	£24,767	£112,050	0.272	0.221	£24,767	£112,050	£0

HR: Hazard ratio, PFS: Progression free survival, Tivo: Tivozanib, IFN: Interferon, OS: Overall survival, PPS: Post progression survival, AE: Adverse event, HFS: Hand foot syndrome

Figure 29: DSA (tornado diagram) tivozanib versus IFN (tivozanib list price)



5.8.2.2 Versus sunitinib

Table 83: Deterministic analysis - tivozanib (list price) versus sunitinib

				Low estimate				High estimate				
Variable	**Lower**	**Base Case**	**Upper**	**Inc LYs**	**Inc QALYs**	**Inc Cost**	**ICER**	**Inc LYs**	**Inc QALYs**	**Inc Cost**	**ICER**	**Spread**
HR OS TIVO vs SUN	0.549	0.925	1.557	1.017	0.664	£26,293	£39,621	-0.945	-0.612	-£33,117	£54,157	£14,535
Weekly follow up cost in PPS	23.715	46.500	69.285	0.152	0.101	-£133	-£1,311	0.152	0.101	£437	£4,310	£5,621
HR PFS TIVO vs. SUN	0.762	1.050	1.451	0.152	0.130	£67	£513	0.152	0.064	£282	£4,386	£3,873
AE cost for Anaemia	207.825	407.500	607.175	0.152	0.101	£264	£2,598	0.152	0.101	£41	£401	£2,197
Weekly follow up cost in PFS	102.680	201.333	280.457	0.152	0.101	£230	£2,271	0.152	0.101	£89	£881	£1,390
Risk of Asthenia/Fatigue in SUN arm	0.067	0.104	0.142	0.152	0.101	£189	£1,881	0.152	0.102	£115	£1,124	£757
Risk of Asthenia/Fatigue in TIVO arm	0.063	0.100	0.137	0.152	0.102	£116	£1,131	0.152	0.101	£189	£1,873	£742
Risk of Anaemia in SUN arm	0.538	0.598	0.658	0.152	0.101	£176	£1,752	0.152	0.102	£128	£1,251	£501
Utility PPS	0.613	0.650	0.687	0.152	0.094	£152	£1,626	0.152	0.109	£152	£1,391	£234
Utility Anaemia	0.529	0.610	0.769	0.152	0.106	£152	£1,434	0.152	0.092	£152	£1,648	£214
Risk of Anaemia in TIVO arm	0.016	0.040	0.064	0.152	0.102	£142	£1,400	0.152	0.101	£162	£1,600	£200
AE cost for HFS	130.356	255.600	380.844	0.152	0.101	£162	£1,597	0.152	0.101	£142	£1,402	£195
Risk of HFS in SUN arm	0.063	0.099	0.135	0.152	0.101	£161	£1,596	0.152	0.102	£143	£1,404	£192
Risk of Hypertension in TIVO arm	0.216	0.270	0.324	0.152	0.102	£145	£1,421	0.152	0.101	£160	£1,579	£158
Risk of Hypertension in SUN arm	0.191	0.244	0.296	0.152	0.101	£159	£1,576	0.152	0.102	£145	£1,423	£153
Duration Anaemia	19.125	37.500	55.875	0.152	0.098	£152	£1,551	0.152	0.105	£152	£1,451	£100
Risk of HFS in TIVO arm	0.003	0.020	0.037	0.152	0.102	£148	£1,455	0.152	0.101	£156	£1,545	£90
AE cost for Hypertension	69.870	137.000	204.130	0.152	0.101	£150	£1,482	0.152	0.101	£154	£1,517	£35
Utility HFS	0.642	0.680	0.742	0.152	0.102	£152	£1,492	0.152	0.101	£152	£1,512	£19
Duration HFS	30.855	60.500	90.145	0.152	0.101	£152	£1,504	0.152	0.102	£152	£1,495	£9
Utility Hypertension	0.604	0.660	0.744	0.152	0.101	£152	£1,502	0.152	0.102	£152	£1,496	£6
Utility PFS (No AEs)	0.709	0.730	0.751	0.152	0.101	£152	£1,502	0.152	0.102	£152	£1,497	£5
AE cost for Fatigue/Asthenia	41.565	81.500	121.435	0.152	0.101	£156	£1,541	0.152	0.101	£156	£1,538	£3
Duration Hypertension	20.502	40.200	59.898	0.152	0.102	£152	£1,498	0.152	0.101	£152	£1,501	£3
Utility Asthenia/Fatigue	0.521	0.600	0.781	0.152	0.102	£152	£1,499	0.152	0.101	£152	£1,501	£3
Duration Asthenia/Fatigue	29.019	56.900	84.781	0.152	0.101	£152	£1,500	0.152	0.101	£152	£1,499	£1
HR: Hazard ratio, PFS: Progression free survival, TIVO: Tivozanib, SUN: Sunitinib, OS: Overall survival, PPS: Post progression survival AE: Adverse event, HFS: Hand foot syndrome												

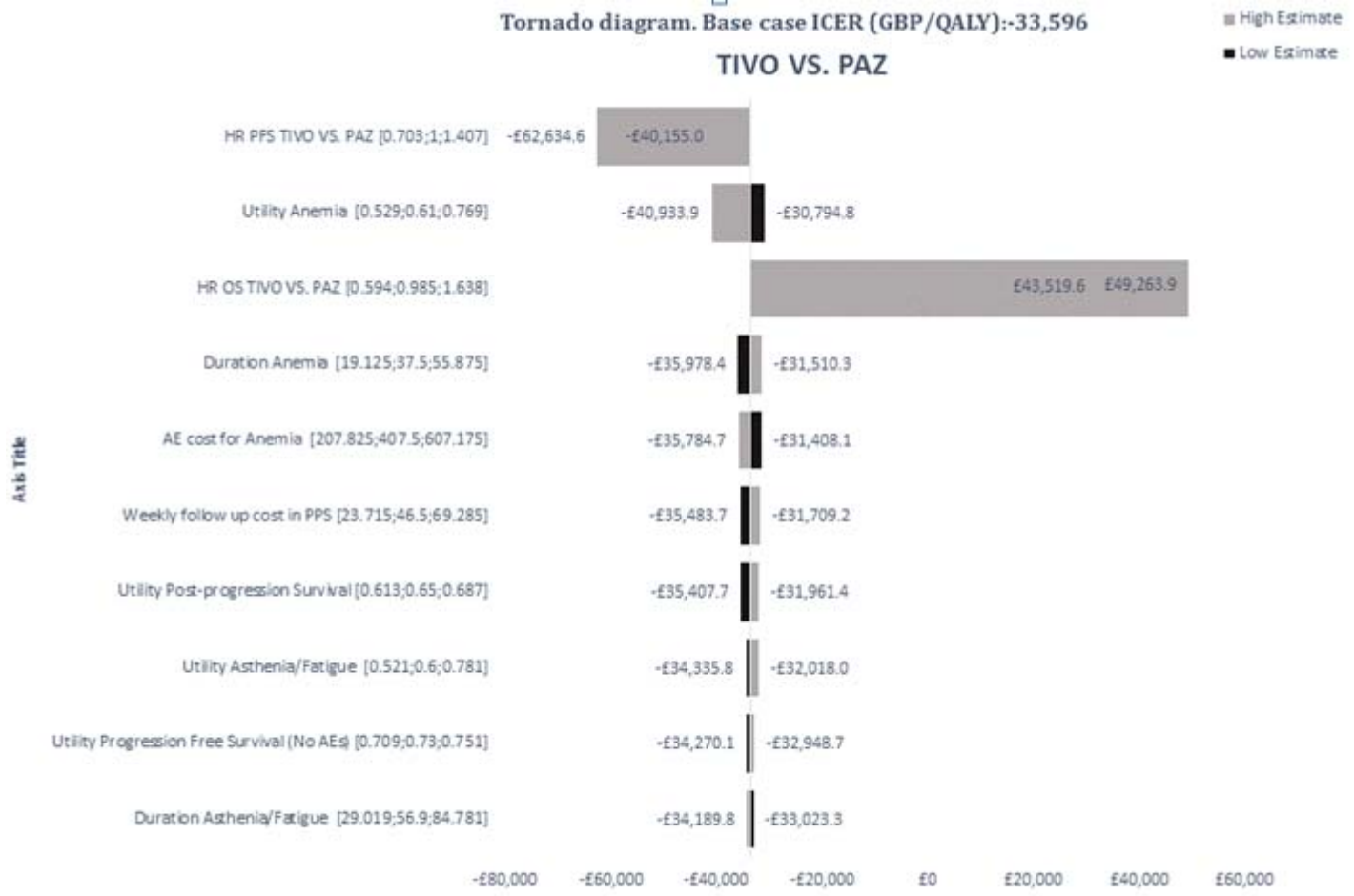
Figure 30: DSA (tornado diagram) tivozanib versus sunitinib (tivozanib list price)

5.8.2.3 Versus pazopanib

Table 84: Deterministic analysis - tivozanib (list price) versus pazopanib

				Low estimate				High estimate				
Variable	Lower	Base Case	Upper	Inc LYs	Inc QALYs	Inc Cost	ICER	Inc LYs	Inc QALYs	Inc Cost	ICER	Spread
HR PFS TIVO vs PAZ	0.703	1.000	1.407	0.031	0.052	-£2,102	-£40,155	0.031	-0.016	£997	-£62,635	£22,480
Utility Anaemia	0.529	0.610	0.769	0.031	0.024	-£742	-£30,795	0.031	0.018	-£742	-£40,934	£10,139
HR OS TIVO Vs PAZ	0.594	0.985	1.638	0.903	0.589	£25,645	£43,520	-1.059	-0.686	-£33,812	£49,264	£5,744
Duration Anaemia	19.125	37.500	55.875	0.031	0.021	-£742	-£35,978	0.031	0.024	-£742	-£31,510	£4,468
AE cost for Anaemia	207.825	407.500	607.175	0.031	0.022	-£694	-£31,408	0.031	0.022	-£791	-£35,785	£4,377
Weekly follow up cost in PPS	23.715	46.500	69.285	0.031	0.022	-£784	-£35,484	0.031	0.022	-£701	-£31,709	£3,774
Utility PPS	0.613	0.650	0.687	0.031	0.021	-£742	-£35,408	0.031	0.023	-£742	-£31,961	£3,446
Utility Asthenia/Fatigue	0.521	0.600	0.781	0.031	0.022	-£742	-£34,336	0.031	0.023	-£742	-£32,018	£2,318
Utility PFS (No AEs)	0.709	0.730	0.751	0.031	0.022	-£742	-£34,270	0.031	0.023	-£742	-£32,949	£1,321
Duration Asthenia/Fatigue	29.019	56.900	84.781	0.031	0.022	-£742	-£33,023	0.031	0.022	-£742	-£34,190	£1,166
Risk of Asthenia/Fatigue in TIVO arm	0.063	0.100	0.137	0.031	0.023	-£779	-£34,107	0.031	0.021	-£706	-£33,050	£1,057
Risk of Asthenia/Fatigue in PAZ arm	0.032	0.061	0.091	0.031	0.022	-£713	-£33,163	0.031	0.023	-£772	-£34,008	£845
Utility HFS	0.642	0.680	0.742	0.031	0.022	-£742	-£33,331	0.031	0.022	-£742	-£34,034	£703
Risk of Hypertension in TIVO arm	0.216	0.270	0.324	0.031	0.023	-£750	-£33,303	0.031	0.022	-£735	-£33,901	£597
Utility Hypertension	0.604	0.660	0.744	0.031	0.022	-£742	-£33,836	0.031	0.022	-£742	-£33,247	£589
Risk of Hypertension in PAZ arm	0.192	0.245	0.297	0.031	0.022	-£735	-£33,891	0.031	0.023	-£750	-£33,312	£578
Duration HFS	30.855	60.500	90.145	0.031	0.022	-£742	-£33,769	0.031	0.022	-£742	-£33,426	£343
AE cost for HFS	130.356	255.600	380.844	0.031	0.022	-£739	-£33,439	0.031	0.022	-£746	-£33,754	£315
Duration Hypertension	20.502	40.200	59.898	0.031	0.022	-£742	-£33,452	0.031	0.022	-£742	-£33,742	£289
AE cost for Hypertension	69.870	137.000	204.130	0.031	0.022	-£744	-£33,673	0.031	0.022	-£741	-£33,520	£153
AE cost for Fatigue/Asthenia	41.565	81.500	121.435	0.031	0.022	-£779	-£35,271	0.031	0.022	-£776	-£35,132	£140
Risk of HFS in PAZ arm	0.022	0.048	0.074	0.031	0.022	-£736	-£33,624	0.031	0.022	-£749	-£33,570	£54
Risk of HFS in TIVO arm	0.003	0.020	0.037	0.031	0.022	-£747	-£33,579	0.031	0.022	-£738	-£33,614	£35
Risk of Anaemia in PAZ arm	0.227	0.282	0.337	0.031	0.021	-£720	-£33,614	0.031	0.023	-£765	-£33,580	£33
Risk of Anaemia in TIVO arm	0.016	0.040	0.064	0.031	0.022	-£752	-£33,589	0.031	0.022	-£733	-£33,604	£14
Weekly follow up cost in PFS	102.680	201.333	280.457	0.031	0.022	-£742	-£33,596	0.031	0.022	-£742	-£33,596	£0
HR: Hazard ratio, PFS: Progression free survival, TIVO: Tivozanib, PAZ: Pazopanib, OS: Overall survival, PPS: Post progression survival AE: Adverse event, HFS: Hand foot syndrome												

Figure 31: DSA (tornado diagram): tivozanib versus pazopanib (tivozanib list price)



5.8.3 Scenario analysis

5.8.3.1 Methods

Four scenario analyses were carried out, all of which explored the impact on ICERs based on the list price.

(a) Use of alternate utility for pre-progression and post-progression health states

The utilities chosen for the base case utilities were based on an analysis of EQ-5D results obtained during the course of the TIVO-1 studies. Although these reflect typical values reported in the literature, previous NICE appraisals for sunitinib (TA169)[2] and pazopanib (TA215)[1] used different utility estimates. Scenario analyses were carried out to explore the impact of these alternative values. As AE utilities are based on a fixed decrement on the pre-progression utility value, this scenario will also incorporate appropriately varied values for this element.

Table 85: Health state utility scenarios

	Base case	Utilities from TA169	Utilities from TA 215
Pre-progression	0.73	0.78	0.70
Post-progression	0.65	0.70	0.59

(b) Reduction in post-progression treatment costs

In the base case we assumed that 60% of all patients were treated with axitinib post-progression, in line with input from our clinical advisors and current NICE guidance (TA333)[3]. There are a number of uncertainties around this assumption:

- The proportion of patients not receiving second-line therapy is uncertain, as no published national statistics exist.
- Not all patients will remain on targeted therapy from the point of progression until death.
- Some patients may be treated with other targeted therapies (eg nivolumab, mTOR inhibitors) which have lower costs than axitinib.

We consequently explored two scenarios in which post-progression medication costs were altered to explore the impact of these uncertainties:

a) The mean cost of second-line treatment was reduced by 50% to explore the impact of the use of cheaper drugs and/or treatment withdrawal prior to death.

b) The proportion of patients receiving second-line therapy with axitinib was increased to 90% to explore the impact of greater than expected use of second-line targeted therapy.

(c) Efficacy estimates derived from all patients treated in trials

In order to accurately address the NICE scope for this appraisal, PFS and OS estimates in the base case have been derived from treatment naïve patients only. As it is possible that some patients considered for treatment may have been previously treated with immunotherapy, however, we re-ran the MTC that drives the efficacy estimates based on all patients recruited and used these estimates of treatment effect as a scenario analysis. It should be noted that all the included trials excluded patients who had previously been treated with a VEGFG-TKI or mTOR inhibitor. This scenario accurately reflects the patient population specified in the anticipated licensed indication for tivozanib.

(d) No discounting of costs or benefits

The base case analysis was carried out using a 3.5% per year discount rate applied to both costs and QALYs. This scenario explores the impact on the results of not applying a discount.

5.8.3.2 Results of scenario analyses

(a) Use of alternate utility for pre-progression and post-progression health states

Table 86: Scenario 1 results (utilities derived from TA169)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus IFN (QALYs)	ICER (£) incremental (QALYs)
At list price								
IFN	£59,585	2.756	2.002					
Sunitinib	£84,199	2.876	2.127	£24,615	0.120	0.126	£196,035	£196,035
Tivozanib	**£84,351**	**3.028**	**2.236**	**£24,767**	**0.272**	**0.235**	**£105,560**	**£1,395**
Pazopanib	£85,094	2.997	2.213	£25,509	0.241	0.211	£120,898	Dominated
ICER: Incremental cost-effectiveness ratio, LYG: Life years gained, QALYs: Quality-adjusted life years								

Table 87: Scenario 1 results (utilities derived from TA215)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus IFN (QALYs)	ICER (£) incremental (QALYs)
At list price								
IFN	£59,585	2.756	2.002					
Sunitinib	£84,199	2.876	2.127	£24,615	0.120	0.126	£196,035	£196,035

Tivozanib	**£84,351**	**3.028**	**2.236**	**£24,767**	**0.272**	**0.235**	**£105,560**	**£1,395**
Pazopanib	£85,094	2.997	2.213	£25,509	0.241	0.211	£120,898	Dominated
ICER: Incremental cost-effectiveness ratio, LYG: Life years gained, QALYs: Quality-adjusted life years								

(b) Reduction in post-progression treatment costs

Table 88: Scenario 2 results (50% reduction in post-progression medication costs)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus IFN (QALYs)	ICER (£) incremental (QALYs)
At list price								
IFN	£35,648	2.756	1.864					
Tivozanib	**£63,602**	**3.028**	**2.085**	**£27,954**	**0.272**	**0.221**	**£126,472**	**£126,472**
Pazopanib	£64,765	2.997	2.063	£29,117	0.241	0.199	£146,364	Dominated
Sunitinib	£66,380	2.876	1.983	£30,732	0.120	0.120	£256,995	Dominated
ICER: Incremental cost-effectiveness ratio, LYG: Life years gained, QALYs: Quality-adjusted life years								

Table 89: Scenario 2 results (90% uptake of post-progression axitinib)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus IFN (QALYs)	ICER (£) incremental (QALYs)
At list price								
IFN	£83,805	2.756	1.864					
Sunitinib	£102,233	2.876	1.983	£18,428	0.120	0.120	£154,105	£154,105
Tivozanib	**£105,351**	**3.028**	**2.085**	**£21,546**	**0.272**	**0.221**	**£97,477**	**£30,729**
Pazopanib	£105,668	2.997	2.063	£21,862	0.241	0.199	£109,897	Dominated
ICER: Incremental cost-effectiveness ratio, LYG: Life years gained, QALYs: Quality-adjusted life years								

(c) Efficacy estimates derived from all patients treated in trials

Table 90: Scenario 3 results (Efficacy estimates derived from all study patients)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus IFN (QALYs)	ICER (£) incremental (QALYs)
At list price								
IFN	£61,024	2.814	1.903					
Tivozanib	**£84,351**	**3.028**	**2.085**	**£23,327**	**0.214**	**0.182**	**£128,047**	**£128,047**
Sunitinib	£87,118	2.972	2.046	£26,094	0.158	0.144	£181,611	Dominated
Pazopanib	£88,484	3.104	2.129	£27,460	0.290	0.226	£121,491	£16,587
ICER: Incremental cost-effectiveness ratio, LYG: Life years gained, QALYs: Quality-adjusted life years								

(d) No discounting of costs or benefits

Table 91: Scenario 4 results (Discount rate set at 0%) – List price

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus IFN (QALYs)	ICER (£) incremental (QALYs)
At list price								
IFN	£65,533	2.991	2.019					
Tivozanib	**£89,967**	**3.236**	**2.224**	**£24,434**	**0.245**	**0.205**	**£119,390**	**£119,390**
Sunitinib	£92,715	3.172	2.180	£27,182	0.181	0.161	£168,636	Dominated
Pazopanib	£94,467	3.323	2.275	£28,934	0.332	0.256	£113,142	£18,533
ICER: Incremental cost-effectiveness ratio, LYG: Life years gained, QALYs: Quality-adjusted life years								

5.8.4 Summary of sensitivity analyses results

The results of the sensitivity analyses are consistent with the expected picture, given that the three targeted therapies (tivozanib, sunitinib and pazopanib) share similar levels of clinical efficacy and differ from in each other in costs by only small amounts.

The results of the DSA demonstrate that the over-riding variables that influence the ICERs in this comparison are those that determine the PFS and OS curves applied to each of the comparators, especially for the tivozanib versus sunitinib and tivozanib versus pazopanib. Figure 23 demonstrates that the curves for the three VEGFR-TKIs are very close to each other in the base case, in accordance with the results of the MTC that showed no significant difference between them in terms of either PFS or OS.

The impact of small changes in these curves can exert an apparently disproportionate effect on the ICERs, due in part to the fact that expenditure on post-progression therapy is a major driver of overall treatment costs (Table 74,

Table 77, Table 80 and Scenario analysis 2). Any alteration to the period between disease progression and death will consequently have a significant impact on overall costs. Given that the base case incremental QALYs between the VEGFR-TKIs are relatively small (0.022 for tivozanib versus pazopanib and 0.101 for tivozanib versus sunitinib) even a small change in overall costs for one treatment can change the ICER significantly.

This dominance of the relative efficacy estimates in the conclusions of the sensitivity analysis is reflected in the PSA scatter plots, which show a near two-dimensional scatter across the North-East – South-West axis, with little or no lateral deviation from this trend, reflecting both the dominance of the PFS and OS outcomes in this model (and relative insignificance of other input variables) and the minimal base case differences in efficacy between targeted therapies.

The distinctive peaking seen in the CEAC curves for tivozanib versus both pazopanib and sunitinib reflect the relatively high proportion of simulations that result in an ICER in the South-West quadrant (38.5% versus sunitinib and 46% versus pazopanib). Increasing the WTP threshold above around £50,000/QALY results in an increasing proportion of these values being rejected, with consequent decline in the relevant CEAC curve.

5.9 Subgroup analysis

No subgroups analyses were conducted. Given that efficacy estimates were derived from an MTC, the range of populations that could be evaluated was restricted to those results that had been published for the comparator technologies. No meaningful subgroups could be identified on this basis.

5.10 Validation

5.10.1 Validation of de novo cost-effectiveness analysis

We used a similar approach to that used in the STA for pazopanib and sunitinib[1 2], which we believe is a valid approach. Table 67 lists the assumptions made in the economic model together with justifications for each assumption.

5.11 Interpretation and conclusions of economic evidence

Tivozanib is a cost-effective treatment option versus sunitinib for the first-line treatment of advanced/metastatic RCC.

In the base case (tivozanib at list price) none of the three targeted therapies is associated with an ICER versus IFN that would be below the conventionally accepted willingness to pay threshold of £30,000/QALY (see Table 71). Of the three, tivozanib offers the lowest ICER versus IFN (£112,050/QALY).). When compared with the other targeted therapies, tivozanib is cost effective versus sunitinib, with an ICER of £1,500/QALY and dominates pazopanib.

The observed results reflect the fact that the efficacy of tivozanib is broadly similar to that of sunitinib and pazopanib and the three treatments share a similar price, once the published PAS prices for sunitinib and pazopanib are taken into account. The ICER differences seen are substantially driven by small differences in the period between disease progression and death, during which period the cost of treatment is substantial.

In the base case, tivozanib is associated with a small incremental utility versus both other VEGFR-TKI, but as expected, sensitivity analysis has shown that the final ICER is highly dependent on changes in this parameter. If one were to ignore the non-significant differences in PFS and OS and model on the basis of equal efficacy, the resulting incremental utilities and post-progression treatment costs would be near identical, with the ICER being determined almost entirely by the acquisition cost of the three drugs.

5.11.1 Are the results from this economic evaluation consistent with the published economic literature?

No published cost-effectiveness data for tivozanib was identified. However, data was identified for pazopanib[28] and sunitinib, together with their NICE STA[1 2]. The results from this economic evaluation are consistent with the STAs for pazopanib and sunitinib, which demonstrated unacceptably high ICERs versus IFN but comparable and acceptable ICERs for sunitinib and pazopanib versus supportive care in patients who were not treated with IFN.

The approach adopted in this model builds on the basis of the core models used in the previous STAs[28 29], although it also includes provision for post-progression targeted therapy, a treatment option that was not available at the time of the previous appraisals. In this regard, the results presented above can be plausibly compared with the previous models.

5.11.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem?

Tivozanib has a licence for the treatment of adult patients with advanced RCC, who have not been previously treated with targeted therapy (VEGF inhibitor or mTOR inhibitor) but who may have previously received immunotherapy (IFN-α or IL). The base case considers treatment naïve patients. Limitations of the data meant that it was not possible to include treatment experienced patients in the MTC (see Section 4.1.2), however, we have carried out a scenario analysis using the overall population (ie patients who were treatment naïve and patients who were pre-treated). This showed results that were qualitatively comparable to those derived from the treatment naïve patients only, with tivozanib dominating sunitinib and being acceptably cost effective versus pazopanib (Table 90). Whilst only a minority of patients in the overall evidence base had previously been treated with cytokines and no study evaluated this population as a primary outcome, this scenario analysis provides reassurance that the health economic performance of tivozanib is unlikely to be substantially different in a mixed population than in the treatment naïve population. It is important to note that in clinical practice almost all patients with advanced disease receive pazopanib or sunitinib and very few patients receive cytokines. Indeed, as first-line VEGFR-TKI has now been in regular use in England since March 2009, the number of cytokine-treated patients in the population who are still to progress and become eligible for targeted therapy is now so small as to be insignificant (see **Section 3.7 Issues relating to current clinical practice** for further elaboration and sources of evidence).

We did not include comparisons with all of the agents outlined in the scope and our rationale for doing so is discussed in **Section 3.7 Issues relating to current clinical practice.**

5.11.3 How relevant (generalisable) is the analysis to clinical practice in England?

The cost-effectiveness analysis is generalisable to clinical practice in England. We have used UK data wherever possible for inputs into the model and have taken advice from UK clinicians practising in the field for the costs of managing RCC.

Given that the pivotal trial for tivozanib compares tivozanib with sorafenib[11] and there is no direct head to head comparative data for tivozanib versus IFN, pazopanib or sunitinib we have used data from a MTC to inform the model. The studies used in the MTC included patients from around the world, including the UK. We believe that the patient populations in the included studies are similar to the UK population. The median age of patients in TIVO-1 was 59 years; most patients were male and white and the most common metastatic sites were lung and lymph nodes. Patient characteristics in the pivotal trials for pazopanib[17] and sunitinib[27] were similar and we believe reflect the characteristics of patients with advanced or metastatic RCC in the UK.

5.11.4 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

5.11.4.1 Strengths

The decision problem was consistent with the NICE scope, with a clear rationale given for the exclusion of some comparators included in the scope (**Section 3.7 Issues relating to current clinical practice)**. Comparators included all therapies routinely used in the NHS, including technologies regarded as current best practice according to clinical advisors and a recent registry study[5]. An NHS perspective on costs was employed (PPS costs were assumed to be unaffected by the technology).

All relevant health effects were considered (PFS, OS and AEs). A cost effectiveness analysis was employed, with QALYs as the primary measure of health benefits. The primary source of data for measurement of HRQOL was data from patients in TIVO-1[11]. The detailed results of EQ-5D-derived utilities from TIVO-1 have not been published but, using the

individual patient data from the trial, we were able to derive estimates for utilities for both pre-progression and post-progression health states.

A 3.5% annual discount rate was used for costs and health effects in the calculation of cost-effectiveness. An additional QALY was given the same weight regardless of the other characteristics of the individuals receiving the health benefit

The cost effectiveness model was developed using established methodology that was used previously to evaluate the cost-effectiveness of sunitinib and pazopanib in prior NICE technology assessments[1 2 28 29].

Given that the pivotal trial for tivozanib compares tivozanib with sorafenib[11] and there is no direct head to head comparative data for tivozanib versus IFN, pazopanib or sunitinib we have used data from a MTC to inform the model. This methodology maintains randomisation across studies and is not associated with the limitations inherent in naïve or unadjusted indirect comparisons.

Goodness of fit of Weibull survival distributions used in the model was explored. Validity of proportional hazards assumption required by model was examined.

Costs of services were based on NHS reference costs where appropriate.

5.11.4.2 Limitations

Like the previously published economic models for pazopanib and sunitinib the cost-effectiveness analysis is based on several assumptions. As discussed earlier in this dossier, estimates of comparative efficacy and safety were based on a MTC. Lack of data meant that in order to include IFN in the network for treatment naïve patients we had to use data from the overall study population (treatment naïve and pretreated patients) in TARGET[67] which compared sorafenib with placebo to enable two routes linking tivozanib and IFN. We recognise that this is a limitation of our work, however, have taken a pragmatic approach in order to include OS with IFN in the MTC.

Within the MTC for PFS one clinical trial comparing sorafenib with placebo yielded results that were discordant with the rest of the network[73]. The consequence was that the estimated HRs for tivozanib versus all three comparators were higher than would have been the case if this study had been excluded. However, in order to avoid an implication of cherry-picking, we chose to base the model on the total network, without making any exclusions. This

conservative approach may have disadvantaged tivozanib but was considered to be the most transparent and appropriate strategy.

As outlined in the clinical section, the OS results for the TIVO-1 study are substantially impacted by a post-progression one-way crossover from the tivozanib arm to the sorafenib arm, even though the difference in OS remained non-significant. Correcting for this effect yielded OS survival curves in the two arms that were essentially identical (see Figure 9). For the purposes of the MTC however, from which the survival estimates for the model were drawn, the original ITT analysis was used. This decision reflected the fact that, for many of the comparator studies included in the MTC, although post-progression crossover may have occurred, formal corrected analyses were not available for most. Analysis based on corrected results for some studies but not others would have introduced uncontrollable bias and was consequently not undertaken. It is likely that, had the corrected OS data for tivozanib been used, more favourable ICER results would have been obtained. The approach adopted can therefore be considered conservative.

We modelled costs of post-progression treatment with axitinib, in line with current NICE guidance for the treatment of advanced RCC and advice from clinical experts, however, there is considerable uncertainty associated with these assumptions. A significant proportion of overall treatment costs is attributable to post-progression treatment as the cost of axitinib is substantially greater than any of the primary treatments modelled. Our clinical advisor advised that 60% of patients with progression will go on to further targeted therapy – an estimate that is considerably greater than that assumed in the budget impact analysis that accompanies the NICE axitinib guidance[3]. We explored these assumptions as scenario analyses and identified that reduced use of axitinib substantially improves the ICERs for tivozanib versus the other VEGFR-TKIs. The approach adopted in the base case can therefore be regarded as a conservative scenario.

Data on costs were not collected during the clinical trials, therefore we have used costs estimated from secondary sources, all of which are UK based and validated by a clinical expert. Costs of comparator VEGFR-TKIs were based on the published PAS discounts applied for the NHS, rather than the list price. This was felt to best reflect the current budgetary context for the NHS but may be regarded as a conservative assumption. Had we used the full list price for sunitinib and pazopanib, the results would have been substantially more favorable for tivozanib.

5.11.5 What further analyses could be carried out to enhance the robustness or completeness of the results?

The sensitivity analyses presented in this document are an attempt to evaluate the impact of uncertainties in the underlying data; however, it is inevitable that some uncertainty will remain. The key aspect of the model that remains subject to significant uncertainty is the impact of post-progression treatment costs. Ideally the handling of this issue would have been based on the pattern of current UK clinical practice. Unfortunately the most recently published data only cover the period 2009-2012[5]. Given that this is a rapidly changing therapeutic area, these are unlikely to reflect the current true picture. In the absence of more recent analysis, this uncertainty has to remain.

6 Assessment of factors relevant to the NHS and other parties

- Based on published epidemiological data and assumptions used in previous NICE STAs, we estimate that there are 3,297 patients per year in England, who would be considered eligible for treatment with first-line VEGFR-TKI. Our clinical advisors suggest that approximately 90% of these will currently be treated, equating to 2,967 patients per year.
- The budget impact model assumes that those patients who receive first-line VEGFR-TKI will receive either pazopanib, sunitinib or tivozanib.
- The budget impact of tivozanib in year 1 (2017) will be a cumulative saving of [redacted] at the list price.
- The budget impact of tivozanib in year 5 (2021) will be a cumulative saving of [redacted] at the list price.

6.1 Burden of disease

Based on published epidemiological data and assumptions used in previous NICE STAs, we estimate that there are 3,297 patients per year in England, who would be considered eligible for treatment with first-line VEGFR-TKI (Table 92). Our clinical advisors suggest that approximately 90% of these will currently be treated, equating to 2,967 patients per year.

Table 92: Number of patients suitable for treatment with tivozanib

	Number	**Data source**
Number of people with new kidney cancer diagnoses in England	9,023	Office for National Statistics[351]
86% of kidney cancer patients have RCC	7,760	Cancer Research[36]
44% of RCC patients have advanced or metastatic disease at presentation	3,414	National Cancer Registration and Analysis Service[48]
Of the remaining 56% who present with localised disease, 33% will relapse following surgical treatment	1,434	Cohen & McGovern[49]; cited in NICE TA169[50]
Total patients in England with advanced or metastatic RCC	4,848	3,414 + 1,434
68% of patients have an ECOG score of 0-1 and are eligible for first-line treatment with first-line VEGFR-TKI	3,297	Elson et al[51]; cited in NICE TA169[50]
90% of eligible patients currently receive treatment with first-line VEGFR-TKI	**2,967** (32.9% of all new kidney cancer cases)	Personal communication Dr Robert Jones

6.2 Assumptions for budget impact assessment

6.2.1 Current treatments

Currently there are three options approved by NICE for the first-line treatment of patients with advanced or metastatic RCC: sunitinib, pazopanib and IFN. As discussed in **Section 3.7 Issues relating to current clinical practice.** IFN is now used very rarely in this indication. This is borne out by the RECCORD registry that reviewed treatment options is this patient group[5]. Based on an analysis of registry data from seven UK centres, looking at RCC patients treated between 2009 and 2012, they found that 90.3% of patients were treated with sunitinib or pazopanib, 1.0% with IFN or IL, with the remainder receiving other VEGFR-TKI or mTOR inhibitors. As it is unlikely that the percentage of patients receiving immunotherapy has increased in the intervening 5 years, for the purposes of this budget impact analysis we have assumed that all patients will be treated with targeted therapy using VEGFR-TKI, with 90% receiving sunitinib or pazopanib, the comparators used for the economic analysis.

6.2.2 Current treatment costs

The current cost of pazopanib in England, including PAS, is £457.73 per week.

The current cost of sunitinib in England, including PAS is zero for the first 6 weeks, then £784.70 per week for 4 weeks, followed by 2 weeks untreated.

Based on the median PFS for tivozanib from the TIV0-1 study (11.9 months), we can estimate that median total treatment cost for pazopanib is £23,802 and for sunitinib is £24,326.

There are no publicly available data to identify the relative proportions of eligible RCC patients receiving sunitinib and pazopanib. The RECCORD registry [5] covered a period largely before the NICE approval of pazopanib, so gives little insight into the current market. Equally, sales data for the two VEGFR-TKI are unhelpful, as sunitinib is also indicated in other types of cancer. However, given the similarity in median cost for the two treatments, it is unlikely that the results of our budget impact assessment will be significantly affected by the market split. In the absence of definitive data, we have taken the anticipated market share of 40% quoted by the manufacturer of pazopanib in their submission to NICE in 2011[29], with the remainder of prescribing being attributable to sunitinib.

6.2.3 Cost and market share for tivozanib

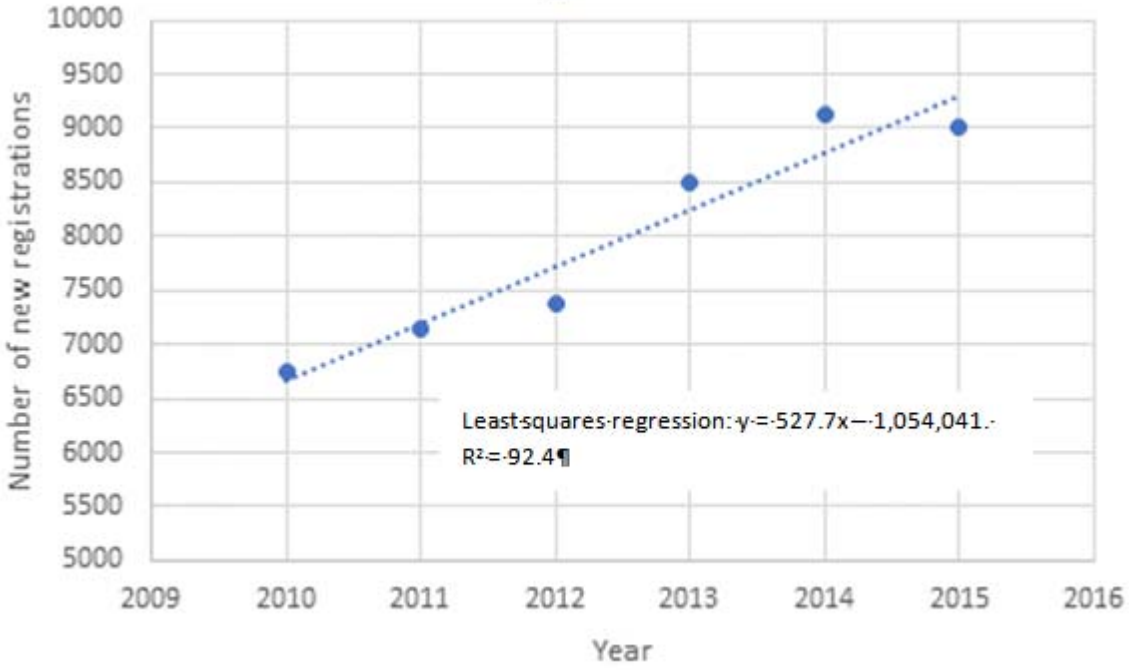
Based on the proposed list price, the cost of tivozanib treatment is expected to be [redacted] per week for 3 weeks followed by 1 week untreated. On this basis, the median overall treatment cost per patient with tivozanib is [redacted]

Market share is expected to be 3% in year 1 rising to 15% by year 5.

6.2.4 RCC incidence trends

Over the period 2010-2015 the number of new cancer registrations for kidney cancers in England has risen by approximately 5.5% per year (Figure 32).

Figure 32: New registrations for kidney cancer: England 2010-2015[35 115]



Extrapolating the observed trend forward, we can estimate the number of new registrations anticipated over the period 2017-21. Applying the limits described in Table 92 above, we have arrived at forward estimates of the number of patients eligible for treatment with tivozanib over the same period (Table 93), based on an assumption that tivozanib will displace sunitinib and pazopanib in proportion to their current usage.

Table 93: Projected budget impact of tivozanib use within the NHS in England: 2017-2021

	2017	2018	2019	2020	2021
New kidney cancer cases[1]	10,359	10,886	11,414	11,942	12,470
Patients likely to be treated with VEGF inhibitor[2]	3,406	3,580	3,753	3,927	4,100
Cost of pazopanib treatment[3]	£32,430,282	£34,082,410	£35,734,539	£37,386,667	£39,038,795
Cost of sunitinib treatment[3]	£49,716,350	£52,249,100	£54,781,849	£57,314,599	£59,847,348
Cost based on current treatments[4]	£82,155,489	£86,340,818	£90,526,146	£94,711,475	£98,896,804
Tivozanib market share[5]	3%	6%	9%	12%	15%
Number of patients treated with tivozanib[6]	102	215	338	471	615
Analysis based on list price					
Cost of tivozanib treatment[7]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall cost based on tivozanib use[8]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Net saving[9]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cumulative saving[10]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Notes

1. Based on linear extrapolation of Office for National Statistics cancer registration statistics for England 2010-2015
2. Based on 32.9% of all kidney cancer patients treated with VEGFR-TKI (from Table 92)
3. Based on 12 months treatment at current NHS prices for pazopanib and sunitinib (including PAS)
4. Assuming 40%:60% market split between pazopanib and sunitinib
5. Assumption from EUSA Pharma
6. Market share multiplied by number of treated patients
7. Based on 12 months treatment at proposed NHS price
8. Total cost based on market share of tivozanib, with remainder of patients treated with pazopanib and sunitinib
9. Total cost using tivozanib, pazopanib and sunitinib subtracted from total cost using pazopanib and sunitinib
10. Cumulative saving of the 5-year projected period

7 References

1. National Institute for Health and Care Excellence. Pazopanib for the first-line treatment of advanced renal cell carcinoma. NICE technology appraisal guidance 215. Available at http://www.nice.org.uk/Guidance/TA215, 2011.
2. National Institute for Health and Care Excellence. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. NICE technology appraisal guidance TA169. Available at http://www.nice.org.uk/Guidance/TA169., 2009.
3. National Institute for Health and Care Excellence. Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment. NICE technology appraisal guidance 333. Available at http://www.nice.org.uk/Guidance/TA333., 2015.
4. National Institute for Health and Care Excellence. Nivolumab for previously treated advanced renal cell carcinoma. NICE technology appraisal guidance TA417. Available at https://www.nice.org.uk/guidance/ta417/resources/nivolumab-for-previously-treated-advanced-renal-cell-carcinoma-82604608264645, 2016.
5. Wagstaff J, Jones R, Hawkins R, et al. Treatment patterns and clinical outcomes in patients with renal cell carcinoma in the UK: insights from the RECCORD registry. *Ann Oncol* 2016;27(1):159-65. doi: 10.1093/annonc/mdv504 [published Online First: 2015/10/23]
6. Bristol Myers Squibb Ltd J. Opdivo Summary of Product Characteristics 2017 [Available from: https://www.medicines.org.uk/emc/medicine/30476.
7. National Institute for Health and Care Excellence. Everolimus for advanced renal cell carcinoma after previous treatment Technology appraisal guidance 432. Available at https://www.nice.org.uk/guidance/ta432/resources/everolimus-for-advanced-renal-cell-carcinoma-after-previous-treatment-82604720798917, 2017.
8. Novartis Pharmaceuticals UK Ltd. Afinitor Tablets Summary of Product Characteristics 2016 [Available from: http://www.medicines.org.uk/emc/medicine/22281.
9. National Institute for Health and Care Excellence. Appraisal consultation document. Cabozantinib for previously treated advanced renal cell carcinoma. Available at https://www.nice.org.uk/guidance/GID-TA10075/documents/appraisal-consultation-document-2, 2017.
10. Ipsen. Cabometyx Summary of Product Characteristics 2016 [Available from: http://www.medicines.org.uk/emc/medicine/32431.
11. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. *J Clin Oncol* 2013;31(30):3791-9. doi: 10.1200/jco.2012.47.4940 [published Online First: 2013/09/11]
12. EUSA Pharma (UK) Limited. Draft Summary of Product Characteristics for Fotivda (tivozanib), 2017.
13. EUSA Pharma (UK) Limited. Data on file (post-hoc analysis of PFS adjusted for baseline demographics and geographical region), 2017.
14. Nosov DA, Esteves B, Lipatov ON, et al. Antitumor activity and safety of tivozanib (AV-951) in a phase II randomized discontinuation trial in patients with renal cell carcinoma. *J Clin Oncol* 2012;30(14):1678-85. doi: 10.1200/jco.2011.35.3524 [published Online First: 2012/04/12]

15. AVEO Pharmaceuticals I. Clinical study report Protocol AV-951-10-202. A Phase 2 and Biomarker Study of Tivozanib in Subjects With Advanced Renal Cell Carcinoma 2015.
16. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. *N Engl J Med* 2013;369(8):722-31. doi: 10.1056/NEJMoa1303989 [published Online First: 2013/08/24]
17. Sternberg CN, Davis ID, Mardiak J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2010;28(6):1061-8. doi: 10.1200/jco.2009.23.9764 [published Online First: 2010/01/27]
18. Motzer RJ, Hutson TE, Tomczak P, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27(22):3584-90. doi: 10.1200/jco.2008.20.1293 [published Online First: 2009/06/03]
19. AVEO Pharmaceuticals I. Clinical study report protocol AV-951-09-301. A phase 3, randomized, controlled, multi center, open-label study to compare tivozanib (AV 951) to sorafenib in subjects with advanced renal cell carcinoma., 2016.
20. Sternberg CN, Hawkins RE, Wagstaff J, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. *Eur J Cancer* 2013;49(6):1287-96. doi: 10.1016/j.ejca.2012.12.010 [published Online First: 2013/01/17]
21. Porta C, Levy A, Hawkins R, et al. Impact of adverse events, treatment modifications, and dose intensity on survival among patients with advanced renal cell carcinoma treated with first-line sunitinib: a medical chart review across ten centers in five European countries. *Cancer Medicine* 2014;3(6):1517-26. doi: 10.1002/cam4.302
22. Mohamed AF, Hauber AB, Neary MP. Patient benefit-risk preferences for targeted agents in the treatment of renal cell carcinoma. *Pharmacoeconomics* 2011;29(11):977-88. doi: 10.2165/11593370-000000000-00000 [published Online First: 2011/08/23]
23. Rini BI, Cohen DP, Lu DR, et al. Hypertension as a biomarker of efficacy in patients with metastatic renal cell carcinoma treated with sunitinib. *J Natl Cancer Inst* 2011;103(9):763-73. doi: 10.1093/jnci/djr128 [published Online First: 2011/04/30]
24. Hamnvik OP, Choueiri TK, Turchin A, et al. Clinical risk factors for the development of hypertension in patients treated with inhibitors of the VEGF signaling pathway. *Cancer* 2015;121(2):311-9. doi: 10.1002/cncr.28972 [published Online First: 2014/09/23]
25. Cella D, Ivanescu C, Esteves B, et al. Treatment benefit of tivozanib hydrochloride vs sorafenib on health-related quality of life among patients with advanced/metastatic renal cell carcinoma (mRCC): TIVO-1 study results, 2017.
26. National Institute for Health and Care Excellence. Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma. NICE technology appraisal guidance 178. Available at http://www.nice.org.uk/Guidance/TA178, 2009.

27. Motzer RJ, Hutson TE, Tomczak P, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. *N Engl J Med* 2007;356(2):115-24. doi: http://dx.doi.org/10.1056/NEJMoa065044
28. Kilonzo M, Hislop J, Elders A, et al. Pazopanib for the first-line treatment of patients with advanced and/or metastatic renal cell carcinoma : a NICE single technology appraisal. *Pharmacoeconomics* 2013;31(1):15-24. doi: 10.1007/s40273-012-0006-5 [published Online First: 2013/01/19]
29. Glaxo Smith Kline. Pazopanib (Votrient®) for the first-line treatment of patients with advanced renal cell carcinoma (RCC). Manufacturer's submission 2010.
30. Cowey CL. Profile of tivozanib and its potential for the treatment of advanced renal cell carcinoma. *Drug Des Devel Ther* 2013;7:519-27. doi: 10.2147/dddt.s31442 [published Online First: 2013/07/03]
31. Mulders P. Vascular endothelial growth factor and mTOR pathways in renal cell carcinoma: differences and synergies of two targeted mechanisms. *BJU Int* 2009;104(11):1585-9. doi: 10.1111/j.1464-410X.2009.08987.x [published Online First: 2010/01/08]
32. Bhargava P, Robinson MO. Development of second-generation VEGFR tyrosine kinase inhibitors: current status. *Curr Oncol Rep* 2011;13(2):103-11. doi: 10.1007/s11912-011-0154-3 [published Online First: 2011/02/15]
33. Novartis Pharmaceuticals UK Ltd. Summary of Product Characteristics Votrient 200 mg and 400 mg film coated tablets 2106 [updated 27 Jan 2016. Available from: http://www.medicines.org.uk/emc/medicine/231482016.
34. Pfizer Limited. Summary of Product Characteristics SUTENT 12.5mg, 25mg, 37.5mg and 50mg Hard Capsules 2016 [updated 1 April 2016. Available from: http://www.medicines.org.uk/emc/medicine/18531/SPC2016.
35. Office for National Statistics. Cancer registration statistics England: First release, 2015. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/firstrelease2015, 2017.
36. Cancer Research UK. Kidney cancer statistics. Avaiulable at http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer/incidence#heading-Four 2016 [Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer.
37. Rini BI, Campbell SC, Escudier B. Renal cell carcinoma. *Lancet* 2009;373(9669):1119-32. doi: 10.1016/s0140-6736(09)60229-4 [published Online First: 2009/03/10]
38. Ljungberg B, Bensalah K, Bex A, et al. Guidelines on renal cell carcinoma. European Association of Urology. , 2015.
39. Swinburn P, Lloyd A, Nathan P, et al. Elicitation of health state utilities in metastatic renal cell carcinoma. *Curr Med Res Opin* 2010;26(5):1091-6. doi: 10.1185/03007991003712258 [published Online First: 2010/03/17]
40. Cella D. Beyond traditional outcomes: improving quality of life in patients with renal cell carcinoma. *Oncologist* 2011;16 Suppl 2:23-31. doi: 10.1634/theoncologist.2011-S2-23 [published Online First: 2011/03/05]
41. Health and Social Care Information Centre. Hospital Episode Statistics, Admitted Patient Care - England, 2014-15 2015 [Available from: http://www.hscic.gov.uk/hesdata.

42. Hagiwara M, Hackshaw MD, Oster G. Economic burden of selected adverse events in patients aged >/=65 years with metastatic renal cell carcinoma. *J Med Econ* 2013;16(11):1300-6. doi: 10.3111/13696998.2013.838570 [published Online First: 2013/09/06]
43. Escudier B, Porta C, Schmidinger M, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016;27(suppl 5):v58-v68. doi: 10.1093/annonc/mdw328 [published Online First: 2016/09/25]
44. Heng DY, Xie W, Regan MM, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. *J Clin Oncol* 2009;27(34):5794-9. doi: 10.1200/jco.2008.21.4809 [published Online First: 2009/10/15]
45. Hagiwara M, Borker R, Oster G. Economic burden of adverse events in patients with metastatic renal cell carcinoma. *Clin Ther* 2013;35(12):1955-63.e2. doi: 10.1016/j.clinthera.2013.10.010 [published Online First: 2013/12/03]
46. Mickisch G, Gore M, Escudier B, et al. Costs of managing adverse events in the treatment of first-line metastatic renal cell carcinoma: bevacizumab in combination with interferon-alpha2a compared with sunitinib. *Br J Cancer* 2010;102(1):80-6. doi: 10.1038/sj.bjc.6605417 [published Online First: 2009/11/19]
47. National Institute for Health and Care Excellence. NICE Pathways: Renal cancer overview 2017 [Available from: https://pathways.nice.org.uk/pathways/renal-cancer.
48. National Cancer Registration and Analysis Service. Cancer breakdown by stage 2014. Available at: http://www.ncin.org.uk/view?rid=3006 2016.
49. Cohen HT, McGovern FJ. Renal-cell carcinoma. *N Engl J Med* 2005;353(23):2477-90. doi: 10.1056/NEJMra043172 [published Online First: 2005/12/13]
50. National Institute for Health and Care Excellence. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. Costing template and report. Avaiable at https://www.nice.org.uk/guidance/ta169/resources, 2009.
51. Elson PJ, Witte RS, Trump DL. Prognostic factors for survival in patients with recurrent or metastatic renal cell carcinoma. *Cancer Res* 1988;48(24 Pt 1):7310-3. [published Online First: 1988/12/15]
52. National Institute for Health and Care Excellence. Everolimus for the second-line treatment of advanced renal cell carcinoma. NICE technology appraisal guidance 219. Available at http://www.nice.org.uk/Guidance/TA219., 2011.
53. National Institute for Health and Care Excellence. Single Technology Appraisal Tivozanib for treating renal cell carcinoma Final scope, 2017.
54. Hutson TE, Rathmell WK, Feng B, et al. Phase 2 clinical evaluation of preclinically defined biomarkers for vascular endothelial growth factor tyrosine kinase inhibitor tivozanib in renal cell carcinoma. *Ann Oncol* 2014;25(Supplement 4):iv58-iv64.
55. Overall survival results from a phase III study of tivozanib hydrochoride versus sorafenib in patients with renal cell carcinoma (poster). American Society of Clinical Oncology Genitourinary Symposium 2013; Orlando, Florida

56. Tivozanib versus sorafenib as initial targeted therapy for patients with advanced renal cell carcinoma: Results from a Phase III randomized, open-label, multicenter trial (Abstract 4501) Oral presentation. Annual Meeting of American Society of Clinical Oncology (ASCO); 2012; Chicago.
57. Tivozanib vs sorafenib targeted therapy for advanced renal cell carcinoma: Final results of a phase III trial (901) and efficacy results of a 2nd line tivozanib extension study (902). (Poster). Amercian Society of Oncology Annual Meeting 2015; Chicago, Illinois.
58. AVEO Pharmaceuticals I. Clinical study report AV-951-07-201 A phase 2, placebo-controlled, randomized, discontinuation trial of tivozanib (AV-951) in patients with renal cell carcinoma., 2011.
59. Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial (Protocol). *J Clin Oncol* 2013. http://jco.ascopubs.org.www.socprox.net/content/suppl/2013/09/09/JCO.2012.47.4940.DC1/Protocol_JCO.2012.47.4940.pdf.
60. Motzer R, Eisen T, Hutson TE, et al. Overall survival results from a phase III study of tivozanib hydrochloride versus sorafenib in patients with renal cell carcinoma (abstract). *J Clin Oncol* 2013;31(suppl 6):Abstract 350.
61. Efficacy and safety data from patients with advanced renal cell cancer treated with tivozanib hydrochloride after progression on sorafenib. American Society of Clinical Oncology Genitourinary Cancers Symposium; 2013; Orlando, Florida.
62. Motzer R, Nasov D, Tomczak P, et al. Efficacy and safety data from patients with advanced renal cell cancer treated with tivozanib hydrochloride after progression on sorafenib (abstract). *J Clin Oncol* 2013;31(Suppl 6):Abstract 364.
63. Hutson T, Nosov D, Tomczak P, et al. Tivozanib vs sorafenib targeted therapy for advanced renal cell carcinoma: Final results of a phase III trial (901) and efficacy results of a 2nd line tivozanib extension study (902). *J Clin Oncol* 2015; 33: (suppl; abstr 4557).
64. AVEO Pharmaceuticals I. Clinical study report protocol AV-951-09-301. A phase 3, randomized, controlled, multi center, open-label study to compare tivozanib (AV 951) to sorafenib in subjects with advanced renal cell carcinoma 2012.
65. Mulders P, Hawkins R, Nathan P, et al. Cediranib monotherapy in patients with advanced renal cell carcinoma: results of a randomised phase II study. *Eur J Cancer* 2012;48(4):527-37. doi: 10.1016/j.ejca.2011.12.022 [published Online First: 2012/01/31]
66. Eichelberg C, Vervenne WL, De Santis M, et al. SWITCH: A Randomised, Sequential, Open-label Study to Evaluate the Efficacy and Safety of Sorafenib-sunitinib Versus Sunitinib-sorafenib in the Treatment of Metastatic Renal Cell Cancer. *Eur Urol* 2015;68(5):837-47. doi: 10.1016/j.eururo.2015.04.017 [published Online First: 2015/05/09]
67. Escudier B, Eisen T, Stadler WM, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. *N Engl J Med* 2007;356(2):125-34. doi: 10.1056/NEJMoa060655 [published Online First: 2007/01/12]
68. Yang JC, Haworth L, Sherry RM, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. *N*

Engl J Med 2003;349(5):427-34. doi: 10.1056/NEJMoa021491 [published Online First: 2003/08/02]
69. Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. *N Engl J Med* 2007;356(22):2271-81. doi: 10.1056/NEJMoa066838 [published Online First: 2007/06/01]
70. Armstrong AJ, Halabi S, Eisen T, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): A multicentre, open-label, randomised phase 2 trial. *The Lancet Oncology* 2016;17(3):378-88. doi: http://dx.doi.org/10.1016/S1470-2045(15)00515-X
71. Tomita Y, Naito S, Sassa N, et al. Sunitinib versus sorafenib as first-line therapy for patients with metastatic renal cell carcinoma with favorable or intermediate MSKCC risk factors: A multicenter randomized trial, CROSS-J-RCC. *J Clin Oncol* 2014;32(4)
72. Eisen T, Loembe AB, Shparyk Y, et al. A randomised, phase II study of nintedanib or sunitinib in previously untreated patients with advanced renal cell cancer: 3-year results. *Br J Cancer* 2015;113(8):1140-7. doi: 10.1038/bjc.2015.313 [published Online First: 2015/10/09]
73. Escudier B, Szczylik C, Hutson TE, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2009;27(8):1280-9. doi: 10.1200/jco.2008.19.3342 [published Online First: 2009/01/28]
74. Tannir NM, Jonasch E, Albiges L, et al. Everolimus Versus Sunitinib Prospective Evaluation in Metastatic Non-Clear Cell Renal Cell Carcinoma (ESPN): A Randomized Multicenter Phase 2 Trial. *Eur Urol* 2016;69(5):866-74. doi: http://dx.doi.org/10.1016/j.eururo.2015.10.049
75. Hutson TE, Lesovoy V, Al-Shukri S, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. *Lancet Oncol* 2013;14(13):1287-94. doi: 10.1016/s1470-2045(13)70465-0 [published Online First: 2013/11/12]
76. Motzer RJ, Barrios CH, Kim TM, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. *J Clin Oncol* 2014;32(25):2765-72. doi: 10.1200/jco.2013.54.6911 [published Online First: 2014/07/23]
77. Negrier S, Perol D, Ravaud A, et al. Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. *Cancer* 2007;110(11):2468-77. doi: 10.1002/cncr.23056 [published Online First: 2007/10/13]
78. Gleave ME, Elhilali M, Fradet Y, et al. Interferon gamma-1b compared with placebo in metastatic renal-cell carcinoma. Canadian Urologic Oncology Group. *The New England journal of medicine* 1998; 338(18). http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/737/CN-00149737/frame.html
http://www.nejm.org/doi/pdf/10.1056/NEJM199804303381804.
79. Negrier S, Escudier B, Lasset C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Français d'Immunothérapie. *The New England journal of medicine* 1998; 338(18).

http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/738/CN-00149738/frame.html
http://www.nejm.org/doi/pdf/10.1056/NEJM199804303381805.
80. Negrier S, Jager E, Porta C, et al. Efficacy and safety of sorafenib in patients with advanced renal cell carcinoma with and without prior cytokine therapy, a subanalysis of TARGET. *Med Oncol* 2010;27(3):899-906. doi: 10.1007/s12032-009-9303-z [published Online First: 2009/09/17]
81. Clark JI, Atkins MB, Urba WJ, et al. Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: a cytokine working group randomized trial. *J Clin Oncol* 2003;21(16):3133-40. doi: 10.1200/jco.2003.02.014 [published Online First: 2003/06/18]
82. Dexeus FH, Logothetis CJ, Sella A, et al. Interferon alternating with chemotherapy for patients with metastatic renal cell carcinoma. *American Journal of Clinical Oncology: Cancer Clinical Trials* 1989;12(4):350-54.
83. Motzer RJ, Rakhit A, Thompson JA, et al. Randomized multicenter phase II trial of subcutaneous recombinant human interleukin-12 versus interferon-α2a for patients with advanced renal cell carcinoma. *J Interferon Cytokine Res* 2001;21(4):257-63. doi: http://dx.doi.org/10.1089/107999001750169934
84. Zhao J, Zhu Y, Zhang C, et al. Sorafenib or sunitinib as postoperative adjuvant therapy for Chinese patients with locally advanced clear cell renal cell carcinoma at high risk for disease recurrence. *Urol Oncol* 2013;31(8):1800-5. doi: 10.1016/j.urolonc.2012.04.019 [published Online First: 2012/06/05]
85. Zhou A. Anlotinib versus sunitinib as first line treatment for metastatic renal cell carcinoma (mRCC): Preliminary results from a randomized phase II clinical trial. *J Clin Oncol* 2016;34(Suppl):Abstract 4565.
86. Hutson TE, Al-Shukri S, Stus VP, et al. Overall survival analysis from a randomised phase III trial of axitinib vs sorafenib as first-line therapy in patients with metastatic renal cell carcinoma. *Eur J Cancer* 2015;51:S476-S77.
87. Dias S, Welton NJ, Sutton AJ, et al. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials (last updated September 2016), 2011.
88. Phase 2 clinical evaluation of preclinically defined biomarkers for vascular endothelial growth factor tyrosine kinase inhibitor tivozanib in renal cell carcinoma. European Society for Medical Oncology; 2014; Madrid, Spain.
89. ClinicalTrials.gov. A Rollover Protocol to Allow Continued Access to Tivozanib (AV 951) for Subjects Enrolled in Other Tivozanib Protocols 2015 [Available from: https://clinicaltrials.gov/ct2/show/study/NCT01369433.
90. Pazopanib for the first line treatment of patients with advanced and/or metastatic renal cell carcinoma: A Single Technology Appraisal (Project record). *Health Technology Assessment Database* 2011; (2). http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32011000776/frame.html.
91. Hoyle M, Green C, Thompson-Coon J, et al. Cost-effectiveness of temsirolimus for first line treatment of advanced renal cell carcinoma. *Value Health* 2010;13(1):61-8. doi: 10.1111/j.1524-4733.2009.00617.x [published Online First: 2009/10/07]

92. Hoyle M, Green C, Thompson-Coon J, et al. Cost-effectiveness of sorafenib for second-line treatment of advanced renal cell carcinoma. *Value Health* 2010;13(1):55-60. doi: 10.1111/j.1524-4733.2009.00616.x [published Online First: 2009/10/07]
93. Thompson Coon J, Hoyle M, Green C, et al. Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation. *Health Technol Assess* 2010;14(2):1-184, iii-iv. doi: 10.3310/hta14020 [published Online First: 2009/12/24]
94. British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary, Issue 72. London: BMJ Group and RPS Publishing. September 2016.
95. Carroll KJ. On the use and utility of the Weibull model in the analysis of survival data. *Control Clin Trials* 2003;24(6):682-701. [published Online First: 2003/12/10]
96. Cella D, Pickard AS, Duh MS, et al. Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomised phase III trial. *Eur J Cancer* 2012;48(3):311-23. doi: 10.1016/j.ejca.2011.05.017 [published Online First: 2011/06/22]
97. Zbrozek AS, Hudes G, Levy D, et al. Q-TWiST analysis of patients receiving temsirolimus or interferon alpha for treatment of advanced renal cell carcinoma. *Pharmacoeconomics* 2010;28(7):577-84. doi: 10.2165/11535290-000000000-00000 [published Online First: 2010/06/17]
98. Chabot I, Rocchi A. How do cost-effectiveness analyses inform reimbursement decisions for oncology medicines in Canada? the example of Sunitinib for first-line treatment of metastatic renal cell carcinoma. *Value Health* 2010;13(6):837-45. doi: http://dx.doi.org/10.1111/j.1524-4733.2010.00738.x
99. Castellano D, del Muro XG, Perez-Gracia JL, et al. Patient-reported outcomes in a phase III, randomized study of sunitinib versus interferon-{alpha} as first-line systemic therapy for patients with metastatic renal cell carcinoma in a European population. *Ann Oncol* 2009;20(11):1803-12. doi: 10.1093/annonc/mdp067 [published Online First: 2009/06/25]
100. Cella D, Li JZ, Cappelleri JC, et al. Quality of life in patients with metastatic renal cell carcinoma treated with sunitinib or interferon alfa: results from a phase III randomized trial. *J Clin Oncol* 2008;26(22):3763-9. doi: 10.1200/jco.2007.13.5145 [published Online First: 2008/08/02]
101. Cella D, Michaelson MD, Bushmakin AG, et al. Health-related quality of life in patients with metastatic renal cell carcinoma treated with sunitinib vs interferon-alpha in a phase III trial: final results and geographical analysis. *Br J Cancer* 2010;102(4):658-64. doi: 10.1038/sj.bjc.6605552 [published Online First: 2010/01/28]
102. Cohen L, Cole SW, Sood AK, et al. Depressive symptoms and cortisol rhythmicity predict survival in patients with renal cell carcinoma: role of inflammatory signaling. *PLoS One* 2012;7(8):e42324. doi: 10.1371/journal.pone.0042324 [published Online First: 2012/08/08]
103. DeGroot U, Redekop W, Oosterwijk E, et al. Patient and disease characteristics are important determinants of health-related quality of life of patients with metastatic renal cell carcinoma results from a population-based registry. *Value Health* 2014;17(7):A649. doi: http://dx.doi.org/10.1016/j.jval.2014.08.2355

104. Escudier B, Roigas J, Gillessen S, et al. Phase II study of sunitinib administered in a continuous once-daily dosing regimen in patients with cytokine-refractory metastatic renal cell carcinoma. *J Clin Oncol* 2009;27(25):4068-75. doi: 10.1200/jco.2008.20.5476 [published Online First: 2009/08/05]
105. Goebell PJ, Münch A, Müller L, et al. A cross-sectional investigation of fatigue in advanced renal cell carcinoma treatment: Results from the FAMOUS study. *Urologic Oncology: Seminars and Original Investigations* 2014;32(3):362-70. doi: http://dx.doi.org/10.1016/j.urolonc.2013.09.009
106. Hagiwara M. Utility values among patients (pts) with metastatic renal cell carcinoma (mRCC) receiving first-line treatment with pazopanib (PZ) and sunitinib (SU). *J Clin Oncol* 2016;34(Suppl):Abstract e21068.
107. Litwin MS, Fine JT, Dorey F, et al. Health related quality of life outcomes in patients treated for metastatic kidney cancer: A pilot study. *J Urol* 1997;157(5):1608-12. doi: http://dx.doi.org/10.1016/S0022-5347(01)64807-9
108. Yang S, De Souza P, Alemao E, et al. Quality of life in patients with advanced renal cell carcinoma treated with temsirolimus or interferon-α. *Br J Cancer* 2010;102(10):1456-60. doi: http://dx.doi.org/10.1038/sj.bjc.6605647
109. Sternberg CN, Hawkins RE, Szczylik C, et al. A randomized, double-blind phase III study (VEG105192) of pazopanib (paz) versus placebo (pbo) in patients with advanced/metastatic renal cell carcinoma (mRCC): Updated safety results. *J Clin Oncol* 2011;29(7)
110. Hansen RN, Hackshaw MD, Nagar SP, et al. Health care costs among renal cancer patients using pazopanib and sunitinib. *Journal of managed care & specialty pharmacy* 2015;21(1):37-44, 44a-d. doi: 10.18553/jmcp.2015.21.1.37 [published Online First: 2015/01/07]
111. Hill A, Gotham D, Fortunak J, et al. Target prices for mass production of tyrosine kinase inhibitors for global cancer treatment. *BMJ Open* 2016;6(1) doi: http://dx.doi.org/10.1136/bmjopen-2015-009586
112. James N, Pascoe J, Zachariah A, et al. Effect of the UK postcode lottery on survival of patients with metastatic renal cancer: an audit of outcomes in patients with metastatic renal cancer suitable for treatment with tyrosine kinase inhibitors. *Clin Oncol (R Coll Radiol)* 2009;21(8):610-6. doi: 10.1016/j.clon.2009.06.007 [published Online First: 2009/08/22]
113. Department of Health. Reference Cost Collection: National Schedule of Reference Costs - Year 2015-16 - NHS trust and NHS foundation trusts. Available at https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016 2016.
114. Curtis L, Burns A. Unit Costs of Health and Social Care 2016. Available at http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php 2017 [
115. Office for National Statistics. Cancer registration statistics. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/previousReleases.

8 Appendices

1 Draft Summary of Product Characteristics

2 Supporting documentation from systematic literature review

3 Summary of methodology for the discontinuation study and the biomarker study

4 Additional information for the mixed treatment comparison

5 Quality assessment of cost-effectiveness studies

6 Checklist of confidential information

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Tivozanib for treating renal cell carcinoma [ID591]

Dear Eusapharma,

The Evidence Review Group, BMJ-TAG, and the technical team at NICE have looked at the submission received on 5th April 2017 from EUSA Pharma Ltd. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Thursday 11 May 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Ross Dent, Technical Lead (ross.dent@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (Stephanie.yates@nice.org.uk).

Yours sincerely

Nicola Hay
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

On behalf of:

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. **Priority question**: The inverse probability of censoring weighted (IPCW) analysis method used to account for crossover in TIVO-1 may not provide a robust estimate of clinical effectiveness, and no alternative method of crossover adjustment has been presented. The IPCW may not be the most appropriate because there was a very high level of crossover in TIVO-1 which means that undue weight is given to the small number of patients who did not crossover. Two approaches that would provide more robust estimates of the clinical effectiveness of tivozanib are outlined below. Clinical advice sought by the ERG supports the company's position that the previously treated population is not relevant to clinical practice in England and that immunotherapy is not offered to untreated patients. Please choose 1 of the options below and provide alternative analyses comparing tivozanib with pazopanib and sunitinib in the untreated population for the following outcomes:

- Progression-free survival
- Overall survival
- Grade 3+ diarrhoea
- Grade 3+ fatigue
- Grade 3+ hypertension
- Grade 3+ liver disorder (e.g. raised alanine aminotransferase)

OPTION 1 – Revise the mixed treatment comparison and crossover adjustment for overall survival

The following changes would help improve the robustness of the results from the mixed treatment comparison:

- Explore and present the results of alternative methods to adjust for the confounding effect of one-way crossover on overall survival in TIVO-1 (e.g. Rank Preserving Structural Failure Time [RPSFT] and the Iterative Parameter Estimation [IPE] algorithm). Please refer to NICE DSU Technical Support Document 16[1] and present the strengths and weaknesses of the different approaches explored.

- Limit the mixed treatment comparison for all outcomes listed above to the studies in Figure 1 for the untreated population. The mixed treatment comparison evidence networks in the submission were extensive, but the studies included and the decision to focus on the untreated population means that they are likely to be too heterogeneous to

NICE National Institute for Health and Care Excellence

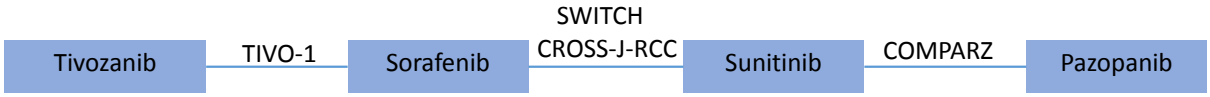
Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

generate robust estimates. If a different structure is chosen to that suggested inFigure 2 Figure 1, a network including TARGET is unlikely to provide reliable estimates of untreated patients as the population of TARGET had all progressed on one prior systemic therapy (the subset of 161 that is discussed in the company submission [page 80] was naïve only to cytokines).

- Provide a thorough description of amount of crossover/subsequent therapy use and any adjustments made in each of the studies included in the mixed treatment comparison for overall survival.
- Provide an assessment of clinical and methodological heterogeneity between studies included in the mixed treatment comparison.
- Include a discussion of any potential bias in the mixed treatment comparison and the potential direction of that bias.
- Provide the full quality assessments for each study in the mixed treatment comparison.

Figure 1. Suggested mixed treatment comparison primary structure for the untreated population



OPTION 2 – Conduct a matching-adjusted indirect comparison (MAIC)

This method could reduce the uncertainty introduced by methodological (e.g. differential crossover protocols) and clinical (e.g. variation in baseline prognosis) heterogeneity between studies in the mixed treatment comparisons which cannot be adjusted for. If a matching-adjusted indirect comparison is undertaken, methods to adjust for the one-way crossover in TIVO-1 will not be necessary as it does not rely on the within-trial comparison with sorafenib; only the tivozanib treatment arm is used.

The method could be used to adjust the TIVO-1 population using individual patient data to more closely match a trial (or trials) of the relevant comparators. For example, the TIVO-1 trial population could be adjusted to match the characteristics of the COMPARZ trial to provide estimates of tivozanib compared with pazopanib and sunitinib.

If this option is chosen, guidance is provided in the Technical Support Document 18 issued by the Decision Support Unit.[2]

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

All the important prognostic factors need to be incorporated to reduce bias in the matching-adjusted indirect comparison. Any prognostic factors not adjusted for need to be explicitly stated and a judgement made on the likely impact not accounting for them would have on the results.

A2. **Priority question**: The submission states that 26% of tivozanib patients received next-line therapy compared with 65% of sorafenib patients (Table 16 of the submission), whereas in the 2016 clinical study report[3] Table 27 notes that 57.7% of tivozanib patients received subsequent anti-cancer therapy compared with 78.2% of sorafenib patients and Table 30 reports 38.4% of tivozanib and 75.7% of sorafenib patients did. Please clarify how many patients in each treatment arm of TIVO-1 received subsequent therapy.

A3. **Priority question:** The interim clinical study report for TIVO-1[4] states that the first patient was enrolled on 11 February 2010 and the last patient completed the study on 10 June 2013. Please provide the following information:

- Date of enrolment of first patient into the extension study;
- Date of enrolment of last patient into TIVO-1 and into the extension study;
- Date of completion of the last patient in the extension study;
- Date of last follow-up assessment for TIVO-1 and the extension study.

A4. **Priority question:** Please provide mean (and standard deviation) and median (with range) duration of follow-up for patients included in the analysis of (i) progression-free survival and (ii) overall survival.

A5. **Priority question:** Please provide the most recent individual clinical study reports for TIVO-1 and the extension study AV-951-09-902.

A6. **Priority question:** Please provide overall survival results from the analysis comparing patients in each treatment arm of TIVO-1 who remained on the treatment that they had been randomised to at the end of follow-up or stopped treatment without subsequent therapy (as described on page 49 of the company submission, and in the Motzer 2013 poster[5]).

A7. **Priority question**: For progression free survival in TIVO-1, please provide full details of how many people in each treatment group were censored and for what reasons (numbers given as 104 and 87 for tivozanib and sorafenib, respectively, in Table 17 of the 2016 clinical study report).

A8. Please clarify whether all diagnoses of progressive disease were confirmed by independent radiology review. The first two sentences and the last sentence of the paragraph below taken from the company submission seem to contradict each other.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

"*All imaging scans were evaluated by an independent radiology review, blinded to study treatment. Patients with radiological evidence of PD as assessed by the investigator had confirmation by blinded independent review within 48 hours. This independent review to confirm investigator-called PD was a separate process from the third-party review of response performed by the core imaging laboratory to assess the primary end-point. Confirmation of PD was not required if significant clinical deterioration, appearance of new lesions, or >50% increase in measurable disease per RECIST was noted by the investigator*".

A9. Page 54 of the 2016 clinical study report notes that treatment with the study drug could be interrupted for up to 2 weeks, and interruptions longer than 2 weeks led to the patient stopping treatment, "*unless there was clear benefit from treatment, in which case the investigator and medical monitor reviewed the patient's condition in order to resume treatment*". Please give details of how "clear benefit" was determined.

A10. Please provide the following information to help clarify why so few of the dose interruptions led to discontinuation (clinical study report, Table 7 and Table 47):

- Table 47 of the 2016 clinical study report shows that 139 people in the sorafenib group and 30 people in the tivozanib group had interruptions attributed to reasons "other" than adverse effects. Please give details of "other" reasons for treatment interruption.
- Please provide the number of people in each group with treatment interruptions lasting less than 2 weeks.
- Please provide the number of people in each group with treatment interruptions lasting longer than 2 weeks who restarted treatment because there was clear benefit (see A9).
- Please provide the median (and range) and mean (with standard deviation) duration of dose interruption for both groups.

A11. The protocol, registration and clinical study reports for TIVO-1 (AV-951-09-301) described the study as parallel, with treatment switches only permitted upon entry into the extension study (AV-951-09-902). However, Figure 2 in the 2016 clinical study report suggests that 147 people in the sorafenib group received tivozanib before entering the extension study. Please clarify whether any treatment switches occurred in the AV-951-09-301 study, prior to the commencement of the extension protocol. If so, was this a protocol amendment?

A12. For progression-free survival, overall survival, response rates and adverse events, please state whether the data were collected solely under the AV-951-09-301 protocol, or under AV-951-09-301 and AV-951-09-902.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

A13. Please provide an estimate of effect (either risk ratio or odds ratio) for overall response rate in TIVO-1.

A14. Figure 2 in the 2016 clinical study report indicates that 147 patients originally randomised to sorafenib went on to receive tivozanib as next-line therapy and that 14 people switched to tivozanib during the extension study. The company submission states that 156 patients originally randomised to sorafenib went on to receive tivozanib as next-line therapy. Please confirm the correct number and outline why there is a difference in reported numbers.

A15. Please confirm that box E in figure 2 of the 2016 clinical study report represents patients who did not have disease progression on sorafenib during TIVO-1 and who did not enter the extension protocol. If this is correct, please give the reasons why the 68 patients did not enter the extension study.

A16. Please confirm that box B in figure 2 of the 2016 clinical study report represents patients randomised to receive tivozanib in TIVO-1 who did not enter the extension study. Please give a breakdown of the status of these 172 patients (i.e. stopped treatment with tivozanib due to disease progression, lost to follow-up, declined entry to AV-951-09-902).

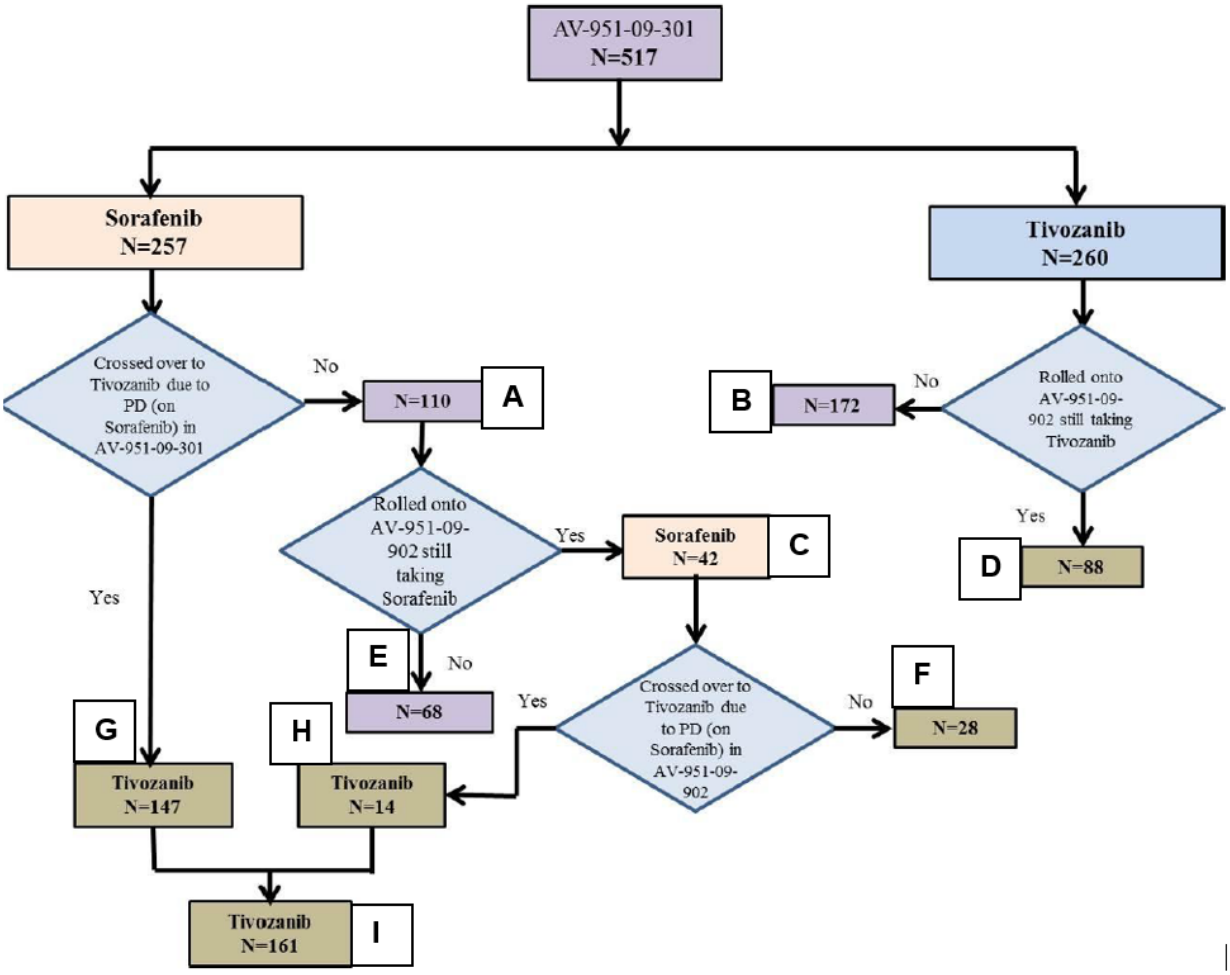
A17. The company submission states that 153 patients had progressive disease or died while taking tivozanib compared with 168 taking sorafenib. However, Figure 3 in the 2016 clinical study report indicates that 151 patients in the tivozanib arm completed the study with progressive disease compared with 171 taking sorafenib. Figure 3 in the 2016 clinical study report also shows that 49 patients randomised to tivozanib and 26 randomised to sorafenib were classed as ongoing (“an artefact of the data transfer date for disposition data being before the end of study”). Please clarify the discrepancies in the numbers reported in the company submission and the 2016 clinical study report and also whether the patients classed as ongoing have been included in any analysis.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 2. Figure 2 from the 2016 clinical study report (page 82)



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Section B: Clarification on cost-effectiveness data

Trial data

B1. **Priority question:** The data cut from the TIVO-1 trial and extension study used in the model is from July 2013. At the last measurement point for overall survival (~month 40), around 45% of patients had yet to have an event, representing immature data.

a. Given that the data cut is from 4 years ago, are more mature follow up data for the TIVO-1 trial and extension study available?

b. If yes, then please use the later data cut for the economic model, updating all tables and figures in the submission to reflect the new data. If not, please provide an explanation as to why mature follow up data is not available.

Treatment effectiveness

The following questions are dependent on the methods chosen for the indirect treatment comparison. See questions B2 to B5 if implementing crossover adjustments (option 1) for the TIVO-1 trial and the mixed treatment comparison, otherwise skip to questions B6 and B7 if implementing the matching-adjusted indirect comparison method (option 2).

B2. **Priority question:** A Cox proportional hazards model was used to generate hazard ratios for progression-free survival and overall survival for tivozanib compared with sorafenib based on data from the TIVO-1 trial. However formal assessment of proportional hazards is not presented in the submission. In addition, assumptions around proportional odds and accelerated failure time were not explored. Please provide the following plots and use them to provide an assessment of whether the proportional hazard, proportional odds or accelerated failure time assumption holds for PFS and OS in the TIVO-1 trial (please refer to DSU TSD 14[6] for guidance):

a. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – test for **proportional hazards**.
b. Log(survival function / (1-survival function)) plots versus Log(time) – test for **proportional odds**.
c. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – test for **accelerated failure time**.

B3. **Priority question:** If proportional hazards, proportional odds or accelerated failure time is not found to hold for the TIVO-1 trial please explore alternative methods to generate treatment effectiveness (such as those outlined DSU TSD 14[6]).

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

B4. **Priority question:** The mixed treatment comparison uses the Cox proportional hazards model to produce pairwise hazard ratios, yet an assessment of proportional hazards for each trial included in the mixed treatment comparison is not presented in the submission. Please provide an assessment of whether the proportional hazards assumption holds for each trial in the mixed treatment comparison. For an example of what is required, refer to the on-going appraisal of cabozantinib for treating renal cell carcinoma: GID-TA10075, Appraisal Committee 1 committee papers, Company Submission section 4.10.3 (https://www.nice.org.uk/guidance/gid-ta10075/documents/committee-papers).

B5. **Priority question:** If proportional hazards is not found to hold for the trials in the mixed treatment comparison please explore other methods to generate the indirect comparison estimates, such as those outlined in Ouwens *et al.* 2010[7] and Jansen 2011[8] and implemented in GID-TA10075: cabozantinib for treating renal cell carcinoma, AC1 committee papers, CS section 4.10.4 (https://www.nice.org.uk/guidance/gid-ta10075/documents/committee-papers).

B6. **Priority question:** The main trial comparing pazopanib and sunitinib is the COMPARZ trial[9] which could be used in conjunction with the TIVO-1 trial to estimate comparable treatment effects for the three treatments using a matching-adjusted indirect comparison. One of the expected outputs from the matching-adjusted indirect comparison is adjusted progression-free survival and overall survival Kaplan–Meier curves for tivozanib. Using the adjusted tivozanib curves and digitised sunitinib and pazopanib curves from the COMPARZ trial[9], please provide the following plots and use them to perform an assessment of whether the proportional hazard, proportional odds or accelerated failure time assumption holds for PFS and OS in the (please refer to DSU 14[6] for guidance):

a. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – test for **proportional hazards**.
b. Log(survival function / (1-survival function)) plots versus Log(time) – test for **proportional odds**.
c. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – test for **accelerated failure time**.

B7. **Priority question:** If proportional hazards, proportional odds or accelerated failure time is not found to hold for the assessments performed in question B6, please explore alternative methods to generate treatment effectiveness (such as those outlined DSU TSD 14[6]).

B8. **Priority question:** The Weibull distribution was used for the extrapolation of the tivozanib Kaplan–Meier data with the justification that, "*the Weibull approach is widely adopted for this type of analysis"*. No exploration of other distributions is

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

presented in the submission. From visual inspection of the plots presented in Figure 21 of the company submission, the Weibull curves do not appear to fit the data well. As no other curves were presented in the submission, it is not possible to review any statistical goodness of fit tests or clinical validation of the alternative curves that the company could have used. Please provide:

- Analyses using alternative parametric distributions incorporating the analyses performed in questions B2–B7 (depending on the methods chosen for the indirect treatment comparison) and using DSU TSD 14[6] as guidance, to identify the most appropriate extrapolation of the progression-free survival and overall survival Kaplan–Meier data for tivozanib and comparator treatments for use in the economic model.
- Please provide plots of each curve under consideration for progression-free survival and overall survival compared to the progression-free survival and overall survival Kaplan–Meier plots.
- Please provide mean, median and landmark estimates of progression-free survival and overall survival for all treatments based on the extrapolated curves.

Subsequent therapy

B9. **Priority question:** In the economic model it is assumed that 60% of patients with disease progression go on to receive axitinib and 40% receive BSC. Please provide the actual subsequent therapy profile (treatments and proportions of patients on each treatment) for each treatment from the trials used in the matching-adjusted indirect comparison or mixed treatment comparison. Please use this data as well as costs for each treatment (drug and monitoring) and mean duration of treatment to estimate accurate subsequent therapy costs. Where a drug is not routinely used in the NHS, please assume the equivalent NHS drug (e.g. where a VEGFR-TKI is used second line in a study that is unavailable in the NHS, please substitute it with axitinib).

Adverse events

B10. Please clarify if adverse events included in the mixed treatment comparison are treatment related or treatment emergent.

B11. The data in Table 41 of the company submission relates to the overall population. Please provide figures for the untreated population and use this data in a scenario analysis.

B12. Please check the figures in Table 52 of the company submission against the figures presented in Table 32 of the company submission and update the model accordingly.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

In particular the odds ratio for hypertension for tivozanib compared with pazopanib and tivozanib compared with interferon does not match in both tables.

B13. Please clarify why diarrhoea is not included in Table 53 and is not used in the model even though it was identified in the mixed treatment comparison for inclusion in the model.

B14. Please include a scenario analysis in the model where the rates of treatment-related adverse events (severity grade 3 or above with an incidence of >5%) observed in the pivotal trials for the comparators are used in the model instead of the incidence estimated in the mixed treatment comparison.

Health related quality of life

B15. **Priority question:** Please provide the following tables relating to the quality of life analyses cited in the 2016 clinical study report: Tables 14.2.25, 14.2.26, 14.2.27, 14.3.11, 14.3.12, 14.3.1.15 and 16.2.6.2.6?

B16. Please clarify if utilities used for progression-free survival and post-progression survival are based on the untreated population or the entire trial population.

Resource use and costs

B17. The company submission mentions on page 18 that an 890 µg capsule is available. Please confirm the cost of the smaller dose capsule.

B18. Please provide the mean dose intensity of each treatment, including appropriate measures of uncertainty (such as standard errors, confidence intervals, etc.) and include a scenario analysis adjusting treatment costs by dose intensity.

B19. Please clarify why blood tests have not been included in resource use assumptions for patients on active treatments.

B20. Please carry out a scenario analysis including the costs of blood tests (every month) and thyroid function tests (every 3 months) for patients receiving active treatment.

Systematic literature review

B21. Please clarify whether an established methodology was followed to carry out the systematic literature review for cost-effectiveness, costs and quality of life studies. If so, please provide a reference.

B22. Please clarify why the systematic literature search for cost-effectiveness studies was restricted to studies published from 1995 onwards.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Probabilistic sensitivity analysis

B23. Credible intervals were used for the measurement of uncertainty for the progression-free survival and overall survival hazard ratios in the probabilistic sensitivity analysis (page 149 of the company submission). This approach is not appropriate as the methodology used to produce the hazard ratios means that the estimates are correlated and as such uncertainty cannot be calculated independently. Please amend the probabilistic sensitivity analysis to use progression-free and overall survival hazard ratio CODA data obtained from WinBUGS (refer to DSU TSD 6 for guidance[10] and present the following:

- Probabilistic sensitivity analysis pairwise comparison results (list price).
- Cost effectiveness acceptability curves for the pairwise comparisons (list price).
- Cost effectiveness scatter plots for the pairwise comparisons (list price).

Section C: Textual clarifications and additional points

C1. Please give details of the TAURUS study (NCT01673386; AV-951-12-205), along with a rationale for not including it in the submission.

C2. The proposed summary of product characteristics provided in the submission appendix refers to, “five renal cell carcinoma monotherapy studies”, that constitute the safety data. Please provide a list of references and identifiers for these studies, including rationale for why any were not included in the submission.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

References

1. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. ScHARR, University of Sheffield, 2014.
2. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, NJ W. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE2016 9th January 2017. Available from: http://www.nicedsu.org.uk/TSD18%20Population%20adjustment%20TSD%20-%20FINAL.pdf.
3. AVEO Pharmaceuticals I. Clinical study report protocol AV-951-09-301. A phase 3, randomized, controlled, multi center, open-label study to compare tivozanib (AV 951) to sorafenib in subjects with advanced renal cell carcinoma. 2016.
4. AVEO Pharmaceuticals I. Clinical study report protocol AV-951-09-301. A phase 3, randomized, controlled, multi center, open-label study to compare tivozanib (AV 951) to sorafenib in subjects with advanced renal cell carcinoma 2012.
5. Motzer R, Eisen T, Hutson TE, Szczylik C, Krygowski M, Strahs A, et al., editors. Overall survival results from a phase III study of tivozanib hydrochoride versus sorafenib in patients with renal cell carcinoma (poster). American Society of Clinical Oncology Genitourinary Symposium 2013; Orlando, Florida
6. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. ScHARR, University of Sheffield, 2011.
7. Ouwens MJ, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. Res Synth Methods. 2010;1(3-4):258-71.
8. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol. 2011;11:61.
9. Motzer R, Hutson TE, Reeves J, Hawkins R, Guo J, Nathan P, et al. Randomized, open-label, phase III trial of pazopanib versus sunitinib in first-line treatment of patients with Metastatic Renal Cell Carcinoma (MRCC): Results of the COMPARZ trial. Annals of Oncology.Conference:37th ESMO Congress Vienna Austria. Conference Start: 20120928 Conference End: 1002. Conference Publication: (var.pagings). 23 (pp ix13).
10. Dias S, Sutton AJ, Welton NJ, Ades AE. Embedding Evidence Synthesis in Probabilistic Cost-Effectiveness Analysis: Software Choices. NICE Decision Support Unit Technical Support Documents. London2012.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Tivozanib for treating renal cell carcinoma [ID591]

Dear Eusapharma Ltd,

The Evidence Review Group, BMJ-TAG and the technical team at NICE have two additional clarification questions for your response.

Please provide your written response to the clarification questions by **5pm on Thursday 11 May 2017.** Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Kind regards,

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Ross Dent, Technical Lead (ross.dent@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (Stephanie.yates@nice.org.uk).

Yours sincerely

Nicola Hay
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

On behalf of:
Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

1. **Priority question**: Throughout the company submission the primary end-point of progression free survival was reported to be based on independent radiology review for the overall intention to treat population. Estimates for the treatment naive population were then used in the mixed treatment comparison to produce progression free survival hazard ratios. However, in the economic model, the tivozanib Kaplan Meier data is appears to be based on the overall intention to treat investigator review of PFS (median PFS 14.7 months in the economic model corresponds to median PFS mentioned on page 67 of the company submission). Please provide a scenario analysis using the independent radiology review Kaplan Meier data for the treatment naive population.

2. **Priority question**: Further investigation of the overall survival Kaplan Meier data used in the economic model reveals the median overall survival for tivozanib is 36.04 months. In the company submission (page 71, Figure 7) and elsewhere in the report, overall survival for tivozanib is reported as 28.2 months (29 months in Figure 8, page 72 of the company submission) which is based on the overall intention to treat population.

   A1. Please clarify why there are different estimates of median overall survival in section 4.7.2.2 in the company submission.
   A2. Please clarify why there is a difference in what is reported in the company submission and estimated in the economic model for median overall survival.
   A3. Please clarify which data are correct and update the model as necessary, focusing on Kaplan Meier data for the treatment naive population, or provide justification as to why the original data used in the model is appropriate.
   A4. Please provide the numbers at risk for overall survival for the treatment naive population based on the response to question 2 c. In addition please clarify why the numbers at risk provided in Figure 7 of the company submission for tivozanib between month 17-21 drop and then increase from month 22 onwards.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Single technology appraisal

Tivozanib for treating renal cell carcinoma [ID591]

Dear Eusapharma,

The Evidence Review Group, BMJ-TAG, and the technical team at NICE have looked at the submission received on 5th April 2017 from EUSA Pharma Ltd. In general they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification on the clinical and cost effectiveness data (see questions listed at end of letter).

The ERG and the technical team at NICE will be addressing these issues in their reports.

Please provide your written response to the clarification questions by **5pm** on **Thursday 11 May 2017**. Your response and any supporting documents should be uploaded to NICE Docs/Appraisals.

Two versions of your written response should be submitted; one with academic/commercial-in-confidence information clearly marked and one with this information removed.

Please underline all confidential information, and separately highlight information that is submitted as commercial in confidence in turquoise, and all information submitted as academic in confidence in yellow.

If you present data that are not already referenced in the main body of your submission and that are academic/commercial in confidence, please complete the attached checklist for confidential information.

Please do not embed documents (PDFs or spreadsheets) in your response because this may result in them being lost or unreadable.

If you have any queries on the technical issues raised in this letter, please contact Ross Dent, Technical Lead (ross.dent@nice.org.uk). Any procedural questions should be addressed to Stephanie Yates, Project Manager (Stephanie.yates@nice.org.uk).

Yours sincerely

Nicola Hay
Technical Adviser – Appraisals
Centre for Health Technology Evaluation

On behalf of:

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Dr Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for confidential information

Section A: Clarification on effectiveness data

A1. **Priority question**: The inverse probability of censoring weighted (IPCW) analysis method used to account for crossover in TIVO-1 may not provide a robust estimate of clinical effectiveness, and no alternative method of crossover adjustment has been presented. The IPCW may not be the most appropriate because there was a very high level of crossover in TIVO-1 which means that undue weight is given to the small number of patients who did not crossover. Two approaches that would provide more robust estimates of the clinical effectiveness of tivozanib are outlined below. Clinical advice sought by the ERG supports the company's position that the previously treated population is not relevant to clinical practice in England and that immunotherapy is not offered to untreated patients. Please choose 1 of the options below and provide alternative analyses comparing tivozanib with pazopanib and sunitinib in the untreated population for the following outcomes:

- Progression-free survival
- Overall survival
- Grade 3+ diarrhoea
- Grade 3+ fatigue
- Grade 3+ hypertension
- Grade 3+ liver disorder (e.g. raised alanine aminotransferase)

OPTION 1 – Revise the mixed treatment comparison and crossover adjustment for overall survival

The following changes would help improve the robustness of the results from the mixed treatment comparison:

- Explore and present the results of alternative methods to adjust for the confounding effect of one-way crossover on overall survival in TIVO-1 (e.g. Rank Preserving Structural Failure Time [RPSFT] and the Iterative Parameter Estimation [IPE] algorithm). Please refer to NICE DSU Technical Support Document 16[1] and present the strengths and weaknesses of the different approaches explored.

As outlined in NICE DSU Technical Support Document 16, the RPSFT and the IPE algorithm represent randomisation-based methods for estimating counterfactual survival times, that is survival times that would have been observed without switching in clinical trials in which crossover has occurred. The IPCW method represents an observational-based approach,

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

whereby data for switchers are censored at the point of switch and remaining observations are weighted with the aim of removing any censoring-related selection bias.

A review of the literature of statistical methods for adjusting for crossover and recent HTA decisions in oncology reveals that in cases where crossover is fairly frequent, as was seen in TIVO-1 then the RPSFT approach may be more appropriate than the IPCW approach [Jönsson, 2014]. However, in cases where there is adequate information on confounding factors then the IPCW approach may be more appropriate. In the TIVO-1 study we have frequent crossover in the sorafenib arm, but we also have abundant information on confounding factors and we know that confounding is an issue in the study.

The original decision to use the IPCW approach to crossover correction, rather than RPSFT or IPE was predicated on the underlying assumptions and limitations of the two methods. Both RPSFT and IPE assume:

- There is “common treatment effect”, which is to say that the effect of the treatment under evaluation is equivalent, regardless of when the treatment is administered
- The only difference between arms is the randomised treatment, with all other variables that could influence crossover being evenly distributed

For IPCW, neither of these assumptions apply but, because the weighting used in the model depends on the distribution of baseline characteristics predictive of crossover, all such characteristics must be known.

Considering the RPSFT and IPE, neither of the key requirements were met in the case of the TIVO-1 study.

Common treatment effect

Because crossover occurs in the context of disease progression, it is inevitable that these patients are at a more advanced stage of disease by this point. Additionally, the possibility of a sequential treatment benefit cannot be captured. This phenomenon has been well demonstrated in the SWITCH study, which was carried out in a treatment-naïve population of patients with advanced RCC [Eichelberg 2015]. In SWITCH, 365 patients were randomised to receive either sunitinib or sorafenib, switching to the alternative arm on progression. PFS curves for the two arms were essentially the same over the total treatment duration (Figure 1). However, examination of the pre-progression and post-progression curves reveals substantial differences between arms (Figure 2). This is particularly apparent when examining the curves for sorafenib. The gradient for the pre-progression curve (SO-SU arm) is substantially shallower than that for post-progression treatment with sorafenib (SU-SO arm). It is consequently clear that common treatment effect cannot be assumed in this clinical context.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 1: Overall PFS results (SWITCH study)

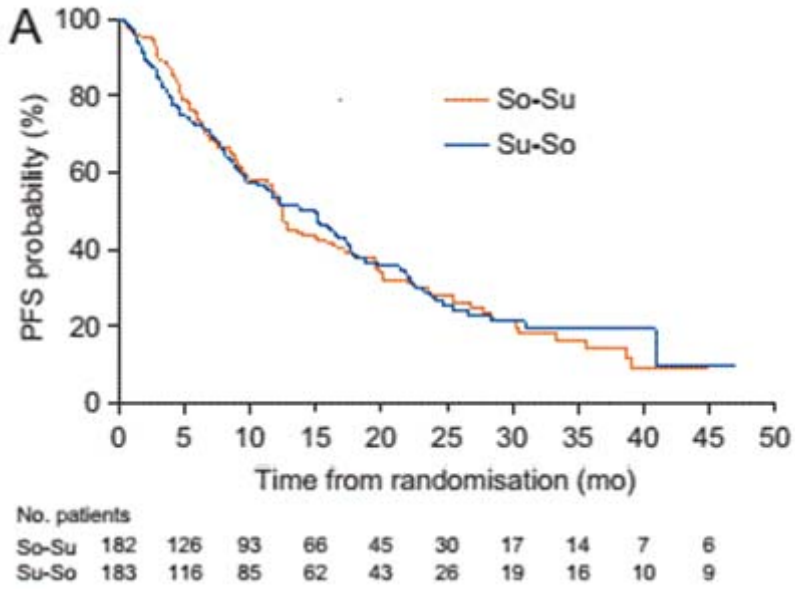
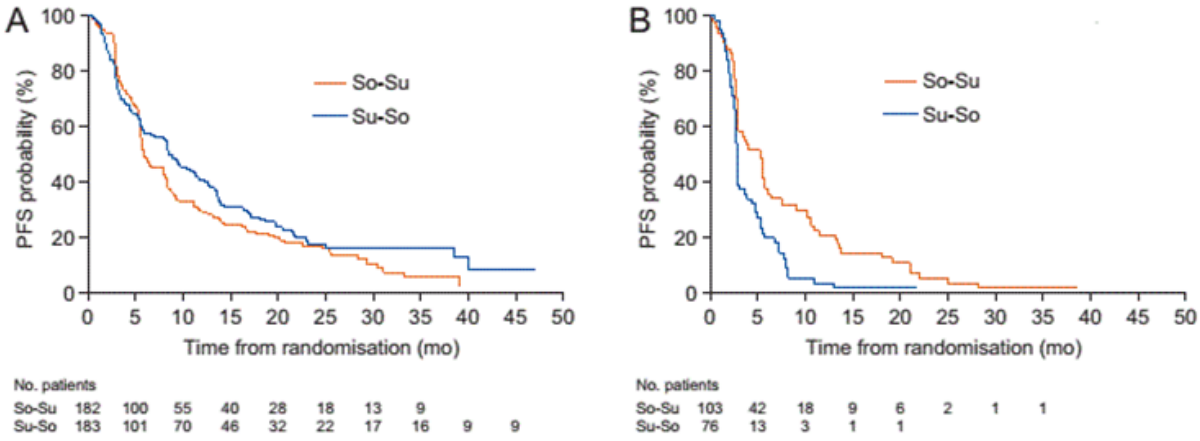


Figure 2: PFS results split by pre- and post- progression (SWITCH study)
A: PFS on first treatment (first progression)
B: PFS on second treatment (second progression)



Equally distributed baseline predictors

In the TIVO-1 study, we know that there were imbalances in baseline characteristics, particularly with regard to ECOG performance status, MSKCC prognostic group and the number of metastatic sites, all of which were shown in the pre-specified subgroup analyses to be predictive of disease progression (see page 68-69 in our original submission).

From the point of view of the IPCW, although the omission of unknown baseline confounders can never be excluded in an RCT, it appeared that it was less likely to offer a compromised assessment of the crossover correction, and consequently we used this for our primary analysis.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

In response to the request from the ERG, we have attempted, nonetheless, to undertake an additional crossover analysis, using the RPSFT approach. Although the breach of the assumption of common treatment effect cannot be overcome, we have adopted a stratified approach in order to mitigate the problem of baseline predictor imbalance – in effect presenting a mixed model.

RPSFT method

We used standard RPSFT methods; our approach consisted of the following steps:

- Obtain an estimate of the effect of exposure to tivozanib on survival time, ψ*
- Estimate the hazard ratio for OS for randomisation to tivozanib versus randomisation to sorafenib with no crossover to tivozanib by fitting a Cox proportional hazards regression model to tivozanib crossover times as observed in the TIVO-1 trial and re-censored adjusted failure times for sorafenib patients based on the estimate of exp(ψ*).

Four separate RPSFT analyses were performed: Log-rank and Wilcoxon tests based on the unstratified and and stratified populations. Stratification was computed for patient baseline characteristics based on:

- ECOG performance status
- MSKCC risk category
- Number of metastatic disease sites.

These characteristics were chosen since we know that there was a between-groups imbalance in these characteristics in TIVO-1 and they are known to be predictive of progression risk. Patients theoretical maximum follow-up time was defined by the time from patient's randomisation date to the final data cut-off date (July 10, 2013).

Results: unstratified analysis

Results of the RPSFT analyses derived from the Log-rank and Wilcoxon tests are shown in Table 1. In the RPSFT the estimated values of the causal effect parameter (ψk) was performed using a grid search (Range -2 to 2).

Table 1: Estimated causal rate ratio (ψ) for OS for tivozanib among naïve patients in the TIVO-1 trial derived from the unstratified data (tivozanib: n=181; sorafenib: n=182)*

	Log-rank test	Wilcoxon Test
*ψ**	0.46	0.4
Standard error	0.623	0.627
95%CI	-0.78 to 1.66	-0.8 to 1.62
exp(*ψ**)	1.584	1.491
95%CI	0.458 to 5.259	0.449 to 5.053

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

The causal effect estimates (ψ^*) suggest that continuous treatment with tivozanib decreases the survival time by a factor exp (-0.46) and exp (-0.4) in the Log-rank and Wilcoxon tests, respectively.

Results: final stratified analysis

The objective of stratification is to produce groups within which the confounder does not vary, then evaluate the exposure-outcome association within each stratum of the confounder. So within each stratum, the confounder cannot confound because it does not vary across the exposure-outcome. If there is a difference between the crude result and stratified result then confounding is likely.

Table 2: Estimated causal rate ratio (ψ^*) for OS for tivozanib among naïve patients in the TIVO-1 trial derived from the stratified data (tivozanib: n=181; sorafenib: n=182)

	Log-rank test	Wilcoxon Test
ψ^*	0.05	0.05
Standard error	0.986	0.951
95%CI	-1.882 to 1.952	-1.813 to 1.913
exp(ψ^*)	1.05	1.05
95%CI	0.152 to 7.042	0.163 to 6.773

These results indicate that first-line tivozanib has a neutral effect on OS, which negates the results of the unstratified analysis. This is consistent with the IPCW analysis performed in our original submission, where when adjusting for confounders, we obtained near identical survival curves. It is worth noting that, because RPSFT is a rank-preserving method, it is not possible for the counter-factual Kaplan Meier (KM) curves to be inverted in position – the maximum that can be achieved is neutrality, as seen in this example.

KM curves were estimated using the observed event times and the observed censoring indicators for each patient in the tivozanib arm. For patients in the sorafenib arm, the adjusted event times Xi (ψ^*) and censoring indicators Δi (ψ^*), were employed, with ψ^*, based on our point estimates.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 3: KM plot of observed survival times (months) for tivozanib patients and RPSFT adjusted and re-censored survival times for sorafenib patients, untreated patients in TIVO-1 trial (Tivozanib: n=181; Sorafenib: n=182), stratified log-rank

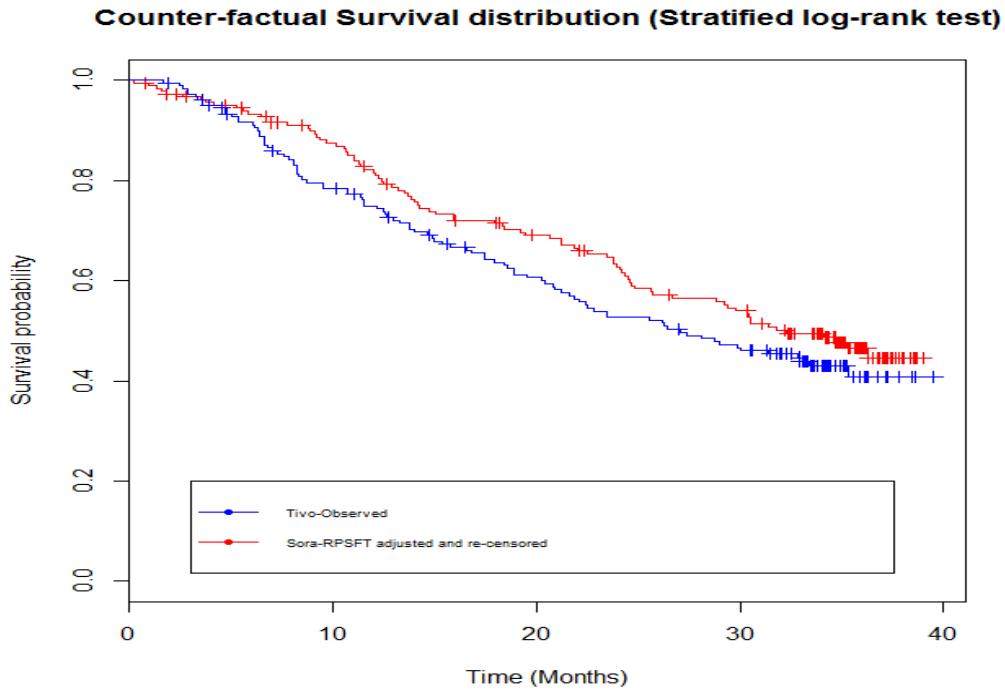
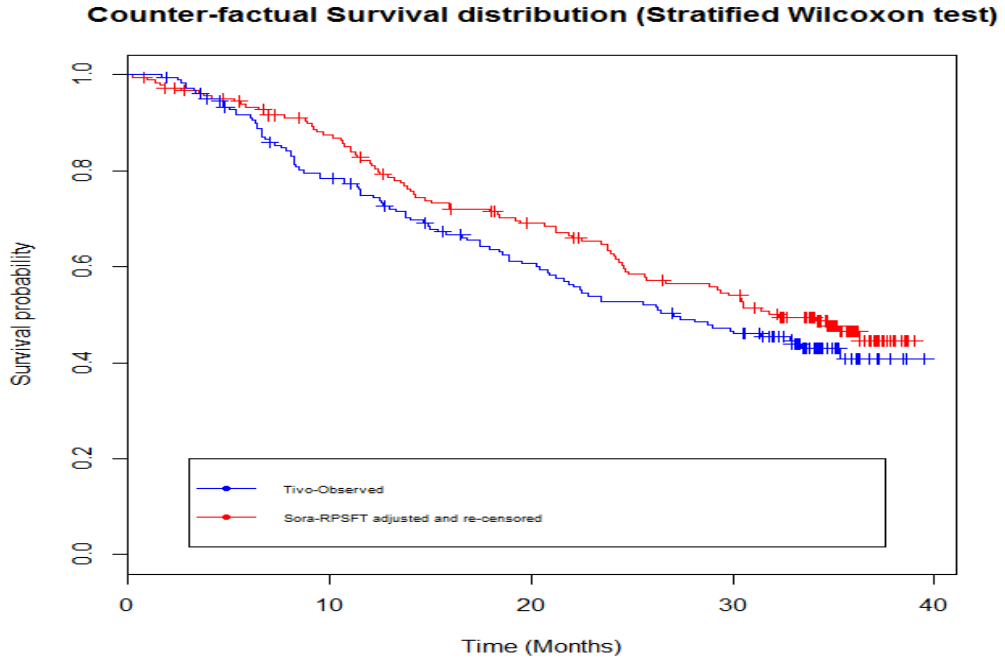


Figure 4: KM plot of observed survival times (months) for tivozanib patients and RPSFT adjusted and re-censored survival times for sorafenib patients, untreated patients in TIVO-1 trial (Tivozanib: n=181; Sorafenib: n=182, stratified Wilcoxon



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Interpretation

As discussed above, the absence of common treatment effect is potentially a significant bias in this RPSFT analysis and, while the stratified approach helps to adjust for baseline imbalances, it is a relatively crude tool for this purpose, compared with the weighting approach used for the IPCW.

However, despite these limitations, the results obtained are broadly in line with those seen for the IPCW, offering confidence to our original conclusions.

References

Eichelberg C, Vervenne WL, De Santis M, et al. SWITCH: A Randomised, Sequential, Open-label Study to Evaluate the Efficacy and Safety of Sorafenib-sunitinib Versus Sunitinib-sorafenib in the Treatment of Metastatic Renal Cell Cancer. Eur Urol 2015; 68(5): 837-47.

Jönsson L, Sandin R, Ekman M et al. Analyzing overall survival in randomized controlled trials with crossover and implications for economic evaluation. Value Health 2014;17(6):707-13.

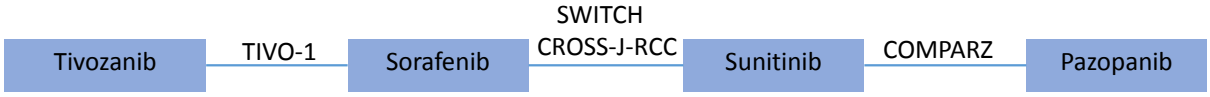
- Limit the mixed treatment comparison for all outcomes listed above to the studies in the figure below for the untreated population. The mixed treatment comparison evidence networks in the submission were extensive, but the studies included and the decision to focus on the untreated population means that they are likely to be too heterogeneous to generate robust estimates. If a different structure is chosen to that suggested in the figure below, a network including TARGET is unlikely to provide reliable estimates of untreated patients as the population of TARGET had all progressed on one prior systemic therapy (the subset of 161 that is discussed in the company submission [page 80] was naïve only to cytokines).
- Provide a thorough description of amount of crossover/subsequent therapy use and any adjustments made in each of the studies included in the mixed treatment comparison for overall survival.
- Provide an assessment of clinical and methodological heterogeneity between studies included in the mixed treatment comparison.
- Include a discussion of any potential bias in the mixed treatment comparison and the potential direction of that bias.
- Provide the full quality assessments for each study in the mixed treatment comparison.

Figure. Suggested mixed treatment comparison primary structure for the untreated population

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140



Mixed treatment comparison: study details

The four studies used in the MTC were used in the original MTC carried out for our initial submission. Since we made the submission we have received additional data from the author of the CROSS-J-RCC study (Tomita) in the form of a poster presented at ASCO GU February 16-18 2017 Orlando, Florida, US which was not identified in our systematic literature review since the conference was held outside of our inclusion dates. The poster provides us with additional information – including study design (crossover on progressive disease or adverse event), patient characteristics and results.

Details of the study methodology are shown in Table 3. All four studies were open label, TIVO-1 and COMPARZ used an assessment board blinded to treatment arm to evaluate radiological data on disease progression.

Table 3: Population and study methodology of relevant RCTs

Trial number (acronym)	Population	Intervention	Comparator	Study methodology	Primary study reference
COMPARZ	Clear cell metastatic RCC, treatment naïve	Pazopanib	Sunitinib	Open label phase III RCT, assessors partly blinded	Motzer et al. 2013
Cross-J-RCC	Clear cell metastatic RCC, treatment naïve	Sunitinib	Sorafenib	Open label crossover RCT, abstract and poster only	Tomita et al. 2014 and 2017
SWITCH	Advanced/ metastatic RCC, treatment naïve or prior cytokine therapy	Sorafenib	Sunitinib	Open label phase III crossover RCT	Eichelberg et al. 2015
TIVO-1	Clear cell recurrent/ metastatic RCC, treatment naïve or prior cytokines	Tivozanib	Sorafenib	Open label phase III RCT, assessors partly blinded	Motzer et al. 2013

Patient characteristics are shown in Table 4.

The TIVO-1 study recruited patients with metastatic or recurrent disease, in this analysis we consider only the treatment naïve patients from TIVO-1. The other three studies only recruited treatment naïve patients. SWITCH recruited patients with metastatic or recurrent disease, whereas COMPARZ and CROSS-J-RCC both recruited patients with metastatic disease.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

In all four studies most patients were male – around three-quarters in TIVO-1, COMPARZ and SWITCH, and slightly higher at 82% in Cross-J-RCC. The median age of patients was late 50s to early 60s, reflecting the course of the disease.

TIVO-1 and COMPARZ were international studies and SWITCH enrolled patients from Europe, in all three studies most participants were white Caucasian. CROSS-J-RCC recruited patients from Japan.

TIVO-1 recruited patients with a clear cell component, as did COMPARZ and Cross-J-RCC. SWITCH enrolled patients with any histology.

Patients in TIVO-1 had good performance status, with all having ECOG performance status 0 or 1. This pattern was seen in the other three studies.

Table 4: Baseline characteristics of patients in the relevant trials in the MTC

Trial number (acronym) **Baseline characteristic**	**Treatment 1**	**Treatment 2**
COMPARZ (N=1110)4	**Pazopanib (n=557)**	**Sunitinib (n=553)**
Age	Median 61, range 18-88	Median 62, range 23-86
Gender	398 male (71%)	415 male (75%)
Ethnicity/ location	Europe: 153 N America: 195 Asia: 188 Australia: 21	Europe: 157 N America: 187 Asia: 179 Australia: 30
Performance status	KPS: 70-80: 141 90-100: 416 MSKCC risk: Favourable: 151 Intermediate: 322 Poor: 67	KPS: 70-80: 130 90-100: 423 MSKCC risk: Favourable: 152 Intermediate: 328 Poor: 52
Disease stage	Advanced or metastatic	Advanced or metastatic
Histology	All clear cell	All clear cell
Prior treatments	Nephrectomy: 459 Radiotherapy: 46	Nephrectomy: 465 Radiotherapy: 42
CROSS-J-RCC (N=124)	**Sunitinib (n=57 with results)**	**Sorafenib (n=63)**
Age	Median 67 (41-79)	Median 66 (44-79)
Gender	46 male (81%)	53 male (84%)
Ethnicity/ location	Japan	Japan
Performance status	Favourable risk:12 Intermediate risk: 45	Favourable risk: 14 Intermediate risk: 49
Disease stage	All metastatic	All metastatic
Histology	All clear cell	All clear cell
Prior treatments	Nephrectomy:88% Radiotherapy: 12%	Nephrectomy: 89% Radiotherapy: 6%

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Trial number (acronym) **Baseline characteristic**	**Treatment 1**	**Treatment 2**
	Cytokines: 7%	Cytokines: 10%
SWITCH	**Sorafenib (n=182)**	**Sunitinib (n=183)**
Age	Median 65, range 40-83	Median 64, range 39-84
Gender	139 male (76%)	135 male (74%)
Ethnicity/ location	Germany, Austria, Netherlands	Germany, Austria, Netherlands
Performance status	ECOG: 0: 116 1: 55 2: 0 MSKCC risk: High: 1 Intermediate: 108 Favourable: 71	ECOG: 0: 106 1: 66 2: 1 MSKCC risk: High: 1 Intermediate: 94 Favourable: 82
Disease stage	All advanced/ metastatic	All advanced/ metastatic
Histology	Any, clear cell: 164	Any, clear cell: 154
Prior treatments	Nephrectomy: 167 Radiotherapy: 16 Cytokines: 3 Other: 13	Nephrectomy: 168 Radiotherapy: 23 Cytokines: 8 Other: 13
TIVO-1 (N=363)	**Tivozanib (n=181)**	**Sorafenib (n=182)**
Age	Median 59, range 23-83	Median 59, range 23-85
Gender	134 male (74%)	137male (75%)
Ethnicity/ location	International White: 173 Asian: 7 Black: 1	International White: 174 Asian: 8 Black: 0
Performance status	ECOG: 0: 85 1: 96	ECOG: 0: 96 1: 86
Disease stage	All recurrent/ metastatic	All recurrent/ metastatic
Histology	All clear cell	All clear cell
Prior treatments	Nephrectomy: 181	Nephrectomy: 182

Two were planned crossover studies (SWITCH and Cross-J-RCC), TIVO-1 only allowed patients in the sorafenib arm to crossover to tivozanib after disease progression. COMPARZ did not report whether or not crossover was allowed.

- SWITCH was a planned sequential treatment study assessing whether sorafenib-sunitinib was more effective than sunitinib-sorafenib: 57% of sorafenib patients received second-line sunitinib and 42% of sunitinib patients received second-line sorafenib. Only data from the first, pre-crossover, arm has been reported here and used in the MTC for PFS, OR and selected AEs.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

- CROSS-J-RCC was a similar design to SWITCH and was also a planned sequential treatment study assessing whether sorafenib-sunitinib was more effective than sunitinib-sorafenib. Data is from a poster, 75% (30/57) of sorafenib patients received second-line sunitinib and 53% (47/63) of sunitinib patients received second-line sorafenib. Only data from the first, pre-crossover, arm has been reported here and used in the MTC for PFS, OR and selected AEs.

- Crossover in TIVO-1 was complex since only patients in the sorafenib arm were allowed to crossover to tivozanib and patients in the tivozanib arm received physician's choice. Unlike the CROSS-J-RCC and SWITCH, a much smaller proportion of patients in the tivozanib received targeted therapy after disease progression on tivozanib. Overall, 63% of sorafenib patients crossed over to tivozanib and 20% of patients in the tivozanib received second-line targeted therapy, see Table 5 for further details.

Table 5: Final assessment of subsequent treatment profile based on all available data (Treatment Naïve patients only)

	Tivozanib (N=182)[1]		Sorafenib (N=181)	
	N	%	N	%
Received randomized therapy only	128	70.3%	57	31.5%
Received subsequent therapy	54	29.7%	124	68.5%
Targeted therapy	37	20.3%	120	66.3%
First targeted treatment used				
Tivozanib	*0*	*0.0%*	*114*	*63.0%*
Other VEGF inhibitor	*17*	*9.3%*	*2*	*1.1%*
mTOR inhibitor	*20*	*11.0%*	*4*	*2.2%*
Non targeted therapy only	17	9.3%	4	2.2%

1. One patient randomised to tivozanib withdrew from the study before treatment and is not included in this table

Quality assessments are provided in the original submission (Table 27, page 90). Since we made the submission we have received additional data from the author of the CROSS-J-RCC study (Tomita). Unfortunately, the poster does not provide us with adequate information to carry out a through quality assessment.

Mixed treatment comparison: methods

Based on the results of the proportional hazards tests (see B2), we concluded that an NMA based on parametric curves was a more suitable method than one based on HRs given that the parametric hazard assumption does not hold for PFS in the TIVO-1 study. Therefore, an NMA method based on a parametric survival model was chosen and implemented as described by Ouwens et al. 2010.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

A Bayesian NMA was carried out using the Weibull distribution on the PFS and OS data. In the analysis, transitivity was used as an underlying model assumption to ensure both direct and indirect comparisons of survival curves across trials based on a common comparator. Model parameters were estimated using a Markov Chain Monte Carlo (MCMC) method using WinBUGs run for 50,000 iterations with the first 30,000 iterations discarded as "burn-in". Convergence of the chains was checked using the Gelman-Rubin statistic. The WinBUGs code is detailed at the end of this question.

Fixed-effects models were considered for this analysis due to the lack of heterogeneity on pairwise comparisons. There were only two trials (SWITCH and CROSS-J-RCC) which compared the same two treatments (sorafenib and sunitinib) and, therefore, the estimation of between trial heterogeneity was considered not to be appropriate.

NMAs based on parametric curves do not assume proportional hazards between the pairwise comparators and therefore this method can be applied to any survival function for which transitivity of treatment effects in the NMA model can be shown. The KM curves in the three selected studies were digitally extracted with DigitizeIt software (http://www.digitizeit.de/). For each treatment, the patient level data including event or censor time, the number of patients at that time, the number of deaths and the number of patients censored during the time interval were recreated by applying the method published in Guyot et al. 2012. The reconstructed data were then used as inputs for the NMA models. The data regeneration was executed in the programming language R.

Mixed treatment comparison: results

Estimates of parameters of each survival curve (Weibull) based on the fixed effect model are presented in Table 6. The estimated median PFS and OS is presented in Table 7.

Table 6: Parameter estimates of Weibull for fixed effects MTC

		OS		PFS	
Weibull	Distribution Parameters	Scale	Shape	Scale	Shape
	Tivozanib	0.0157	1.147	0.0309	1.0871
	Sunitinib	0.0056	1.157	0.0302	1.1371
	Pazopanib	0.0056	1.387	0.022	1.3087

Table 7: Median survival for OS and PFS results based on the MTC using the Weibull function

	MTC Result – Weibull function	
	Median OS (Months)	**Median PFS (Months)**
Tivozanib	27	17
Sunitinib	33	16
Pazopanib	32	14

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 5: Averaged PFS adjusted to the baseline from CROSS-J-RCC study fixed effects (Weibull)

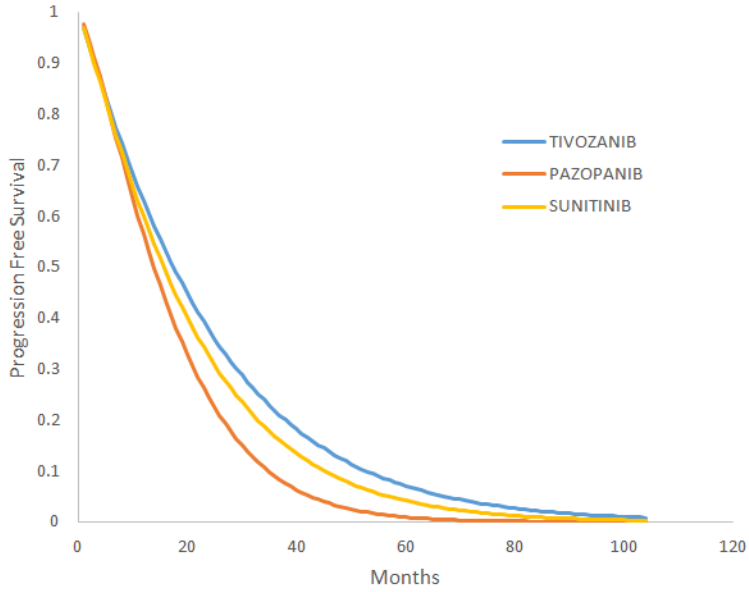
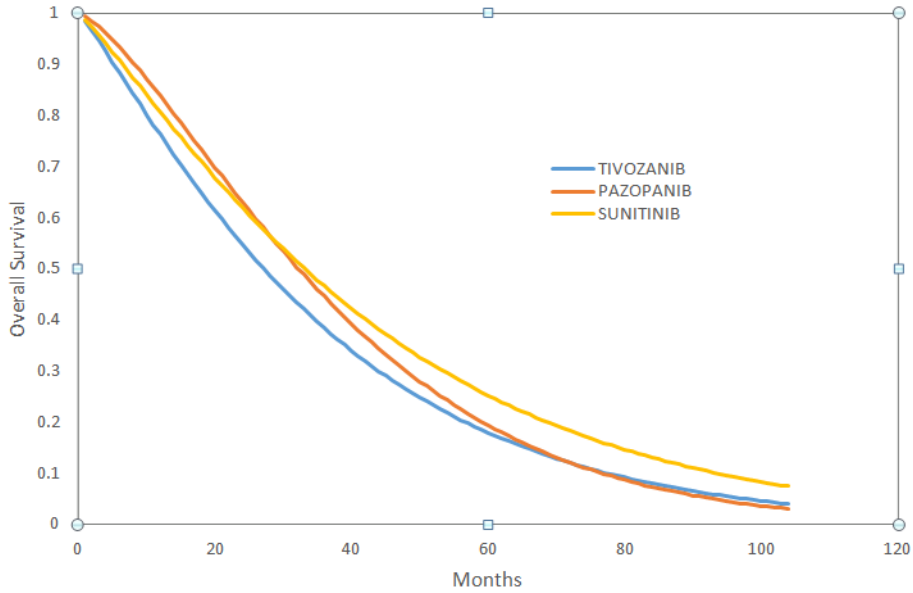


Figure 6: Averaged OS adjusted to the baseline from CROSS-J-RCC study fixed effects (Weibull)



Safety

OR was used for the safety analysis.

Table 8: Pairwise estimates of treatment effects (OR) for specific AEs from NMA (Treatment naïve patients) - diarrhoea

Treatment	Median	95% CrI
TIVO vs SOR	0.3291	[0.086; 1.007]
TIVO vs SUN	0.1131	[0.025; 0.43]
TIVO vs PAZ	0.09738	[0.02; 0.399]

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Table 9: Pairwise estimates of treatment effects (OR) for specific AEs from NMA (Treatment naïve patients) – fatigue/asthenia

Treatment	Median	95% CrI
TIVO vs SOR	1.746	[0.59; 5.662]
TIVO vs SUN	0.6846	[0.173; 2.849]
TIVO vs PAZ	1.22	[0.294; 5.294]

Table 10: Pairwise estimates of treatment effects (OR) for specific AEs from NMA (Treatment naïve patients) – hypertension

Treatment	Median	95% CrI
TIVO vs SOR	1.76	[1.048; 2.985]
TIVO vs SUN	1.422	[0.639; 3.182]
TIVO vs PAZ	1.421	[0.598; 3.391]

Table 11: Pairwise estimates of treatment effects (OR) for specific AEs from NMA (Treatment naïve patients) – ALT Increased

Treatment	Median	95% CrI
TIVO vs SUN	0.2307	[0; 7.128]
TIVO vs SOR	0.1497	[0; 3.698]
TIVO vs PAZ	0.05841	[0; 1.873]

Table 12: Pairwise estimates of treatment effects (OR) for specific AEs from NMA (Treatment naïve patients) – AST Increased

Treatment	Median	95% CrI
TIVO vs SUN	0.134	[0; 3.215]
TIVO vs SOR	0.06602	[0; 1.064]
TIVO vs PAZ	0.0295	[0; 0.753]

As mentioned in the study design section, there were only two studies within this restricted network which compared the same two comparators (CROSS-J-RCC and SWITCH). This meant that the random effects model could not be carried out and therefore it was not possible to test for heterogeneity.

With regard to crossover, the analysis did not adjust for crossover since we did not have patient level data for studies other than TIVO-1. This is a potential source of bias since we know that the one-way crossover in TIVO-1 resulted in an improved OS with sorafenib, which is not surprising since 66% of sorafenib patients received second-line targeted therapy on disease progression versus only 20% of tivozanib patients. When we adjusted for crossover in our original submission using the IPCW method we found that the OS for sorafenib and tivozanib was identical. Cox proportional regression using the IPCW-adjusted dataset revealed a HR for OS (sorafenib patients censored when crossing over to tivozanib) of 1.021; 95% CI 0.671 to 1.553; p=0.923, confirming that the discordant OS seen in the ITT analysis is a result of the one-way crossover.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Economic model: results

Results are presented for the base case result for a population of patients with no previous treatment with either immunotherapy or targeted therapy using tivozanib at list price ([redacted]) Costs used for the comparators (sunitinib and pazopanib) reflect established PAS prices.

Results of the revised model based on restricted NMA network (TIVO-1, SWITCH, COMPARZ and CROSS-J-RCC) requested by the ERG are shown below.

Table 13: Base-case results: pairwise comparisons – tivozanib versus sunitinib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC)

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£72,592	1.893	
SUN	£92,965	2.180	
Increment (TIVO - SUN)	-£20,373	-0.287	£71,104
TIVO: Tivozanib, SUN: Sunitinib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 14: Base-case results: pairwise comparisons – tivozanib versus pazopanib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC)

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£72,592	1.893	
PAZO	£83,541	2.006	
Increment (TIVO - PAZ)	-£10,949	-0.113	£97,138
TIVO: Tivozanib, PAZ: Pazopanib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Table 15: Base-case results (list price for tivozanib) from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus tivozanib (QALYs)	ICER (£) incremental (QALYs)
Tivozanib at list price								
Tivozanib	£72,592	2.692	1.893					
Pazopanib	£83,541	2.930	2.006	£10,949	0.238	0.113	£97,138	£97,138
Sunitinib	£92,965	3.172	2.180	£20,373	0.479	0.287	£71,104	£38,942
ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALYs: Quality-adjusted life years; IFN: Interferon								

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Disaggregated results of the base case incremental cost effectiveness analysis

Versus sunitinib

Table 16: Summary of QALY gain by health state (tivozanib versus sunitinib)

Health state	QALY tivozanib	QALY sunitinib	Increment	Absolute increment	% absolute increment
Pre-progression (no AEs)	1.313	1.102	0.211	0.211	-73.7%
Pre-progression (with AEs)	0.034	0.076	-0.042	0.042	14.8%
Post-progression	0.546	1.001	-0.455	0.455	158.9%
Total	1.893	2.180	-0.287	0.709	100.0%
QALY: Quality-adjusted life year					

Table 17: Summary of costs by health state (tivozanib versus sunitinib)

Health state	Cost tivozanib	Cost sunitinib	Increment	Absolute increment	% absolute increment
At list price					
Pre-progression	£47,199.7	£46,378	£821.4	£821.4	3.7%
Post-progression	£25,392.6	£46,587	-£21,194.5	£21,194.5	96.3%
Total	£72,592.3	£92,965	-£20,373.1	£22,015.9	100.0%
QALY: Quality-adjusted life year					

Table 18: Summary of predicted resource use by category of cost – tivozanib versus sunitinib

Item	Cost tivozanib	Cost sunitinib	Increment	Absolute increment	% absolute increment
At list price					
Medication cost (pre-progression)	£42,197.1	£41,934	£262.7	£262.7	1.2%
Medication cost (post-progression)	£23,117.3	£42,381	-£19,263.5	£19,263.5	87.3%
Total medication cost	£65,314.4	£84,315			88.5%
Management cost (pre-progression)	£4,860.5	£4,281	£579.7	£579.7	2.6%
Management cost (post-progression)	£2,275.3	£4,206	-£1,931.0	£1,931.0	8.8%
AE cost	£142.1	£163	-£21.0	£21.0	0.1%
Total	£72,592.3	£92,965	-£20,373	£22,058	100.0%
AE: Adverse event					

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Versus pazopanib

Table 19: Summary of QALY gain by health state (tivozanib versus pazopanib)

Health state	QALY tivozanib	QALY pazopanib	Increment	Absolute increment	% absolute increment
Pre-progression (no AEs)	1.313	0.936	0.378	0.378	43.5%
Pre-progression (with AEs)	0.034	0.047	-0.013	0.013	1.5%
Post-progression	0.546	1.024	-0.478	0.478	55.0%
Total	1.893	2.006	-0.113	0.868	100.0%
QALY: Quality-adjusted life year					

Table 20: Summary of costs by health state (tivozanib versus pazopanib)

Health state	Cost tivozanib	Cost pazopanib	Increment	Absolute increment	% absolute increment
At list price					
Pre-progression	£47,199.7	£36,009	£11,190.7	£11,190.7	33.6%
Post-progression	£25,392.6	£47,532	-£22,139.8	£22,139.8	66.4%
Total	£72,592.3	£83,541	-£10,949.2	£33,330.5	100.0%
QALY: Quality-adjusted life year					

Table 21: Summary of predicted resource use by category of cost – tivozanib versus pazopanib

Item	Cost tivozanib	Cost pazopanib	Increment	Absolute increment	% absolute increment
At list price					
Medication cost (pre-progression)	£42,197.1	£32,345	£9,852.0	£9,852.0	29.6%
Medication cost (post-progression)	£23,117.3	£43,328	-£20,211.0	£20,211.0	60.6%
Total medication cost	£65,314.4	£75,673			90.2%
Management cost (pre-progression)	£4,860.5	£3,557	£1,303.7	£1,303.7	3.9%
Management cost (post-progression)	£2,275.3	£4,204	-£1,928.8	£1,928.8	5.8%
AE cost	£142.1	£107	£35.0	£35.0	0.1%
Total	£72,592.3	£83,541.4	-£10,949.2	£33,330.5	100.0%
AE: Adverse event					

References

Tomita Y, Naito S, Sassa N et al. Sunitinib versus sorafenib as first-line therapy followed by sorefenib and sunitinib for patients with metastatic renal cell carcinoma (RCC) with clear cell histology: A multicenter randomized trial, CROSS-J-RCC. Poster presented at ASCO GU February 16-18 2017 Orlando, Florida, US.

Ouwens MJ, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. Res Synth Methods. 2010;1(3-4):258-71.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9.

WinBUGS code

 # Winbugs code for random effects networks meta-analysis model – Overall survival (OS) Naïve patients.

```
Model{
for (i in 1:N){ # N=number of data points in dataset
#likelihood
r[i]~ dbin(p[i],n[i])
p[i]<-1- exp(-h[i]*dt[i]) # hazard h over interval [t,t+dt] expressed as deaths per
unit #person-time (e.g. months)

#random effects model
Log(h[i]) <- nu[i]+ log(time[i])*theta[i]
nu[i]<-mu[s[i],1]+d[s[i],1]*(1-equals(t[i],b[i]))
theta[i]<-mu[s[i],2]+ d[s[i],2]*(1-equals(t[i],b[i]))
}
# priors
d[1,1]<-0
d[1,2]<-0
for(j in 2 :NT){ # NT=number of treatments
d[j,1:2] ~ dmnorm(mean[1:2],prec2[,])
}
for(k in 1 :NS){
mu[k,1:2] ~ dmnorm(mean[1:2],prec2[,])
}
}
```

#Winbugs data set

```
list(N=196, NS=4, NT=4, mean=c(0,0),
prec2 = structure(.Data = c(0.0001,0,0,0.0001), .Dim = c(2,2)))

# initials 1
list(
d=structure(.Data=c(NA,NA,0,0,0,0,0,0), .Dim = c(4,2)),
mu = structure(.Data=c(1,1,1,1,1,1,1,1), .Dim = c(4,2)))

# initials 2
list(
d=structure(.Data=c(NA,NA,0.5,0.5,0.5,0.5,0.5,0.5), .Dim = c(4,2)),
mu = structure(.Data=c(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim = c(4,2)))
```

s[]	r[]	n[]	t[]	b[]	time[]	dt[]
1	0	63	1	1	1	2
1	1	62	1	1	3	2
1	0	62	1	1	5	2
1	2	59	1	1	7	2
1	0	59	1	1	9	2
1	6	53	1	1	11	2
1	2	51	1	1	13	2
1	3	48	1	1	15	2
1	2	45	1	1	17	2
1	5	40	1	1	19	2
1	0	39	1	1	21	2
1	2	37	1	1	23	2
1	2	35	1	1	25	2
1	2	32	1	1	27	2
1	1	31	1	1	29	2
1	2	28	1	1	31	2
1	2	26	1	1	33	2
1	2	23	1	1	35	2
1	0	23	1	1	37	2
1	1	21	1	1	39	2
1	0	19	1	1	41	2

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

1	0	19	1	1	43	2
1	0	19	1	1	45	2
1	0	16	1	1	47	2
1	0	16	1	1	49	2
1	1	14	1	1	51	2
1	0	12	1	1	53	2
1	0	57	2	1	1	2
1	0	57	2	1	3	2
1	2	55	2	1	5	2
1	1	54	2	1	7	2
1	2	52	2	1	9	2
1	1	51	2	1	11	2
1	5	46	2	1	13	2
1	2	44	2	1	15	2
1	3	41	2	1	17	2
1	3	37	2	1	19	2
1	2	35	2	1	21	2
1	1	34	2	1	23	2
1	1	33	2	1	25	2
1	0	33	2	1	27	2
1	0	33	2	1	29	2
1	1	32	2	1	31	2
1	3	29	2	1	33	2
1	1	28	2	1	35	2
1	0	28	2	1	37	2
1	1	26	2	1	39	2
1	1	24	2	1	41	2
1	1	22	2	1	43	2
1	2	19	2	1	45	2
1	0	18	2	1	47	2
1	0	18	2	1	49	2
1	0	15	2	1	51	2
1	0	13	2	1	53	2
2	0	182	1	1	1	2
2	8	169	1	1	3	2
2	10	148	1	1	5	2
2	8	137	1	1	7	2
2	6	127	1	1	9	2
2	8	118	1	1	11	2
2	7	109	1	1	13	2
2	3	105	1	1	15	2
2	4	95	1	1	17	2
2	3	84	1	1	19	2
2	3	76	1	1	21	2
2	4	68	1	1	23	2
2	4	60	1	1	25	2
2	4	50	1	1	27	2
2	0	42	1	1	29	2
2	1	35	1	1	31	2
2	2	29	1	1	33	2
2	1	25	1	1	35	2
2	3	21	1	1	37	2
2	1	18	1	1	39	2
2	0	16	1	1	41	2
2	2	11	1	1	43	2
2	0	9	1	1	45	2
2	0	8	1	1	47	2
2	0	7	1	1	49	2
2	1	180	2	1	1	2
2	11	162	2	1	3	2
2	9	147	2	1	5	2
2	9	135	2	1	7	2
2	6	125	2	1	9	2
2	6	116	2	1	11	2
2	6	106	2	1	13	2
2	7	95	2	1	15	2
2	1	92	2	1	17	2

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

2	5	84	2	1	19	2
2	3	77	2	1	21	2
2	2	67	2	1	23	2
2	1	59	2	1	25	2
2	4	49	2	1	27	2
2	1	40	2	1	29	2
2	2	34	2	1	31	2
2	0	31	2	1	33	2
2	0	29	2	1	35	2
2	3	23	2	1	37	2
2	1	19	2	1	39	2
2	0	17	2	1	41	2
2	0	14	2	1	43	2
2	0	12	2	1	45	2
2	0	10	2	1	47	2
2	0	8	2	1	49	2
3	3	546	2	2	1	2
3	16	515	2	2	3	2
3	29	478	2	2	5	2
3	24	450	2	2	7	2
3	28	421	2	2	9	2
3	30	389	2	2	11	2
3	22	367	2	2	13	2
3	18	348	2	2	15	2
3	17	330	2	2	17	2
3	12	314	2	2	19	2
3	16	297	2	2	21	2
3	7	288	2	2	23	2
3	10	272	2	2	25	2
3	13	249	2	2	27	2
3	12	229	2	2	29	2
3	11	214	2	2	31	2
3	5	206	2	2	33	2
3	14	186	2	2	35	2
3	5	176	2	2	37	2
3	11	161	2	2	39	2
3	7	137	2	2	41	2
3	8	112	2	2	43	2
3	3	92	2	2	45	2
3	9	67	2	2	47	2
3	1	45	2	2	49	2
3	0	28	2	2	51	2
3	3	16	2	2	53	2
3	1	8	2	2	55	2
3	0	557	3	2	1	2
3	19	531	3	2	3	2
3	25	501	3	2	5	2
3	21	474	3	2	7	2
3	18	452	3	2	9	2
3	25	425	3	2	11	2
3	33	391	3	2	13	2
3	15	375	3	2	15	2
3	22	353	3	2	17	2
3	18	333	3	2	19	2
3	25	305	3	2	21	2
3	7	293	3	2	23	2
3	12	276	3	2	25	2
3	7	258	3	2	27	2
3	25	225	3	2	29	2
3	0	221	3	2	31	2
3	5	214	3	2	33	2
3	2	205	3	2	35	2
3	10	189	3	2	37	2
3	11	174	3	2	39	2
3	6	161	3	2	41	2
3	8	130	3	2	43	2
3	4	99	3	2	45	2

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

3	7	65	3	2	47	2
3	2	50	3	2	49	2
3	1	28	3	2	51	2
3	2	20	3	2	53	2
3	2	14	3	2	55	2
4	2	179	1	1	1	2
4	4	172	1	1	3	2
4	3	168	1	1	5	2
4	6	157	1	1	7	2
4	4	151	1	1	9	2
4	9	142	1	1	11	2
4	10	130	1	1	13	2
4	7	123	1	1	15	2
4	3	119	1	1	17	2
4	5	112	1	1	19	2
4	3	108	1	1	21	2
4	3	103	1	1	23	2
4	12	91	1	1	25	2
4	2	68	1	1	27	2
4	2	46	1	1	29	2
4	8	29	1	1	31	2
4	2	23	1	1	33	2
4	3	8	1	1	35	2
4	0	181	4	1	1	2
4	5	175	4	1	3	2
4	7	163	4	1	5	2
4	12	151	4	1	7	2
4	12	139	4	1	9	2
4	4	132	4	1	11	2
4	9	122	4	1	13	2
4	7	114	4	1	15	2
4	4	108	4	1	17	2
4	7	101	4	1	19	2
4	5	96	4	1	21	2
4	7	89	4	1	23	2
4	2	87	4	1	25	2
4	4	68	4	1	27	2
4	4	50	4	1	29	2
4	3	40	4	1	31	2
4	3	22	4	1	33	2
4	1	8	4	1	35	2

END

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

 # Winbugs code for random effects networks meta-analysis model (PFS Analysis) Naïve patients

```
Model{
for (i in 1:N){ # N=number of data points in dataset
#likelihood
r[i]~ dbin(p[i],n[i])
p[i]<-1- exp(-h[i]*dt[i]) # hazard h over interval [t,t+dt] expressed as deaths per
unit #person-time (e.g. months)

#fixed effects model
log(h[i]) <- nu[i]+log(time[i])*theta[i]
nu[i]<-mu[s[i],1]+d[s[i],1]*(1-equals(t[i],b[i]))
theta[i]<-mu[s[i],2]+ d[s[i],2]*(1-equals(t[i],b[i]))
 }
# priors
d[1,1]<-0
d[1,2]<-0
for(j in 2 :NT){ # NT=number of treatments
d[j,1:2] ~ dmnorm(mean[1:2],prec2[,])
}
for(k in 1:NS){
mu[k,1:2] ~ dmnorm(mean[1:2],prec2[,])
 }
}
```

#Winbugs data set

```
list(N=162, NS=4, NT=4, mean=c(0,0),
prec2 = structure(.Data = c(0.0001,0,0,0.0001), .Dim = c(2,2)))

# initials 1
list(
d=structure(.Data=c(NA,NA,0,0,0,0,0,0), .Dim = c(4,2)),
mu = structure(.Data=c(1,1,1,1,1,1,1,1), .Dim = c(4,2)))
# initials 2
list(
d=structure(.Data=c(NA,NA,0.5,0.5,0.5,0.5,0.5,0.5), .Dim = c(4,2)),
mu = structure(.Data=c(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim = c(4,2)))
```

s[]	r[]	n[]	t[]	b[]	time[]	dt[]
1	0	63	1	1	1	2
1	7	56	1	1	3	2
1	7	49	1	1	5	2
1	17	32	1	1	7	2
1	6	26	1	1	9	2
1	2	24	1	1	11	2
1	6	18	1	1	13	2
1	6	12	1	1	15	2
1	2	10	1	1	17	2
1	0	10	1	1	19	2
1	0	10	1	1	21	2
1	0	10	1	1	23	2
1	5	5	1	1	25	2
1	2	3	1	1	27	2
1	0	3	1	1	29	2
1	0	3	1	1	31	2
1	0	3	1	1	33	2
1	2	61	2	1	1	2
1	7	52	2	1	3	2
1	11	40	2	1	5	2
1	5	33	2	1	7	2
1	6	26	2	1	9	2
1	0	24	2	1	11	2
1	2	22	2	1	13	2
1	3	17	2	1	15	2
1	1	14	2	1	17	2
1	0	12	2	1	19	2
1	0	10	2	1	21	2

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

1	2	6	2	1	23	2
1	0	6	2	1	25	2
1	1	5	2	1	27	2
1	0	5	2	1	29	2
1	1	4	2	1	31	2
1	1	3	2	1	33	2
2	7	170	1	1	1	2
2	26	132	1	1	3	2
2	21	100	1	1	5	2
2	33	67	1	1	7	2
2	14	53	1	1	9	2
2	4	49	1	1	11	2
2	7	42	1	1	13	2
2	6	36	1	1	15	2
2	3	32	1	1	17	2
2	1	30	1	1	19	2
2	5	25	1	1	21	2
2	1	22	1	1	23	2
2	2	18	1	1	25	2
2	2	16	1	1	27	2
2	2	14	1	1	29	2
2	4	10	1	1	31	2
2	1	9	1	1	33	2
2	2	7	1	1	35	2
2	0	7	1	1	37	2
2	0	5	1	1	39	2
2	4	176	2	1	1	2
2	38	128	2	1	3	2
2	18	101	2	1	5	2
2	13	88	2	1	7	2
2	12	75	2	1	9	2
2	7	68	2	1	11	2
2	10	57	2	1	13	2
2	10	46	2	1	15	2
2	3	42	2	1	17	2
2	4	36	2	1	19	2
2	4	31	2	1	21	2
2	4	27	2	1	23	2
2	5	22	2	1	25	2
2	0	20	2	1	27	2
2	0	18	2	1	29	2
2	0	17	2	1	31	2
2	0	16	2	1	33	2
2	0	16	2	1	35	2
2	0	16	2	1	37	2
2	3	13	2	1	39	2
3	3	546	2	2	1	2
3	16	515	2	2	3	2
3	29	478	2	2	5	2
3	24	450	2	2	7	2
3	28	421	2	2	9	2
3	30	389	2	2	11	2
3	22	367	2	2	13	2
3	18	348	2	2	15	2
3	17	330	2	2	17	2
3	12	314	2	2	19	2
3	16	297	2	2	21	2
3	7	288	2	2	23	2
3	10	272	2	2	25	2
3	13	249	2	2	27	2
3	12	229	2	2	29	2
3	11	214	2	2	31	2
3	5	206	2	2	33	2
3	14	186	2	2	35	2
3	5	176	2	2	37	2
3	11	161	2	2	39	2
3	7	137	2	2	41	2

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

3	8	112	2	2	43	2
3	3	92	2	2	45	2
3	9	67	2	2	47	2
3	1	45	2	2	49	2
3	0	28	2	2	51	2
3	3	16	2	2	53	2
3	1	8	2	2	55	2
3	0	557	3	2	1	2
3	19	531	3	2	3	2
3	25	501	3	2	5	2
3	21	474	3	2	7	2
3	18	452	3	2	9	2
3	25	425	3	2	11	2
3	33	391	3	2	13	2
3	15	375	3	2	15	2
3	22	353	3	2	17	2
3	18	333	3	2	19	2
3	25	305	3	2	21	2
3	7	293	3	2	23	2
3	12	276	3	2	25	2
3	7	258	3	2	27	2
3	25	225	3	2	29	2
3	0	221	3	2	31	2
3	5	214	3	2	33	2
3	2	205	3	2	35	2
3	10	189	3	2	37	2
3	11	174	3	2	39	2
3	6	161	3	2	41	2
3	8	130	3	2	43	2
3	4	99	3	2	45	2
3	7	65	3	2	47	2
3	2	50	3	2	49	2
3	1	28	3	2	51	2
3	2	20	3	2	53	2
3	2	14	3	2	55	2
4	2	177	1	1	1	2
4	19	156	1	1	3	2
4	14	141	1	1	5	2
4	24	115	1	1	7	2
4	15	100	1	1	9	2
4	22	76	1	1	11	2
4	15	61	1	1	13	2
4	10	51	1	1	15	2
4	8	43	1	1	17	2
4	4	34	1	1	19	2
4	4	24	1	1	21	2
4	2	18	1	1	23	2
4	0	18	1	1	25	2
4	0	18	1	1	27	2
4	1	17	1	1	29	2
4	0	16	1	1	31	2
4	0	179	4	1	1	2
4	24	152	4	1	3	2
4	18	131	4	1	5	2
4	7	124	4	1	7	2
4	16	108	4	1	9	2
4	11	95	4	1	11	2
4	5	90	4	1	13	2
4	7	83	4	1	15	2
4	13	69	4	1	17	2
4	5	63	4	1	19	2
4	6	56	4	1	21	2
4	7	48	4	1	23	2
4	3	42	4	1	25	2
4	2	39	4	1	27	2
4	1	38	4	1	29	2
4	3	34	4	1	31	2

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

END

OPTION 2 – Conduct a matching-adjusted indirect comparison (MAIC)

This method could reduce the uncertainty introduced by methodological (e.g. differential crossover protocols) and clinical (e.g. variation in baseline prognosis) heterogeneity between studies in the mixed treatment comparisons which cannot be adjusted for. If a matching-adjusted indirect comparison is undertaken, methods to adjust for the one-way crossover in TIVO-1 will not be necessary as it does not rely on the within-trial comparison with sorafenib; only the tivozanib treatment arm is used.

The method could be used to adjust the TIVO-1 population using individual patient data to more closely match a trial (or trials) of the relevant comparators. For example, the TIVO-1 trial population could be adjusted to match the characteristics of the COMPARZ trial to provide estimates of tivozanib compared with pazopanib and sunitinib.

If this option is chosen, guidance is provided in the Technical Support Document 18 issued by the Decision Support Unit.(2)

All the important prognostic factors need to be incorporated to reduce bias in the matching-adjusted indirect comparison. Any prognostic factors not adjusted for need to be explicitly stated and a judgement made on the likely impact not accounting for them would have on the results.

A2. **Priority question**: The submission states that 26% of tivozanib patients received next-line therapy compared with 65% of sorafenib patients (Table 16 of the submission), whereas in the 2016 clinical study report[3] Table 27 notes that 57.7% of tivozanib patients received subsequent anti-cancer therapy compared with 78.2% of sorafenib patients and Table 30 reports 38.4% of tivozanib and 75.7% of sorafenib patients did. Please clarify how many patients in each treatment arm of TIVO-1 received subsequent therapy.

The different figures in the submission reflect the time at which each datacut was made and the assumptions underlying the definitions of subsequent therapy.

The data in Table 16 of our submission (26% of tivozanib patients overall received next-line therapy compared with 65% of sorafenib patients) is taken from the published paper [Motzer,

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

2013] and is data with a cut off data of 27 August 2012. This data reflects second line treatment only and does not take into account subsequent lines of therapy

Table 27 in the 2016 clinical study report reflects a summary of the overall survival sweep as of 10 July 2013 for Study AV-951-09-301 and as of 03 June 2013 for Study AV-951-09-902. This data reflects the overall percentage of patients receiving next-line therapy. Importantly, the figure of 57.7% of tivozanib patients receiving subsequent therapy includes 88 individuals who were randomised to tivozanib in study 301, who did not progress but continued tivozanib as part of study 902. The inclusion of these patients in the table is an artefact of the data extraction algorithm used to generate the CSR tables, as these patients actually continued their randomised therapy uninterrupted. This point has been accepted by the CHMP rapporteurs in the course of the EMA submission for tivozanib.

Table 30 reflects the percentage of patients who discontinued who received second line therapy rather than the percentage of patients overall who received second-line therapy.

The table below shows the definitive data for patients receiving subsequent treatment, based on the most comprehensive data available at the latest data cut (July 2013), and includes not only second-line treatment but also subsequent therapy lines. Key groups were:

- Sorafenib patients who progressed in the course of study 301 and were switched to tivozanib
- Sorafenib patients who progressed in the course of study 301 and were switched to other second line therapies
- Tivozanib patients who progressed in the course of study 301 and were switched to other second line therapies
- Sorafenib patients who did not progress in the course of study 301 but were switched to tivozanib on completion of the study
- Patients from both treatment groups who did not progress in the course of study 301 and were switched to other treatments on completion of the study

Where patients were switched initially to non-targeted therapy (immunotherapy, radiotherapy, chemotherapy) and subsequently progressed, if they were given a targeted therapy and third or subsequent line, these patients were included in the “targeted therapy” group. Patients were only documented as receiving non-targeted therapy if they received no targeted therapy at any stage over the follow-up period.

Table 22: Final assessment of subsequent treatment profile based on all available data

	Tivozanib (N=259)[1]		**Sorafenib (N=257)**	
	N	**%**	**N**	**%**
Received randomized therapy only	180[2]	69.5%	83	32.3%
Received subsequent therapy	79	30.5%	174	67.7%
Targeted therapy	53	20.5%	169	65.8%

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

First targeted treatment used				
Tivozanib	0	0.0%	161	62.6%
Other VEGF inhibitor	24	9.3%	4	1.6%
mTOR inhibitor	29	11.2%	4	1.6%
Non targeted therapy only	26	10.0%	5	1.9%
First non-targeted treatment used				
Immunotherapy	13	5.0%	3	1.2%
Radiotherapy	5	1.9%	2	0.8%
Chemotherapy	1	0.4%	0	0.0%
Surgery	2	0.8%	0	0.0%
Other	53	1.9%	0	0.0%

Notes

1. One patient was randomised to tivozanib but withdrew consent before receiving treatment and is excluded from this table
2. 4 patients received tamoxifen and 1 patient received neovastat. One further patient is documented as receiving herbal therapy post-progression, but no further details are given, so it has not been included in this table

Reference

Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol 2013; 31(30): 3791-9.

A3. **Priority question:** The interim clinical study report for TIVO-1(3) states that the first patient was enrolled on 11 February 2010 and the last patient completed the study on 10 June 2013. Please provide the following information:

- Date of enrolment of first patient into the extension study; The first patient enrolled into the extension study enrolled on 17 May 2010.
- Date of enrolment of last patient into TIVO-1 and into the extension study; ; The last patient enrolled into TIVO-1 enrolled on 27 August 2010, the last patient enrolled into the extension study enrolled on 28 December 2011.
- Date of completion of the last patient in the extension study; 4 July 2014.
- Date of last follow-up assessment for TIVO-1 and the extension study: The last 30-day follow-up visit in the extension study was 12 June 2014 and the last long-term follow-up visit in the extension study was 8 April 2014. The last 30-day follow-up visit in the TIVO-1 study was 3 April 2012. The last long-term follow-up visit in the TIVO-1 study was 10 June 2013.

A4. **Priority question:** Please provide mean (and standard deviation) and median (with range) duration of follow-up for patients included in the analysis of (i) progression-free survival and (ii) overall survival.

Progression free survival

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Follow-up (days) for PFS determined by time from initial randomisation to end of study 301. End of follow-up was determined by death, progression, withdrawal, switch to study 902 or end of study.

Table 23: Final assessment of subsequent treatment profile based on all available data

PFS follow-up (days)	All patients	Tivozanib	Sorafenib
Mean	492	571	412
SD	273	266	257
Median	510	595	364
Range	13-1218	13-1218	23-1155

Overall survival

Follow-up (days) for OS determined by time from initial randomisation to end of study 902. End of follow-up was determined by death, withdrawal or end of study.

Table 24: Final assessment of subsequent treatment profile based on all available data

OS follow-up (days)	All patients	Tivozanib	Sorafenib
Mean	734	715	753
SD	361	363	359
Median	861	810	915
Range	13-1218	13-1218	23-1163

A5. **Priority question:** Please provide the most recent individual clinical study reports for TIVO-1 and the extension study AV-951-09-902.

The CSRs provided for TIVO-1 in the original submission are the most recent ones. We enclose a CSR for the extension study AV-951-09-902 with this document.

A6. **Priority question:** Please provide overall survival results from the analysis comparing patients in each treatment arm of TIVO-1 who remained on the treatment that they had been randomised to at the end of follow-up or stopped treatment without subsequent therapy (as described on page 49 of the company submission, and in the Motzer 2013 poster(4)).

OS is not reached in this population, 2 year survival results are shown in Table 23 of the original submission, which is reproduced below.

Table 25: 2-year survival by next-line therapy (Table 23 in original submission)

	Tivozanib		Sorafenib	
	n	2 year survival (%), 95% CI	n	2 year survival (%), 95% CI
Any next-line anti-cancer therapy	68	50 (38-62)	168	64 (56-71)
Next-line VEGFR-TKI	18	55 (31-78)	158	63 (56-71)

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

			(156 receiving tivozanib)	
Still on study treatment or no next-line treatment	192	56 (48-63)	89	54 (43-65)
VEGFR-TKI: Vascular endothelial growth factor receptor-tyrosine kinase inhibitor				

A7. **Priority question**: For progression free survival in TIVO-1, please provide full details of how many people in each treatment group were censored and for what reasons (numbers given as 104 and 87 for tivozanib and sorafenib, respectively, in Table 17 of the 2016 clinical study report).

Table 26: Reason for PFS censorship – study 301

Reason	All patients	Tivozanib	Sorafenib
Remained on treatment at end of study	162	89	73
Withdrawal of consent	16	8	8
Poor compliance	2	0	2
Lack of efficacy	6	4	2
Lost to follow-up	4	2	2
Treatment interruption >2 weeks	1	1	0
Total	191	104	87

A8. Please clarify whether all diagnoses of progressive disease were confirmed by independent radiology review. The first two sentences and the last sentence of the paragraph below taken from the company submission seem to contradict each other.

> "*All imaging scans were evaluated by an independent radiology review, blinded to study treatment. Patients with radiological evidence of PD as assessed by the investigator had confirmation by blinded independent review within 48 hours. This independent review to confirm investigator-called PD was a separate process from the third-party review of response performed by the core imaging laboratory to assess the primary end-point. Confirmation of PD was not required if significant clinical deterioration, appearance of new lesions, or >50% increase in measurable disease per RECIST was noted by the investigator*".

To clarify, there were two radiology reviews:

The study required investigators to continue administering study drug to patients with investigator-determined progressive disease until it was confirmed by a blinded independent central reviewer. The results from the independent confirmation were provided to the investigators within 48 hours. A protocol change meant that PD was not required if significant clinical deterioration, appearance of new lesions, or >50% increase in measurable disease per RECIST was noted by the investigator.

There was also a third-party review of response performed by the core imaging laboratory to assess the primary end-point.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

A9. Page 54 of the 2016 clinical study report notes that treatment with the study drug could be interrupted for up to 2 weeks, and interruptions longer than 2 weeks led to the patient stopping treatment, "*unless there was clear benefit from treatment, in which case the investigator and medical monitor reviewed the patient's condition in order to resume treatment*". Please give details of how "clear benefit" was determined.

Although 'clear benefit' is not specified in the CSR, we have contacted Mike Needle (Chief Medical Officer, AVEO Pharmaceuticals) sponsor of the TIVO-1 study and he confirmed that 'clear benefit' was defined as a clinical response in the opinion of the investigator. It should be noted that all patients in the sorafenib arm had treatment interruption for less than 2 weeks and all bar one patient in the tivozanib arm had treatment interruption for less than 2 weeks (Table 7, 2016 CSR).

A10. Please provide the following information to help clarify why so few of the dose interruptions led to discontinuation (clinical study report, Table 7 and Table 47):

- Table 47 of the 2016 clinical study report shows that 139 people in the sorafenib group and 30 people in the tivozanib group had interruptions attributed to reasons "other" than adverse effects. Please give details of "other" reasons for treatment interruption.
- Please provide the number of people in each group with treatment interruptions lasting less than 2 weeks.
- Please provide the number of people in each group with treatment interruptions lasting longer than 2 weeks who restarted treatment because there was clear benefit (see A9).
- Please provide the median (and range) and mean (with standard deviation) duration of dose interruption for both groups.

Few of the dose interruptions led to discontinuation, since many of the dose interruptions were due to other reasons, particularly in the sorafenib arm (78%, 139/179 patients) and were for a short period of time (1-2 days).

There were more dose interruptions in the sorafenib arm than in the tivozanib arm due to 'other reasons'; this was primarily due to the dosing schedule of the two agents. The dosing schedule for sorafenib was twice daily and sorafenib was given continuously. The treatment schedule for tivozanib was a single daily dose for 21 days followed by 7 days without treatment in a 28 day cycle. Thus, over the 28 day cycle, a patient treated with tivozanib would receive only 21 doses of study drug whereas a patient treated with sorafenib would receive 56 doses. On this basis, the likelihood of a patient missing a dose could be anticipated to be higher in the sorafenib group due to the higher number of doses to be taken and the higher dose frequency. This is supported by evidence which demonstrates

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

that drug compliance is best for medications with a once daily dose schedule and worsens as the frequency of dosing increases

Reasons for dose interruption were primarily missed dose (47% of events, 165/349), late attendance (18% of events, 62/349) and personal issues (10% of events, 36/349). Other reasons included public/personal holiday, error, clinical events, not known, lack of drug availability, minor surgery, only one dose of medication taken, post-surgery, radiotherapy, scheduled surgery, technical problems and visit outside of visit window (see Table below).

Table 27: Reasons for dose interruption (other), data includes dose interruptions in TIVO-1 and in the extension study for patients who continued to take their randomised medication

Reason for interruption (other)	Tivozanib (number of events)	Sorafenib (number of events)
Missed dose	36	165
Late attendance	6	62
Personal issues	10	36
Public holiday/personal holiday	1	23
Error	2	15
Clinical events	1	12
Not known	0	11
Lack of drug availability	3	7
Minor surgery	4	1
Only one dose of medication taken	0	1
Post surgery	1	0
Radiotherapy	1	3
Scheduled surgery	0	1
Technical problem	2	8
Visit outside of visit window	0	4
Total	**67**	**349**

Of the patients who had dose interruptions the majority had their medication interrupted for three or fewer occasions. For all patients in the tivozanib arm and 76.5% of patients in the sorafenib arm the dose interruption did not exceed two doses. Around one third of the total number of interruptions in the sorafenib group (117/349 interruptions) were missed by just seven patients. A detailed review of these seven patients shows that they received treatment for between 10 and 21 days of the 28 day treatment cycles and the proportion of doses missed ranged from 1.6% to a maximum of 5.2%.

All patients in the sorafenib arm had treatment interruption for less than 2 weeks and all bar one patient in the tivozanib arm had treatment interruption for less than 2 weeks.

Data on the median (and range) and mean (with standard deviation) duration of dose interruption for both groups is not available in the CSR. However, the average (mean) daily dose of study drug received was 1.46 mg for tivozanib out of a possible 1.5 mg and 689.36 mg, out of a possible 800 mg for sorafenib (page 154 of 2016 CSR).

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

A11. The protocol, registration and clinical study reports for TIVO-1 (AV-951-09-301) described the study as parallel, with treatment switches only permitted upon entry into the extension study (AV-951-09-902). However, Figure 2 in the 2016 clinical study report suggests that 147 people in the sorafenib group received tivozanib before entering the extension study. Please clarify whether any treatment switches occurred in the AV-951-09-301 study, prior to the commencement of the extension protocol. If so, was this a protocol amendment?

Apologies, the diagram is somewhat confusing. The 147 patients were on sorafenib in AV-951-09-301, progression occurred during AV-951-09-301 and the patients were then immediately rolled into AV-951-09-902. At the end of AV-951-09-301 (December 2011) patients on sorafenib had the option to switch to tivozanib even if they had not progressed on treatment. A proportion of patients did so since tivozanib was provided free of charge whereas sorafenib was not once AV-951-09-301 had ended.

A12. For progression-free survival, overall survival, response rates and adverse events, please state whether the data were collected solely under the AV-951-09-301 protocol, or under AV-951-09-301 and AV-951-09-902.

PFS and response rates were collected under the AV-951-09-301 protocol, whereas OS and AE were collected under AV-951-09-301 and AV-951-09-902.

A13. Please provide an estimate of effect (either risk ratio or odds ratio) for overall response rate in TIVO-1.

Odds ratio of 1.623, 95% CI for odds ratio (1.101, 2.391), p=0.013 (taken from Table 31 in the 2016 CSR).

A14. Figure 2 in the 2016 clinical study report indicates that 147 patients originally randomised to sorafenib went on to receive tivozanib as next-line therapy and that 14 people switched to tivozanib during the extension study. The company submission states that 156 patients originally randomised to sorafenib went on to receive tivozanib as next-line therapy. Please confirm the correct number and outline why there is a difference in reported numbers.

The discrepancy reflects slightly different data processing assumptions. The data in our submission (Table 16) is taken from the published paper [Motzer, 2013]. This identified 156 sorafenib patients who, at the point of data analysis were in the open label follow-up study (AV-951-09-902) and receiving tivozanib. This figure did not distinguish between those who had been switched to tivozanib immediately on entry to study and those who had initially continued on sorafenib, who had subsequently switched to tivozanib.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

The data in Figure 2 of the 2106 CSR is based on the data collected and evaluated up to the data cut off of 10 July 2013 for AV-951-09-301 and 03 June 2013 for AV-951-09-902. This was a cleaned and confirmed version of the interim dataset, and identified a further five patients who had switched to tivozanib prior to the end of March 2012, at which point new ongoing treatment reverted to local sources, rather than being funded through study 902. This yielded a total of 161 patients, of whom 147 had been switched to tivozanib immediately on transfer to study 902.

A15. Please confirm that box E in figure 2 of the 2016 clinical study report represents patients who did not have disease progression on sorafenib during TIVO-1 and who did not enter the extension protocol. If this is correct, please give the reasons why the 68 patients did not enter the extension study.

Box E documents all sorafenib patients who did not switch to tivozanib and includes patients who progressed or died within study 301, as well as those who did not have disease progression. Participation in study 902 was at the discretion of the patient and clinician and the reasons for not participating were incompletely documented. A summary of the available data is shown below.

Of the 68 patients in box E who did not receive tivozanib:

- 36 had disease progression
  - Two withdrew consent
  - One was non-compliant with therapy
  - Three were treated with other therapies
  - For the remaining 30 patients, no reason was recorded
- 19 died prior to disease progression being documented
- 13 had no progression and were still alive at the end of follow-up
  - Three withdrew consent
  - Two were not eligible for study 902
  - One was lost to follow-up
  - For the remaining seven patients, no reason was recorded

A16. Please confirm that box B in figure 2 of the 2016 clinical study report represents patients randomised to receive tivozanib in TIVO-1 who did not enter the extension study. Please give a breakdown of the status of these 172 patients (i.e. stopped treatment with tivozanib due to disease progression, lost to follow-up, declined entry to AV-951-09-902).

As discussed in the previous answer, reasons for patients not progressing to study 902 were incompletely documented.
Of the 172 patients in box B who did not receive tivozanib:

- 113 had disease progression

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

- 33 died prior to disease progression being documented
- 26 had no progression and were still alive at the end of follow-up
    - Five withdrew consent
    - Eight patients were treated with other therapies
    - For the remaining 13 patients, no reason was recorded

A17. The company submission states that 153 patients had progressive disease or died while taking tivozanib compared with 168 taking sorafenib. However, Figure 3 in the 2016 clinical study report indicates that 151 patients in the tivozanib arm completed the study with progressive disease compared with 171 taking sorafenib. Figure 3 in the 2016 clinical study report also shows that 49 patients randomised to tivozanib and 26 randomised to sorafenib were classed as ongoing ("an artefact of the data transfer date for disposition data being before the end of study"). Please clarify the discrepancies in the numbers reported in the company submission and the 2016 clinical study report and also whether the patients classed as ongoing have been included in any analysis.

The submission uses the figures from the published study for the PFS outcome [Motzer 2013], which was based on the interim dataset collected to 15th December 2011, at which point independent radiological assessment of progressive disease was stopped. At this point, the numbers of patients who had experienced progression or death was 153 in the tivozanib arm and 168 in the sorafenib arm.
For the patient disposition figure in the final CSR, which used the July 2013 datacut, a patient was deemed to have completed the study if they received study drug for up to 2 years without discontinuation or if they discontinued due to progressive disease. By these criteria, the corresponding figures were 151 and 171 respectively.

Patients defined as "ongoing" did not qualify as "completed" because they had not been treated for a minimum of 2 years, and had not discontinued or progressed.

For the purposes of the primary analysis, the approach mandated by the protocol was used, with a time to event survival analysis being carried out regardless of the time on treatment, based on the figures quoted by Motzer. As the "ongoing" category reflected a post hoc restriction to patients who had been on treatment for 2 years or more, and did not reflect the protocol definition of outcome, efficacy analyses were not carried out based on this definition.

A further (final) analysis was carried out using the July 2013 datacut. Although this was primarily of relevance to the OS outcome, five patients who had been censored in the original analysis were identified as having died prior to the completion of study 301 (two in the tivozanib group and three in the sorafenib group. Information on these deaths was not available at the time of the original analysis. This changed the numbers experiencing the

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

primary outcome to 156 in the tivozanib group and 170 in the sorafenib group. The table below shows a comparison between the primary PFS outcomes for these two datacuts.

Table 28: PFS as determined by IRR (ITT population) at the primary analysis of December 2011 and the July 2013 analysis

	Tivozanib	**Sorafenib**
PFS by IRR: ITT (December 2011)		
N	260	257
Subjects with disease progression or death	153	168
Median PFS (months) (95%CI)	11.9 (9.3, 14.7)	9.1 (7.3, 9.5)
Hazard ratio	0.797 (0.639, 0.993)	
p value*	0.042	
PFS by IRR: ITT (July 2013)		
N	260	257
Subjects with disease progression or death	156	170
Median PFS (95%CI)	11.5 (9.2, 14.7)	9.1 (7.3, 9.5)
Hazard ratio	0.795 (0.638, 0.990)	
p value*	0.039	

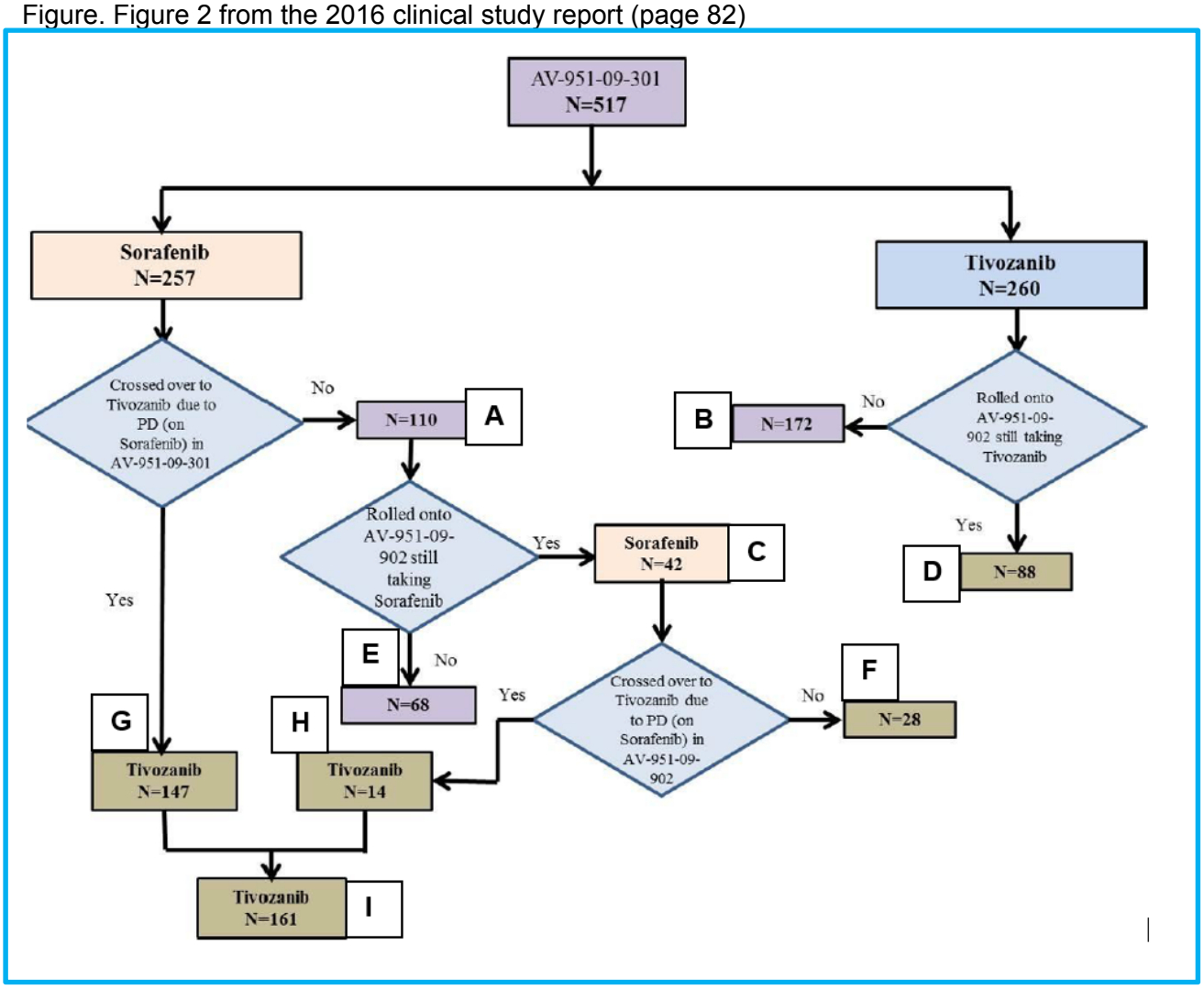
*Log-rank test statistic (p-value) for tivozanib as compared with sorafenib by primary stratified analysis
From Table 17, AV-951-09-301 CSR

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure. Figure 2 from the 2016 clinical study report (page 82)



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Section B: Clarification on cost-effectiveness data

Trial data

B1. **Priority question:** The data cut from the TIVO-1 trial and extension study used in the model is from July 2013. At the last measurement point for overall survival (~month 40), around 45% of patients had yet to have an event, representing immature data.

a. Given that the data cut is from 4 years ago, are more mature follow up data for the TIVO-1 trial and extension study available?

No

b. If yes, then please use the later data cut for the economic model, updating all tables and figures in the submission to reflect the new data. If not, please provide an explanation as to why mature follow up data is not available.

Treatment effectiveness

The following questions are dependent on the methods chosen for the indirect treatment comparison. See questions B2 to B5 if implementing crossover adjustments (option 1) for the TIVO-1 trial and the mixed treatment comparison, otherwise skip to questions B6 and B7 if implementing the matching-adjusted indirect comparison method (option 2).

B2. **Priority question:** A Cox proportional hazards model was used to generate hazard ratios for progression-free survival and overall survival for tivozanib compared with sorafenib based on data from the TIVO-1 trial. However formal assessment of proportional hazards is not presented in the submission. In addition, assumptions around proportional odds and accelerated failure time were not explored. Please provide the following plots and use them to provide an assessment of whether the proportional hazard, proportional odds or accelerated failure time assumption holds for PFS and OS in the TIVO-1 trial (please refer to DSU TSD 14(5) for guidance):

a. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – test for **proportional hazards**.
b. Log(survival function / (1-survival function)) plots versus Log(time) – test for **proportional odds**.
c. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – test for **accelerated failure time**.

Please see figures below for the PFS and OS in the treatment-naïve population of TIVO-1.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 7: Log-cumulative hazard plots versus Log (time) – PFS for naïve patients

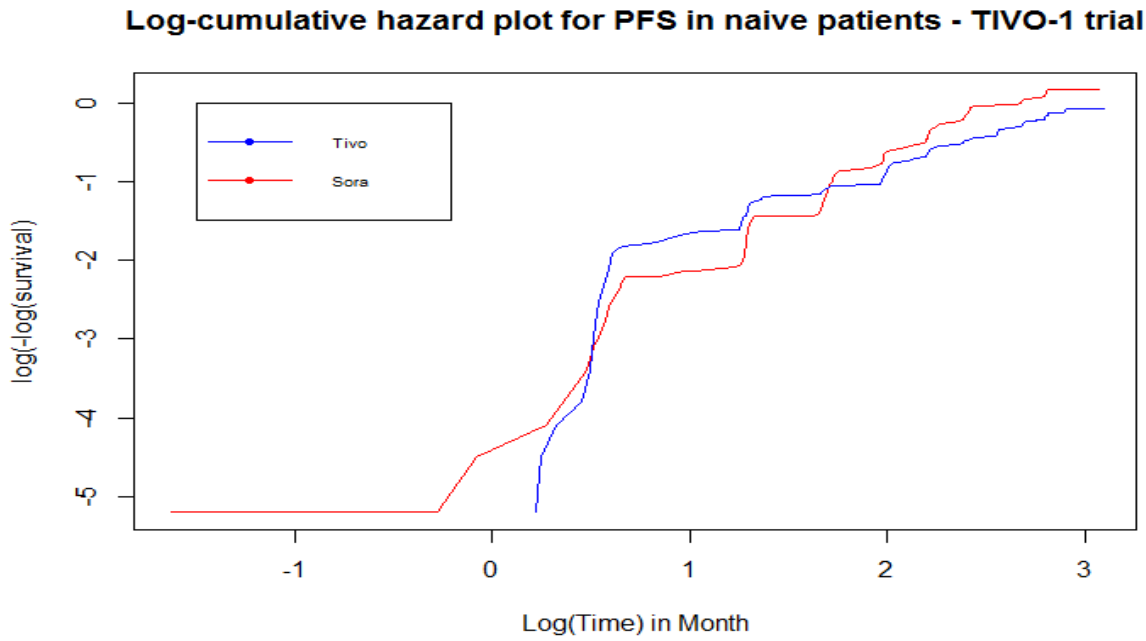
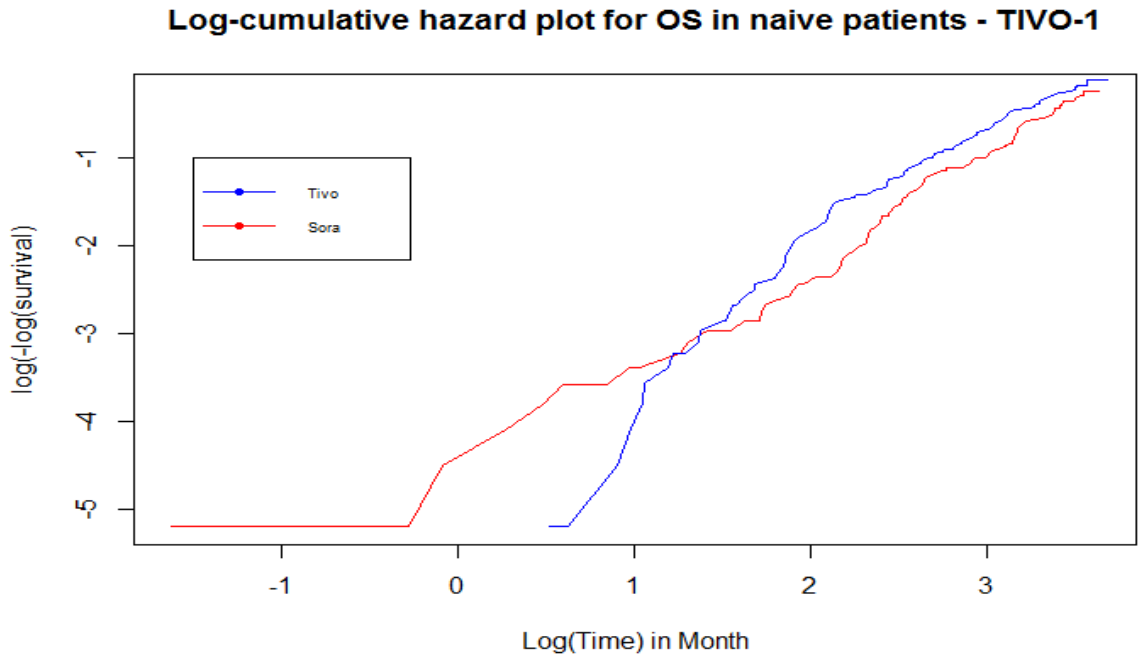


Figure 8: Log-cumulative hazard plots versus Log (time) – OS for naïve patients



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 9: Log (survival function / (1-survival function)) plots versus Log (time) – PFS for naïve patients

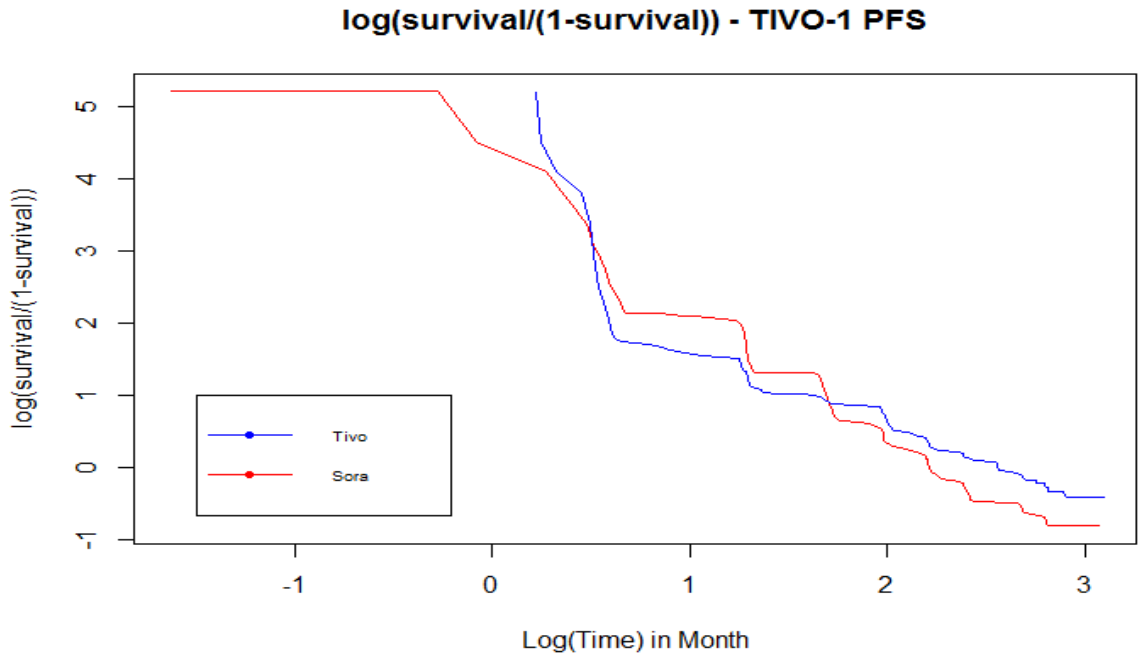
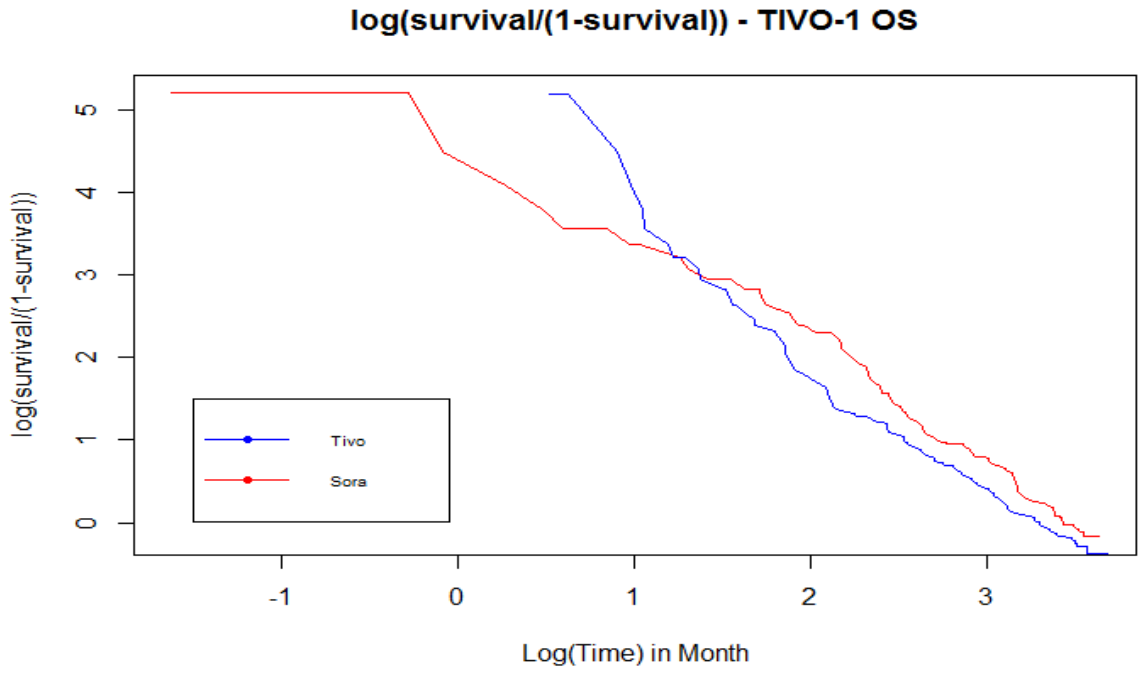


Figure 10: Log (survival function / (1-survival function)) plots versus Log (time) – OS for naïve patients



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 11: Log (inverse standard normal distribution function (1-survival Function)) plots versus Log (time) – PFS for naïve patients

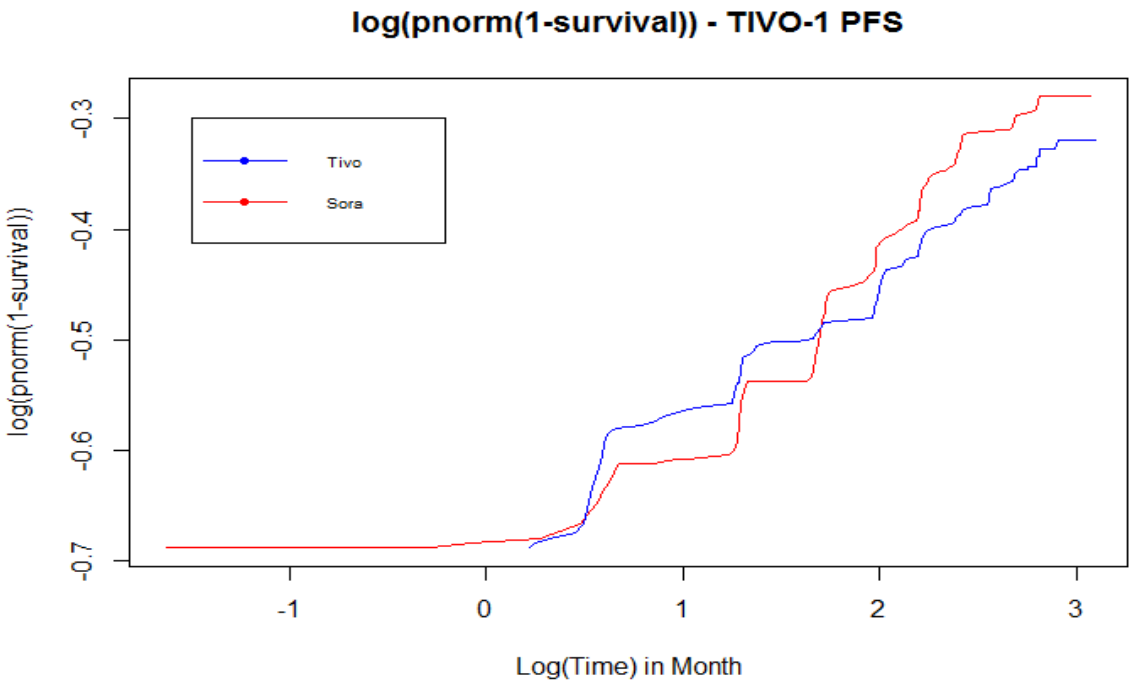
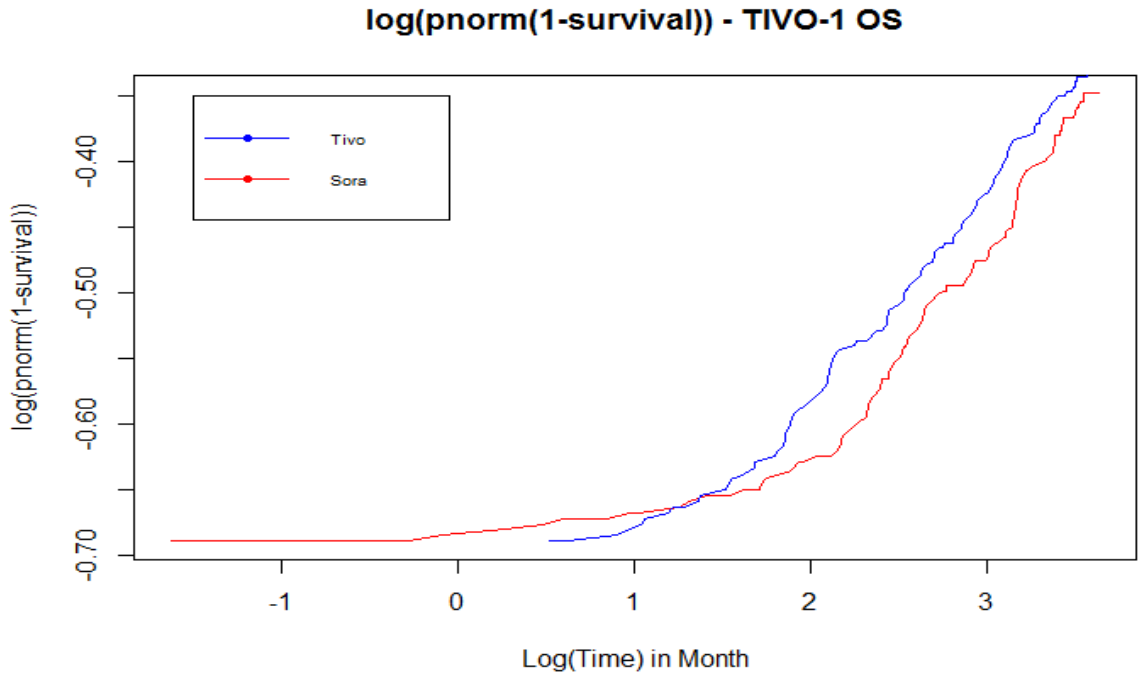


Figure 12: Log (inverse standard normal distribution function (1-survival Function)) plots versus Log (time) – OS for naïve patients



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

B3. **Priority question:** If proportional hazards, proportional odds or accelerated failure time is not found to hold for the TIVO-1 trial please explore alternative methods to generate treatment effectiveness (such as those outlined DSU TSD 14(5)).

The visual inspection of the plots in question B2.a show that the proportional hazard assumption does not hold for PFS, given that the survival curves crossed at around 5-7 months of follow up through the trial. For OS, although there is a clear deviation from linearity within the first 2-3 months, the two plotted lines appear to have a linear trend with approximately constant separation beyond 2-3 months. The violation of proportional hazard in the first 2-3 months is unlikely to have any meaningful impact on the survival estimate and on the model results.

Although the proportional hazard assumption did hold for OS, we will independently fit curves for OS in order to align the methodology with that employed for PFS.

B4. **Priority question:** The mixed treatment comparison uses the Cox proportional hazards model to produce pairwise hazard ratios, yet an assessment of proportional hazards for each trial included in the mixed treatment comparison is not presented in the submission. Please provide an assessment of whether the proportional hazards assumption holds for each trial in the mixed treatment comparison. For an example of what is required, refer to the on-going appraisal of cabozantinib for treating renal cell carcinoma: GID-TA10075, Appraisal Committee 1 committee papers, Company Submission section 4.10.3 (https://www.nice.org.uk/guidance/gid-ta10075/documents/committee-papers).

In the NMA two potential methods were considered to compare PFS and OS endpoints: one based on HRs and the other on the parametric curves (KM). However, an NMA based on the HRs would need to assume that the proportional hazard assumption holds for each pair of comparators. When the proportional hazard assumption is violated the HR parameters change over time and the use of constant HR is not suitable. The first step in confirming the best method to use in the NMA was to check whether the proportional hazard assumption holds for PFS and OS in the TIVO-1 trial. As mentioned above, the proportional hazard assumption did not hold for PFS and we independently fitted the curves for the PFS and OS to generate treatment effectiveness.

Therefore, the NMAs based on parametric curves will be applied. We will digitally extract information from the relevant KM plots applying the algorithm from Guyot et al and re-generating the patient-level data for the trials included within our NMA. NMAs based on parametric curves do not assume proportional hazards between the pairwise comparators and therefore this method can be applied to any survival function for which transitivity of treatment effects in the NMA model can be shown.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

B5. **Priority question:** If proportional hazards is not found to hold for the trials in the mixed treatment comparison please explore other methods to generate the indirect comparison estimates, such as those outlined in Ouwens *et al.* 2010(6) and Jansen 2011(7) and implemented in GID-TA10075: cabozantinib for treating renal cell carcinoma, AC1 committee papers, CS section 4.10.4 (https://www.nice.org.uk/guidance/gid-ta10075/documents/committee-papers).

See B4

B6. **Priority question:** The main trial comparing pazopanib and sunitinib is the COMPARZ trial(8) which could be used in conjunction with the TIVO-1 trial to estimate comparable treatment effects for the three treatments using a matching-adjusted indirect comparison. One of the expected outputs from the matching-adjusted indirect comparison is adjusted progression-free survival and overall survival Kaplan–Meier curves for tivozanib. Using the adjusted tivozanib curves and digitised sunitinib and pazopanib curves from the COMPARZ trial(8), please provide the following plots and use them to perform an assessment of whether the proportional hazard, proportional odds or accelerated failure time assumption holds for PFS and OS in the (please refer to DSU 14(5) for guidance):

a. Log-cumulative hazard plots (Log(-Log(survival function)) versus Log(time) – test for **proportional hazards**.
b. Log(survival function / (1-survival function)) plots versus Log(time) – test for **proportional odds**.
c. Log(inverse standard normal distribution function(1-survival function)) plots versus Log(time) – test for **accelerated failure time**.

Not applicable

B7. **Priority question:** If proportional hazards, proportional odds or accelerated failure time is not found to hold for the assessments performed in question B6, please explore alternative methods to generate treatment effectiveness (such as those outlined DSU TSD 14(5)).

Not applicable

B8. **Priority question:** The Weibull distribution was used for the extrapolation of the tivozanib Kaplan–Meier data with the justification that, "*the Weibull approach is widely adopted for this type of analysis"*. No exploration of other distributions is presented in the submission. From visual inspection of the plots presented in Figure 21 of the company submission, the Weibull curves do not appear to fit the data well. As no other curves were presented in the submission, it is not possible to review any

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

statistical goodness of fit tests or clinical validation of the alternative curves that the company could have used. Please provide:

- Analyses using alternative parametric distributions incorporating the analyses performed in questions B2–B7 (depending on the methods chosen for the indirect treatment comparison) and using DSU TSD 14(5) as guidance, to identify the most appropriate extrapolation of the progression-free survival and overall survival Kaplan–Meier data for tivozanib and comparator treatments for use in the economic model.
- Please provide plots of each curve under consideration for progression-free survival and overall survival compared to the progression-free survival and overall survival Kaplan–Meier plots.
- Please provide mean, median and landmark estimates of progression-free survival and overall survival for all treatments based on the extrapolated curves.

Patient level data from the TIVO-1 study was used to inform PFS and OS in the tivozanib and sorafenib arms of the model. Parametric models (exponential, Weibull, Gompertz, log-logistic and log-normal) were fitted to the patient level data from the TIVO-1 study.

To select the best survival model, the algorithm (SMEEP) as described in the NICE DSU Technical Support Document 14 was followed. The AIC statistics are shown in Table 29 and Table 30. The Log-normal model provides the best fit to the tivozanib and sorafenib PFS data. For the OS data, the log normal and the Weibull provide the best fit to the tivozanib and sorafenib arms, respectively (see Table 1 and Table 2). The log-logistic regression was the next best for both tivozanib and sorafenib for the OS endpoint.

Table 29: Tivozanib arm (TIVO-1): AIC by distribution type

	PFS	OS
Distributions	**AIC**	**AIC**
Exponential	837.65	916.74
Weibull	839.6	915.07
Gompertz	836.18	918.6
Log-logistic	832.1	909.23
Log-normal	824.75	904.46

Table 30: Sorafenib arm (TIVO-1): AIC by distribution type

	PFS	OS
Distributions	**AIC**	**AIC**
Exponential	891.78	860.46
Weibull	890.14	857.2847
Gompertz	893.7	859.19
Log-logistic	877.7	857.2883
Log-normal	877.43	864.49

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 13 to Figure 17 illustrate the KM curves and parametric survival fitted curves for PFS in the tivozanib arm, Figure 18 to Figure 22 illustrate OS in the tivozanib arm, Figure 23 to Figure 27 illustrate PFS in the sorafenib arm and Figure 28 to Figure 32 illustrate OS in the sorafenib arm.

Figure 13: Fitted KM and exponential distribution curves for PFS – tivozanib arm

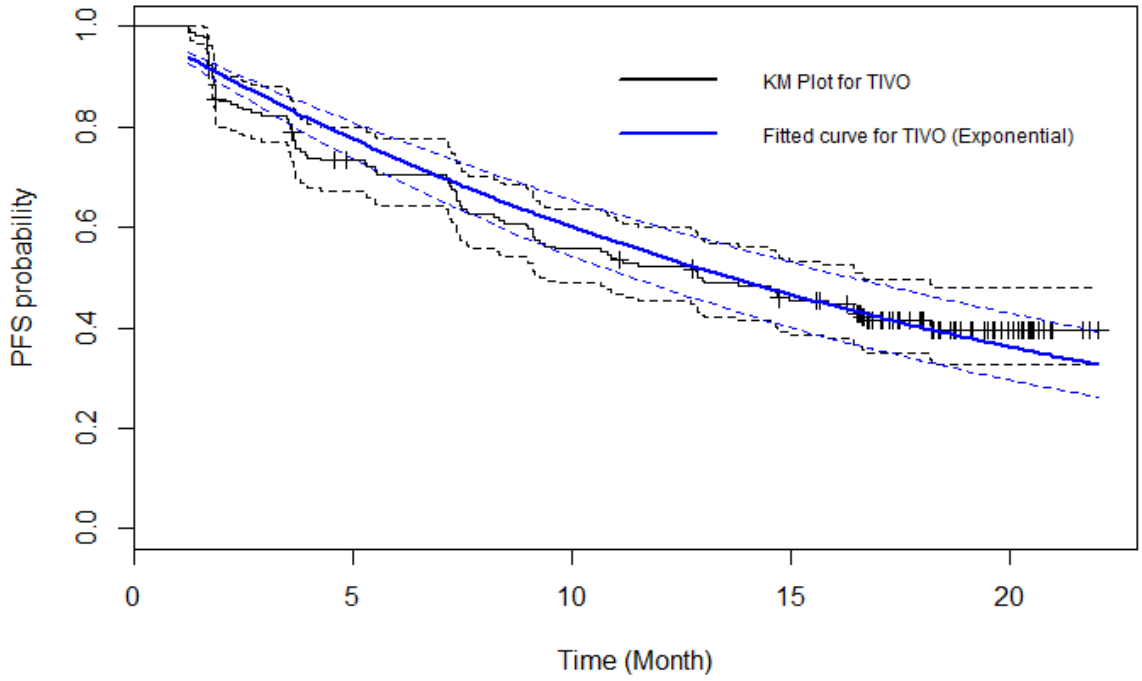
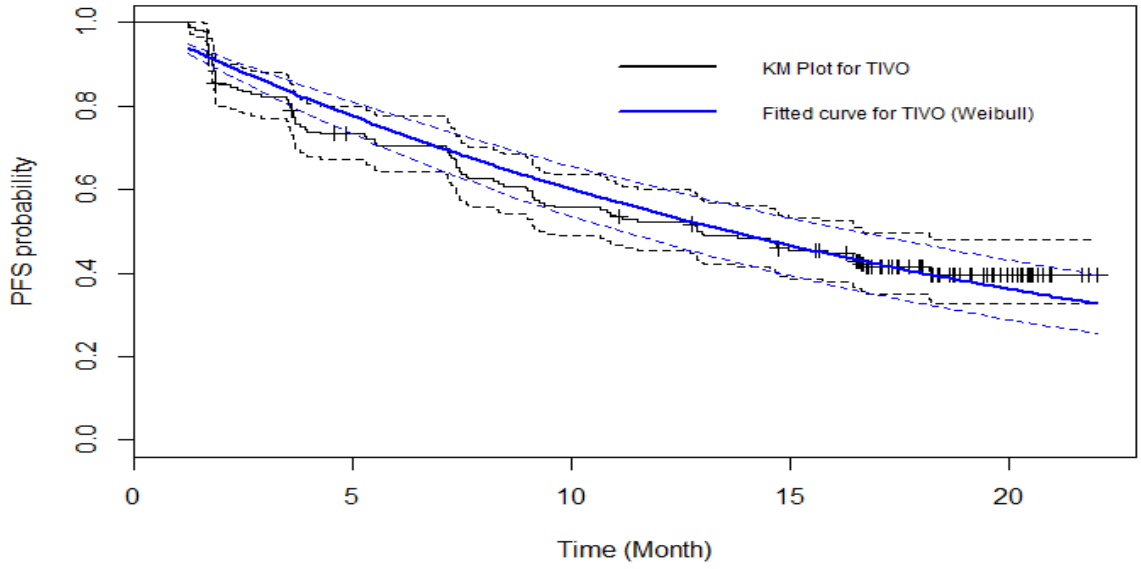


Figure 14: Fitted KM and Weibull distribution curves for PFS – tivozanib arm



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 15: Fitted KM and Gompertz distribution curves for PFS – tivozanib arm

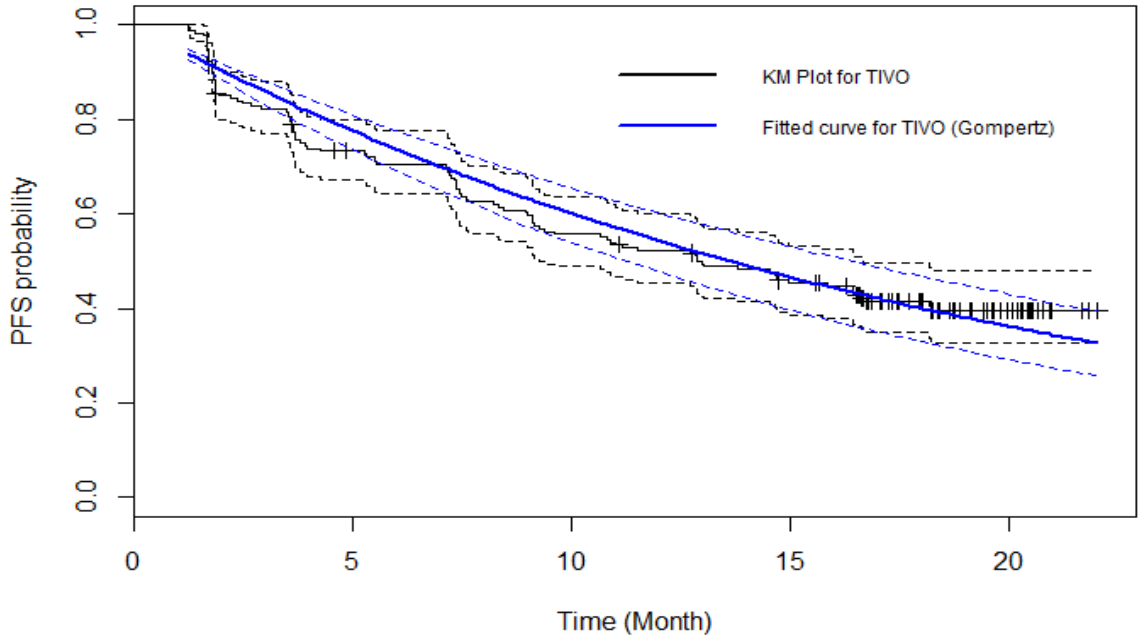
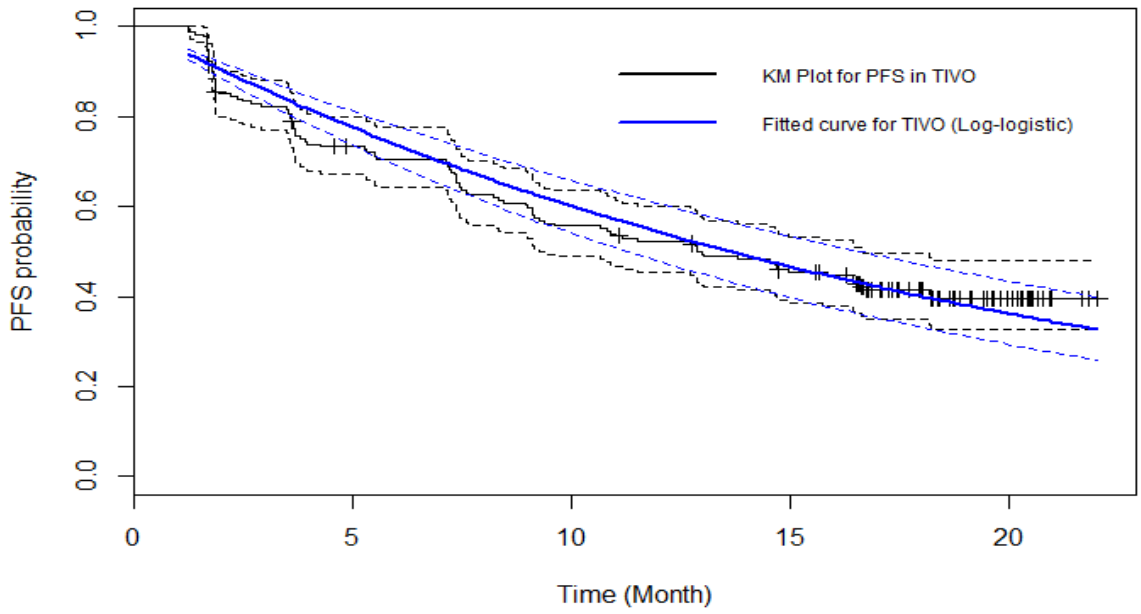


Figure 16: Fitted KM and Log-logistic distribution curves for PFS – tivozanib arm



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 17: Fitted KM and Log-normal distribution curves for PFS – tivozanib arm

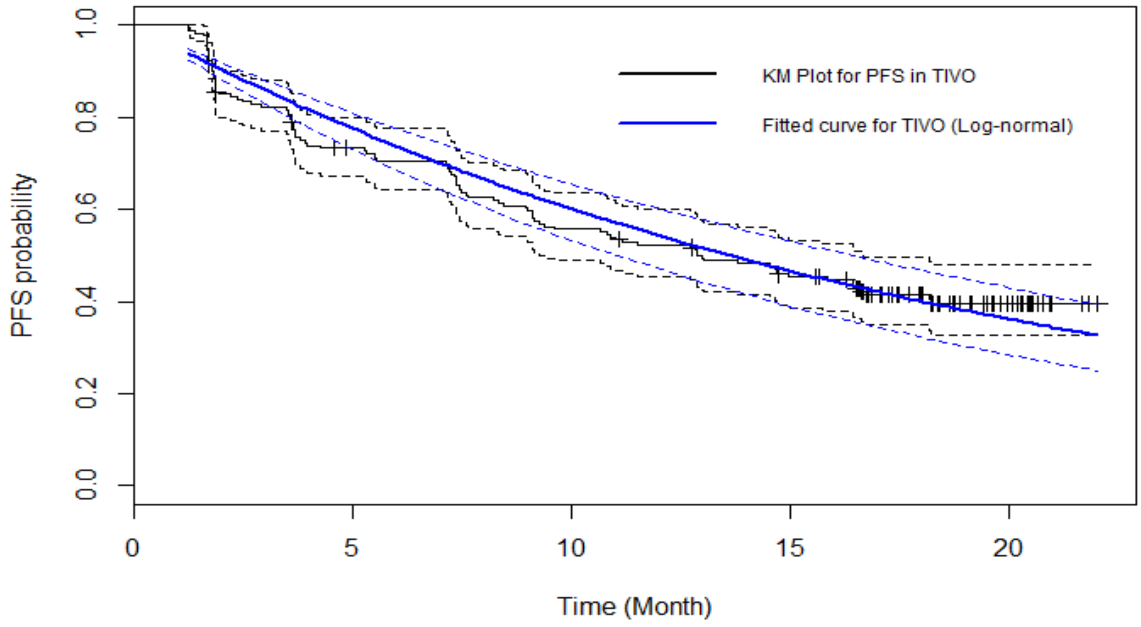
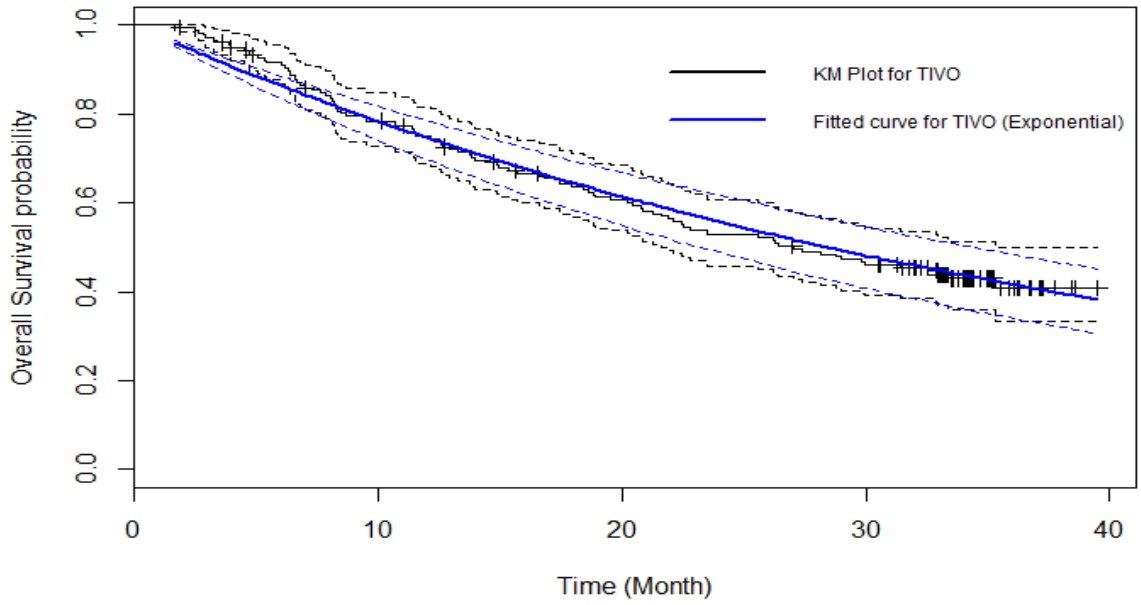


Figure 18: Fitted KM and Exponential distribution curves for OS – tivozanib arm



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 19: Fitted KM and Weibull distribution curves for OS – tivozanib arm

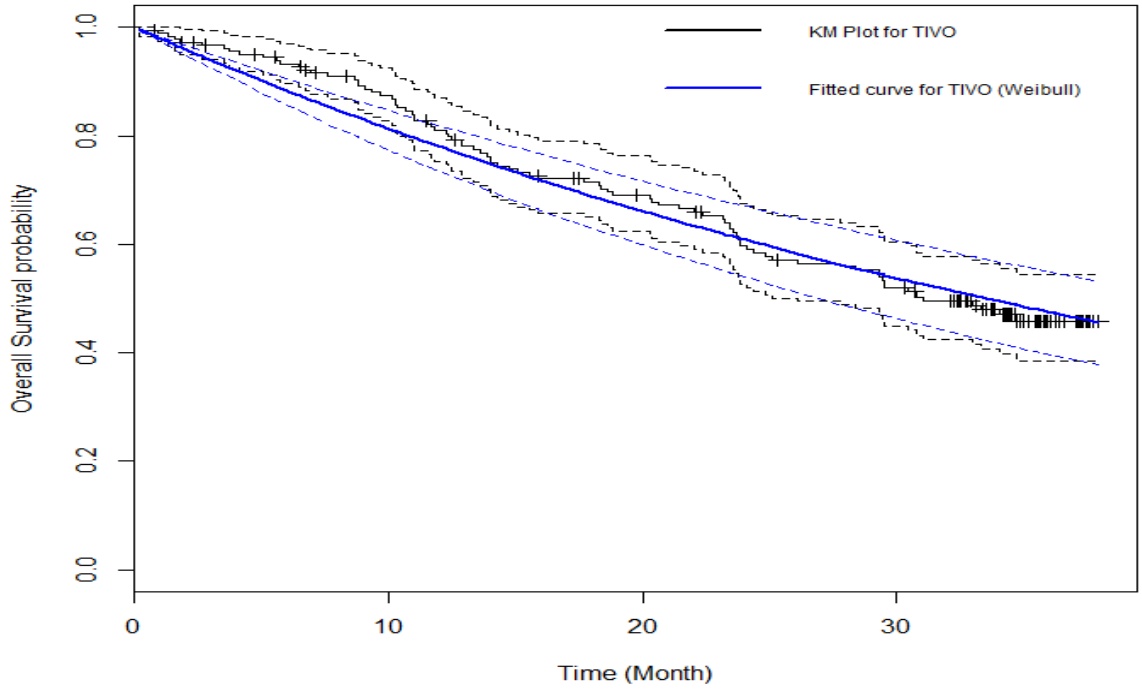
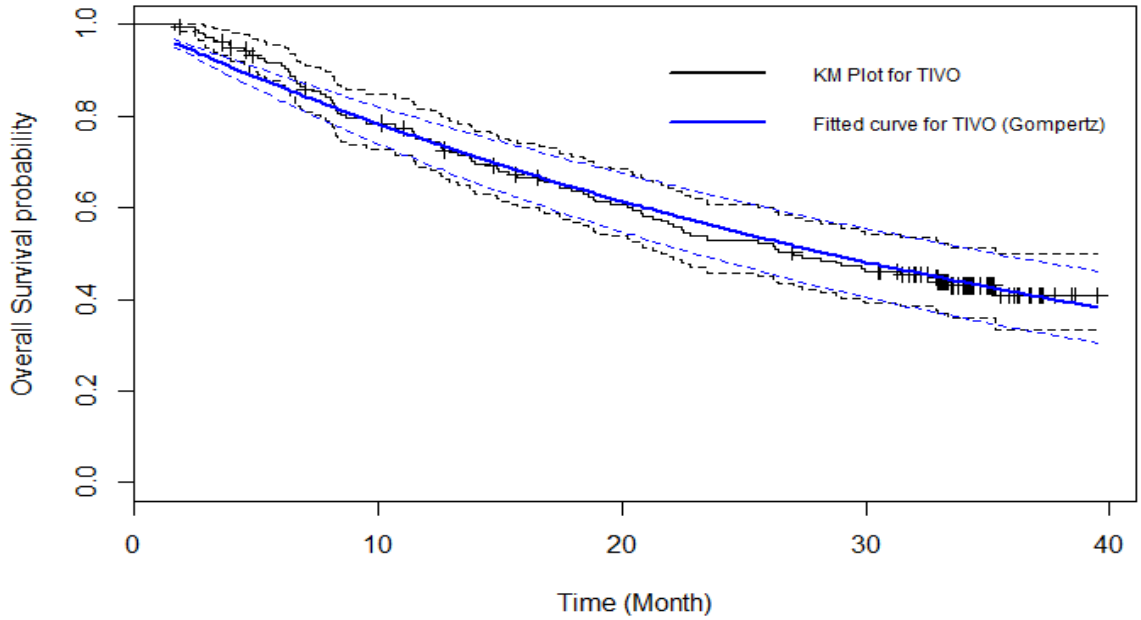


Figure 20: Fitted KM and Gompertz distribution curves for OS – tivozanib arm



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 21: Fitted KM and Log-logistic distribution curves for OS – tivozanib arm

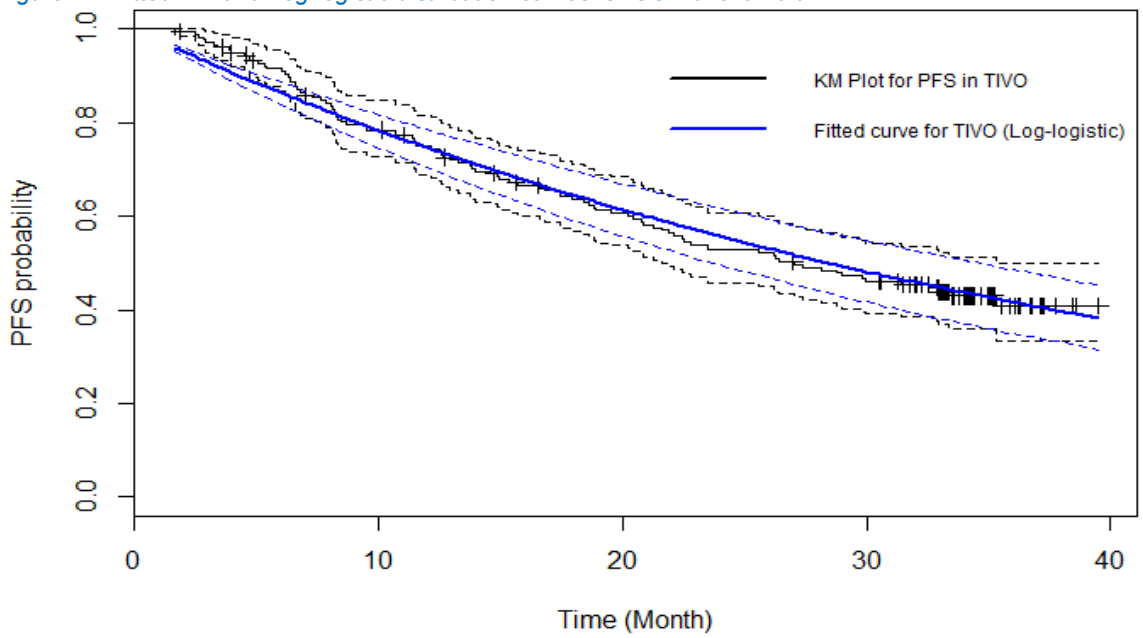
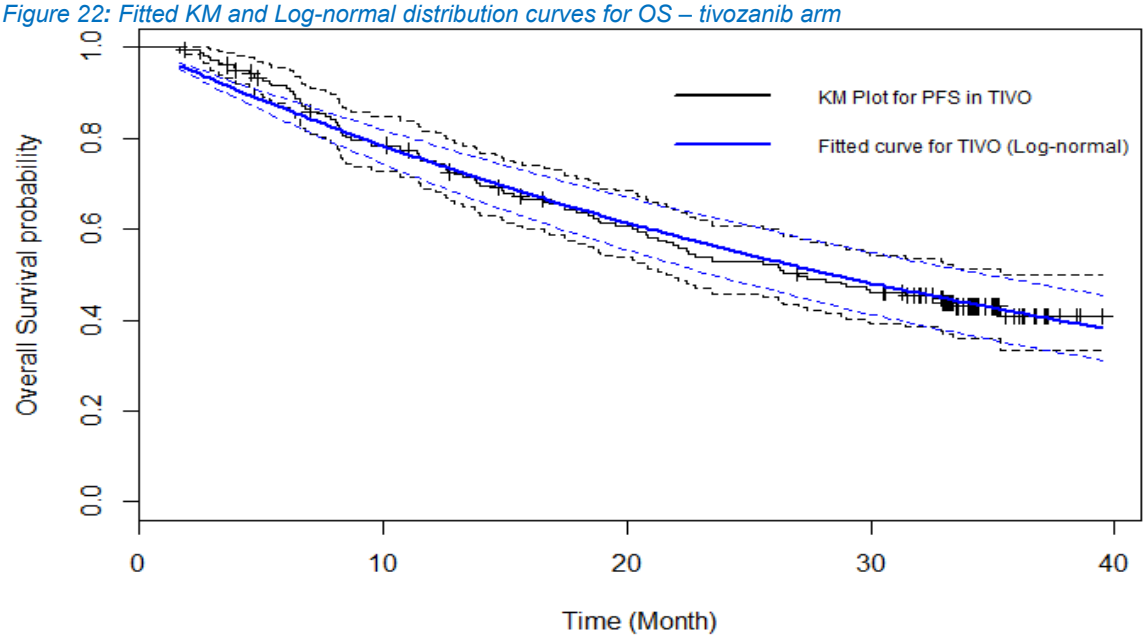


Figure 22: Fitted KM and Log-normal distribution curves for OS – tivozanib arm



Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 23: Fitted KM and Exponential distribution curves for PFS – sorafenib arm

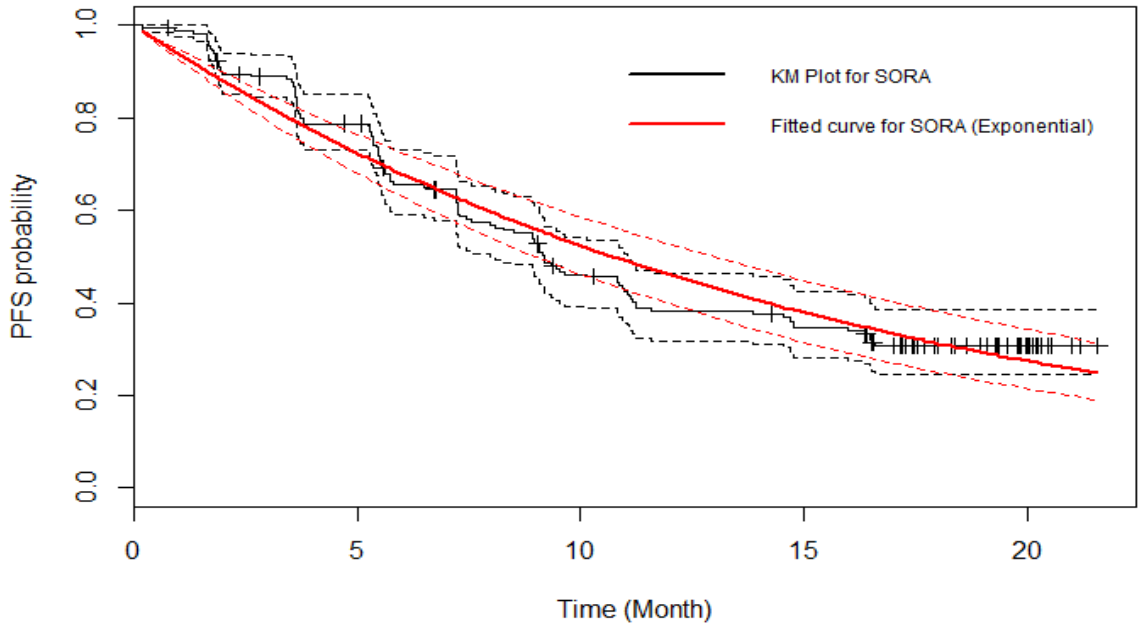
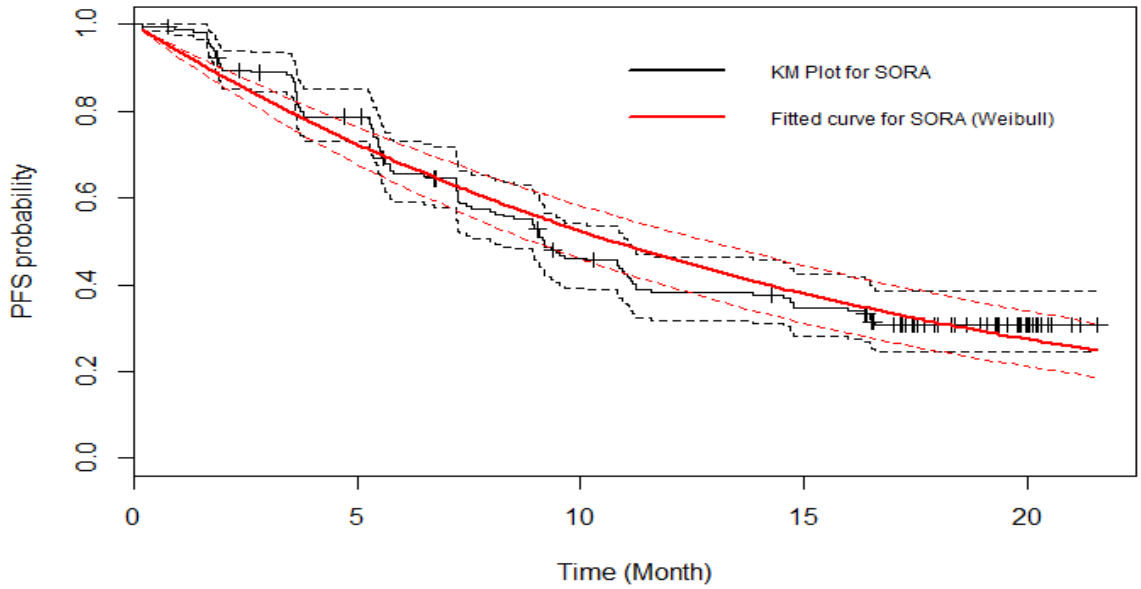


Figure 24: Fitted KM and Weibull distribution curves for PFS – sorafenib arm



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 25: Fitted KM and Gompertz distribution curves for PFS – sorafenib arm

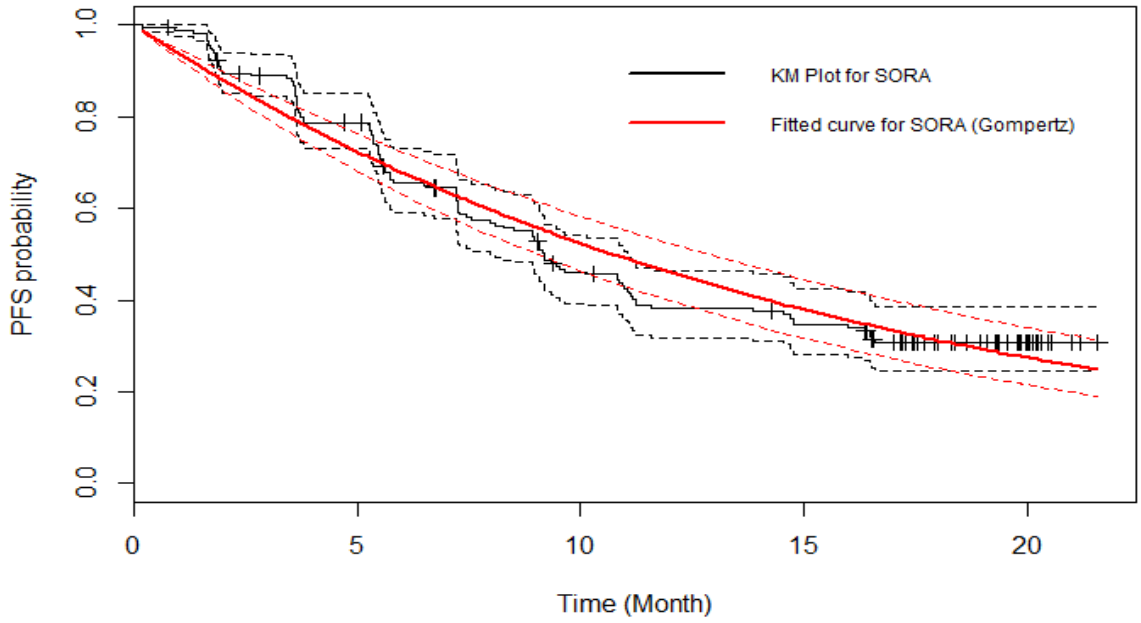
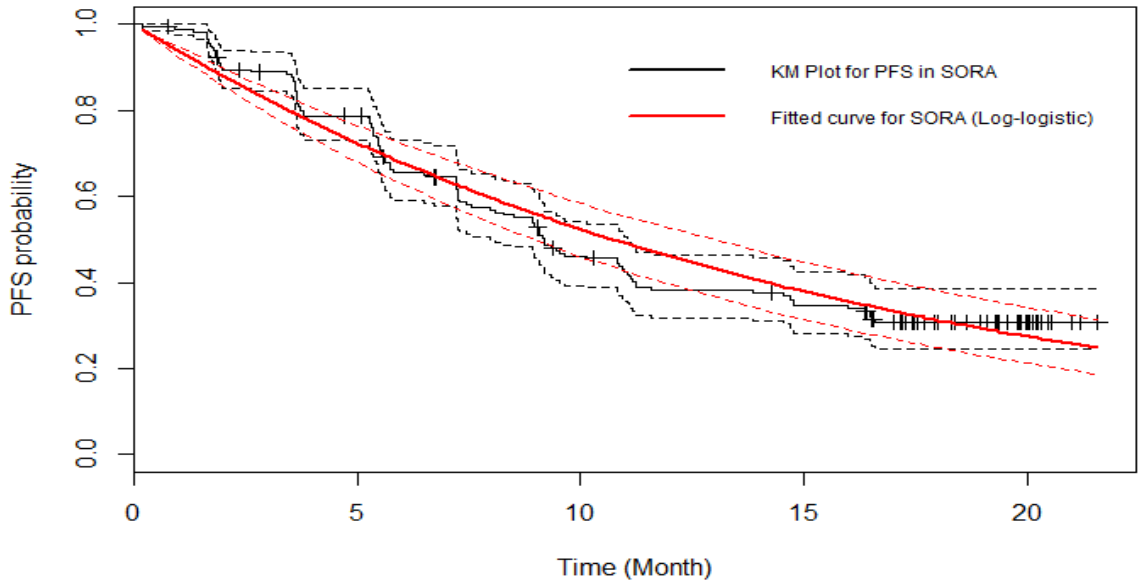


Figure 26: Fitted KM and Log-logistic distribution curves for PFS – sorafenib arm



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 27: Fitted KM and Log-normal distribution curves for PFS – sorafenib arm

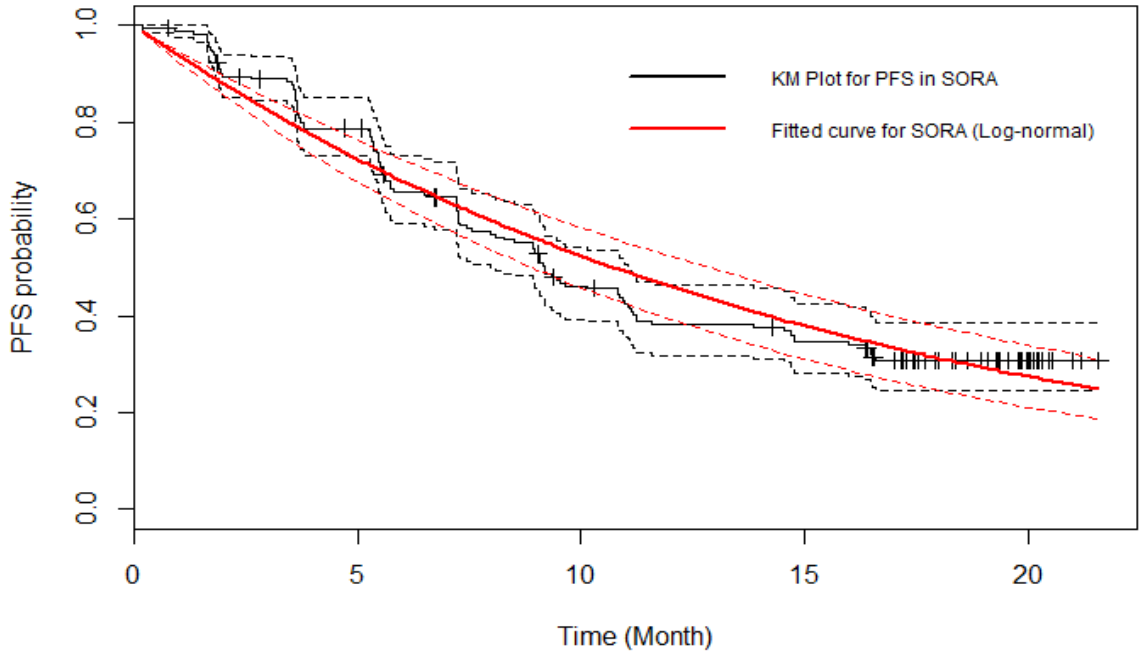
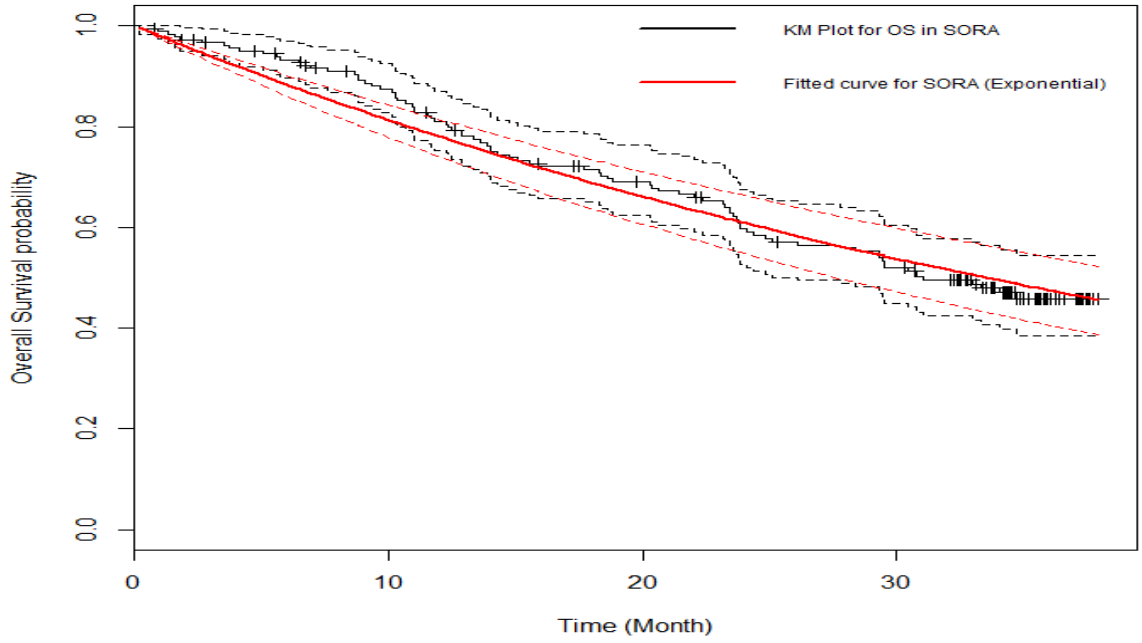


Figure 28: Fitted KM and Exponential distribution curves for OS – sorafenib arm



Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 29: Fitted KM and Weibull distribution curves for OS – sorafenib arm

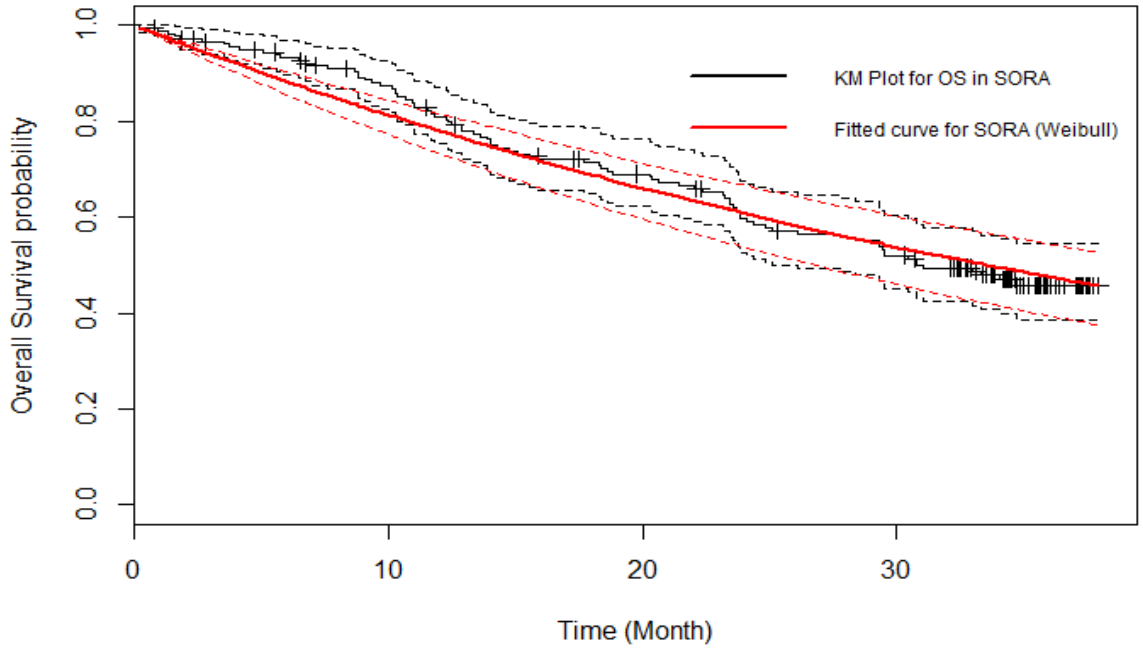
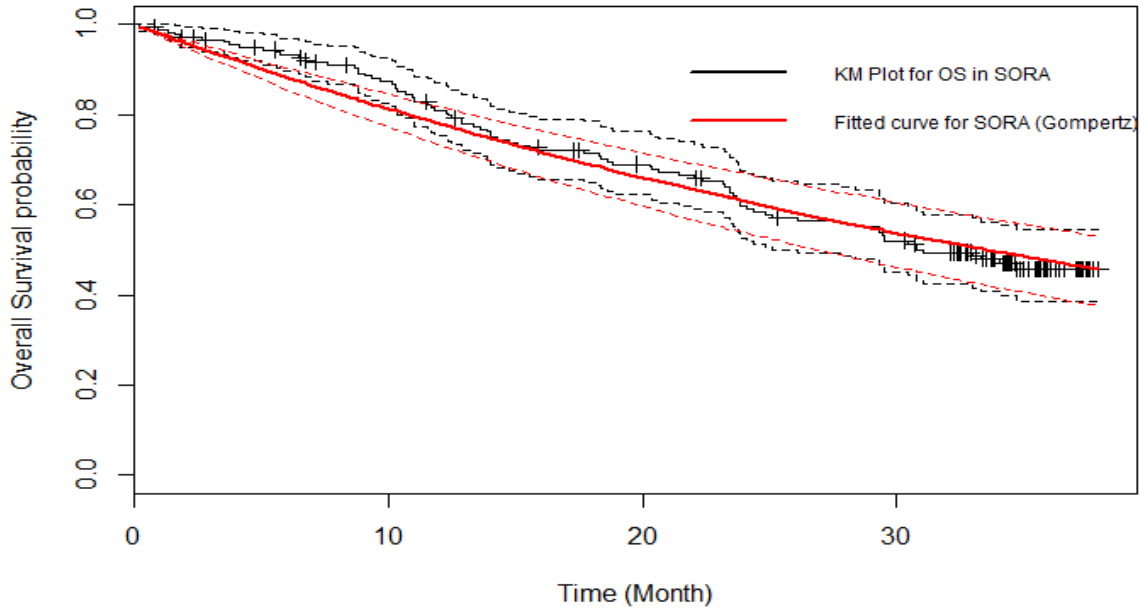


Figure 30: Fitted KM and Gompertz distribution curves for OS – sorafenib arm



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 31: Fitted KM and Log-logistic distribution curves for OS – sorafenib arm

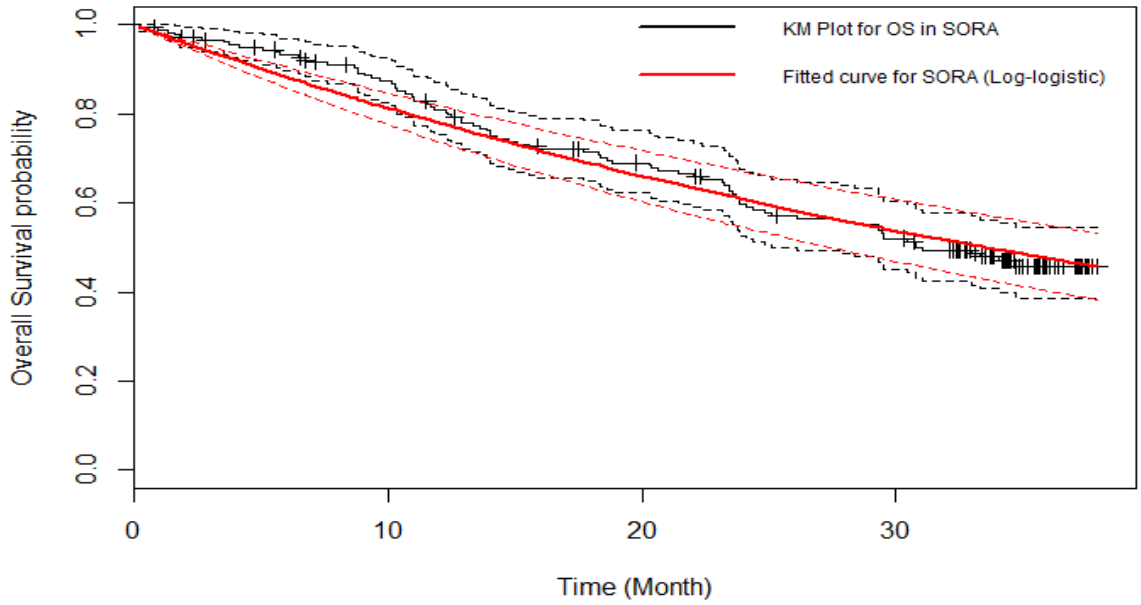
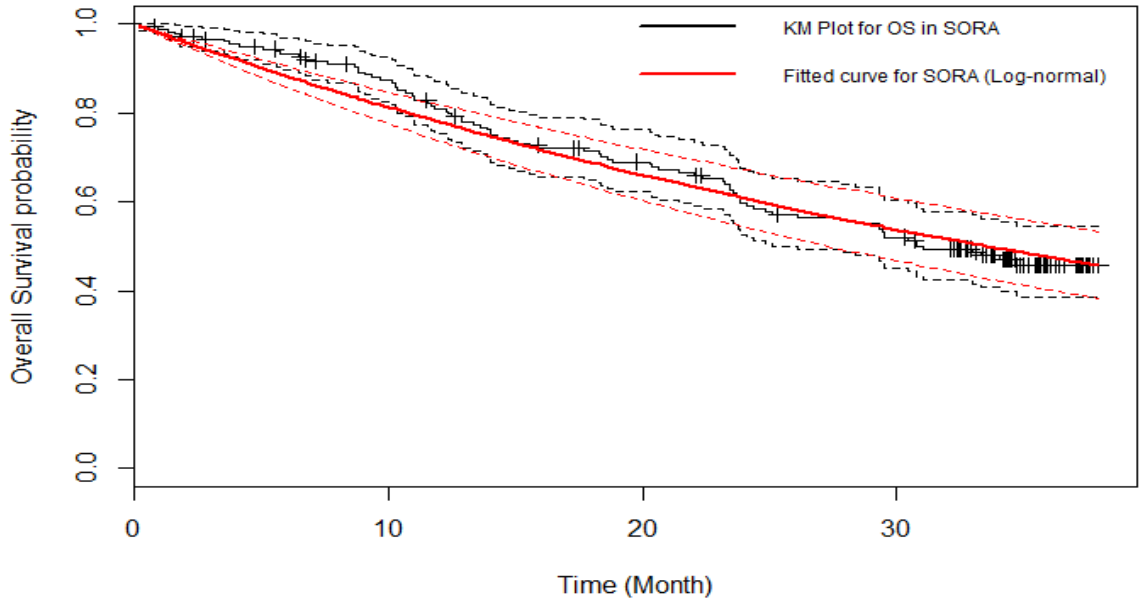


Figure 32: Fitted KM and Log-normal distribution curves for OS – sorafenib arm



Subsequent therapy

B9. **Priority question:** In the economic model it is assumed that 60% of patients with disease progression go on to receive axitinib and 40% receive BSC. Please provide the actual subsequent therapy profile (treatments and proportions of patients on each treatment) for each treatment from the trials used in the matching-adjusted indirect comparison or mixed treatment comparison. Please use this data as well as costs for

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

each treatment (drug and monitoring) and mean duration of treatment to estimate accurate subsequent therapy costs. Where a drug is not routinely used in the NHS, please assume the equivalent NHS drug (e.g. where a VEGFR-TKI is used second line in a study that is unavailable in the NHS, please substitute it with axitinib).

There is a paucity of data on the use of next line therapy; data on the proportion of patients receiving subsequent therapy and the type of therapy used next-line is only available for TIVO-1 and SWITCH. The duration of next-line therapy is only available for SWITCH (Table 3 of the clinical paper).

All four studies in the revised mixed treatment comparison (TIVO-1, SWITCH, Cross J RCC and COMPARZ) were carried out more than 5 years ago and are therefore are unlikely to reflect clinical practice today. We used the 60%/40% split on advice from our clinical advisor, which we believe reflects current clinical practice.

Adverse events

B10. Please clarify if adverse events included in the mixed treatment comparison are treatment related or treatment emergent.

Treatment emergent

B11. The data in Table 41 of the company submission relates to the overall population. Please provide figures for the untreated population and use this data in a scenario analysis.

We have been unable to complete this analysis within the timeframe. We will send it as soon as possible, but understand if the ERG chose not to incorporate it within their report.

B12. Please check the figures in Table 52 of the company submission against the figures presented in Table 32 of the company submission and update the model accordingly. In particular the odds ratio for hypertension for tivozanib compared with pazopanib and tivozanib compared with interferon does not match in both tables.

Apologies, the model is correct, the numbers in Table 52 were incorrect.

Table 31: Pair-wise estimates of treatment effects (OR) for grade +3 AEs derived from MTC (Figure 52 in the original submission)

AE	Tivozanib vs Sunitinib		Tivozanib vs Pazopanib		Tivozanib vs IFN	
	Median	95% CrI	Median	95% CrI	Median	95% CrI
Anaemia	0.029	[0;43.36]	0.112	[0;158.5]	0.039	[0;59.04]
Asthenia/Fatigue	0.953	[0.245;4.014]	1.699	[0.417;7.42]	1	[0.255;4.252]
HFS	0.186	[0.033;0.835]	0.407	[0.069;1.935]	1.838	[0.278;11.39]

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Hypertension	1.2	[0.474;3.109]	1.191	[0.447;3.255]	14.41	[3.875;63.36]
AE: Adverse event, IFN: Interferon, HFS: Hand-foot syndrome						

B13. Please clarify why diarrhoea is not included in Table 53 and is not used in the model even though it was identified in the mixed treatment comparison for inclusion in the model.

In the submission we state 'For the purposes of the economic model, only AEs of severity grade 3 or above that had an incidence of 5% or more in any treatment arm were incorporated in the analysis, as the cost and utility impact of lesser AE grades or lower incidence, is likely to be insignificant in this clinical and financial context.'
Grade 3 diarrhoea was below 5% in all the treatments included in our model (see table below).

Table 32: Estimates of risk of grade 3 AE derived from NMA

Adverse event	% of AEs in TIVO	95% CI		% of AEs in SUN	95% CI		% of AEs in PAZO	95% CI		% of AEs in IFN	95% CI	
Anaemia	0.04	0.016	0.064	0.60	0.538	0.658	0.28	0.267	0.297	0.53	0.459	0.590
Asthenia/fatigue	0.10	0.063	0.137	0.10	0.067	0.142	0.06	0.052	0.071	0.10	0.063	0.137
Diarrhoea	0.02	0.003	0.037	0.04	0.013	0.058	0.04	0.030	0.054	0.00	0.000	0.011
Hand-foot syndrome	0.02	0.003	0.037	0.10	0.063	0.135	0.05	0.021	0.074	0.01	0.000	0.024
Hypertension	0.27	0.216	0.324	0.24	0.191	0.296	0.24	0.185	0.305	0.03	0.008	0.048
Nausea/Vomiting	0.01	0.000	0.017	0.01	0.000	0.026	0.01	0.000	0.022	0.00	0.000	0.009
Thrombocytopenia	0.00	0.000	0.011	0.02	0.000	0.030	0.00	0.000	0.008	0.01	0.000	0.017

We also consulted with our clinical expert (Dr Rob Jones) who told us that grade 3 diarrhoea covers a broad range of symptoms and that it is an indication to withhold the drug until it resolves. Therefore, grade 3 diarrhoea is usually transient and results in very few hospital admissions/additional hospital visits/additional GP visits.

B14. Please include a scenario analysis in the model where the rates of treatment-related adverse events (severity grade 3 or above with an incidence of >5%) observed in the pivotal trials for the comparators are used in the model instead of the incidence estimated in the mixed treatment comparison.

We have been unable to complete this analysis within the timeframe. We will send it as soon as possible, but understand if the ERG chose not to incorporate it within their report.

Health related quality of life

B15. **Priority question:** Please provide the following tables relating to the quality of life analyses cited in the 2016 clinical study report: Tables 14.2.25, 14.2.26, 14.2.27, 14.3.11, 14.3.12, 14.3.1.15 and 16.2.6.2.6?

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

All attached except for 14.3.11 or 14.3.12, which EUSA are unable to identify

B16. Please clarify if utilities used for progression-free survival and post-progression survival are based on the untreated population or the entire trial population.

Entire trial population

Resource use and costs

B17. The company submission mentions on page 18 that an 890 µg capsule is available. Please confirm the cost of the smaller dose capsule.

[redacted]

B18. Please provide the mean dose intensity of each treatment, including appropriate measures of uncertainty (such as standard errors, confidence intervals, etc.) and include a scenario analysis adjusting treatment costs by dose intensity.

Data on dose intensity is only available for tivozanib and sorafenib in the TIVO-1 study (94% for tivozanib versus 80%). Data on dose intensity is not available for pazopanib (COMPARZ study) or sunitinib (COMPARZ study, Cross J RCC and SWITCH).

B19. Please clarify why blood tests have not been included in resource use assumptions for patients on active treatments.

Clinical advice from our advisors was that there would be no difference blood tests across the VEGFR-TKIs and that therefore they would not be required in the resource use assumptions.

B20. Please carry out a scenario analysis including the costs of blood tests (every month) and thyroid function tests (every 3 months) for patients receiving active treatment.

See B19.

Systematic literature review

B21. Please clarify whether an established methodology was followed to carry out the systematic literature review for cost-effectiveness, costs and quality of life studies. If so, please provide a reference.

The methodology followed for the systematic literature reviews for cost-effectiveness, costs and quality of life followed the recommendations of the Centre for Reviews and Dissemination (https://www.york.ac.uk/crd/guidance/). These systematic reviews used an agreed search strategy of multiple sources, abstracts and full text articles were screened

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

according to agreed inclusion and exclusion criteria and data was extracted into a detailed template.

B22. Please clarify why the systematic literature search for cost-effectiveness studies was restricted to studies published from 1995 onwards.

The systematic literature search for cost-effectiveness studies was limited to those published from 1995 onwards to allow the review to focus on economic analyses that best reflected current clinical practice and costs. Older studies were considered unlikely to have involved the newer targeted therapies that are now standard of care in this population and costs and resource use data used to parameterise the models were considered unhelpful for the current clinical context. The economic analyses identified by this later search date were built on and modified older models, and included evaluations of previous manufacturers' submissions to NICE, which were used to inform the development of the model used in this submission.

Probabilistic sensitivity analysis

B23. Credible intervals were used for the measurement of uncertainty for the progression-free survival and overall survival hazard ratios in the probabilistic sensitivity analysis (page 149 of the company submission). This approach is not appropriate as the methodology used to produce the hazard ratios means that the estimates are correlated and as such uncertainty cannot be calculated independently. Please amend the probabilistic sensitivity analysis to use progression-free and overall survival hazard ratio CODA data obtained from WinBUGS (refer to DSU TSD 6 for guidance(9) and present the following:

- Probabilistic sensitivity analysis pairwise comparison results (list price).
- Cost effectiveness acceptability curves for the pairwise comparisons (list price).
- Cost effectiveness scatter plots for the pairwise comparisons (list price).

We have been unable to complete this analysis within the timeframe. We will send it as soon as possible, but understand if the ERG chose not to incorporate it within their report.

<u>Section C: Textual clarifications and additional points</u>

C1. Please give details of the TAURUS study (NCT01673386; AV-951-12-205), along with a rationale for not including it in the submission.

The TAURUS study was a randomised, double-blind, two-arm crossover study comparing tivozanib and sunitinib in subjects with metastatic RCC who have received no prior systemic therapy for RCC. The study was designed to compare subject treatment preference, as well as overall safety and tolerability, frequency of dose modifications and kidney-specific health

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

outcomes/QoL. The study was not completed, an abbreviated CSR is available should you wish to review it.

C2. The proposed summary of product characteristics provided in the submission appendix refers to, "five renal cell carcinoma monotherapy studies", that constitute the safety data. Please provide a list of references and identifiers for these studies, including rationale for why any were not included in the submission.

Table 33 lists the five studies.

Table 33: Five studies of tivozanib as monotherapy for RCC which provide safety data for the Summary of Product Characteristics

Study Number	Study Title	Number of Patients with RCC Exposed to Study Drug
AV-951-07-201	A Phase 2, Placebo-Controlled, Randomized, Discontinuation Trial of Tivozanib (AV-951) in Patients with Renal Cell Carcinoma	Tivozanib: 272
AV-951-10-202	A Phase 2 and Biomarker Study of Tivozanib in Subjects with Advanced Renal Cell Carcinoma	Tivozanib: 105
AV-951-12-205	A Phase 2 Randomized, Double-Blind, Crossover, Controlled, Multi-Center, Subject Preference Study of Tivozanib Hydrochloride vs. Sunitinib in the Treatment of Subjects with Metastatic Renal Cell Carcinoma	Tivozanib:38 Sunitinib: 41
AV-951-09-301	A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib (AV-951) to Sorafenib in Subjects with Advanced Renal Cell Carcinoma	Tivozanib*259† Sorafenib: 257†
AV-951-09-902	An Extension Treatment Protocol for Subjects who have Participated in a Phase 3 Study of Tivozanib vs. Sorafenib in Renal Cell Carcinoma (Protocol AV-951-09-301) – cross-over patients	Tivozanib: 161‡
Total number of subjects exposed:		Tivozanib*:835 Sorafenib: 257 Sunitinib: 41

* An additional patient in Study AV-951-09-301 was randomized to tivozanib hydrochloride but discontinued prior to dosing.
† Includes patients who continued their respective treatment in AV-951-09-902.
‡ Only includes patients who received sorafenib in Study AV-951-09-301 and then crossed over into Study AV-951-09-902 to receive tivozanib hydrochloride. Patients who rolled over from Study AV-951-09-301 and continued their study treatment (sorafenib or tivozanib hydrochloride) are already counted with Study AV-951-09-301.

Further study details and whether they appear in our original submission are listed below:

- 201 (discontinuation study) is published as Nosov DA, Esteves B, Lipatov ON, et al. Antitumor activity and safety of tivozanib (AV-951) in a phase II randomized discontinuation trial in patients with renal cell carcinoma. J Clin Oncol 2012; 30(14): 1678-85. This study is discussed in detail in the submission (Section 4.11, 4.12.4 and Appendix 3).
- 202 (biomarker study) has not been published; however, data was presented at ESMO in 2014. This study is discussed in detail in the submission (Section 4.11, 4.12.4 and

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Appendix 3). This study was not completed; the primary efficacy analyses of correlations between biomarkers in blood and archived tissue and PFS and objective response were never carried out.

- 205 (patient preference study, TAURUS study) was not completed (see question C1)
- 301 (TIVO-1 study) discussed in detail in the submission.
- 902 (extension study) discussed in detail in the submission.

Additional clarification questions

1. **Priority question**: Throughout the company submission the primary end-point of progression free survival was reported to be based on independent radiology review for the overall intention to treat population. Estimates for the treatment naive population were then used in the mixed treatment comparison to produce progression free survival hazard ratios. However, in the economic model, the tivozanib Kaplan Meier data is appears to be based on the overall intention to treat investigator review of PFS (median PFS 14.7 months in the economic model corresponds to median PFS mentioned on page 67 of the company submission). Please provide a scenario analysis using the independent radiology review Kaplan Meier data for the treatment naive population.

This was an inadvertent error – the model should have been based on the independent radiological review data, in line with the primary outcome analysis of the study. This has been corrected in our revised model

2. **Priority question**: Further investigation of the overall survival Kaplan Meier data used in the economic model reveals the median overall survival for tivozanib is 36.04 months. In the company submission (page 71, Figure 7) and elsewhere in the report, overall survival for tivozanib is reported as 28.2 months (29 months in Figure 8, page 72 of the company submission) which is based on the overall intention to treat population.

A1. Please clarify why there are different estimates of median overall survival in section 4.7.2.2 in the company submission.

This was an error in our submitted model – the wrong curve was inadvertently used. We have now corrected this and the new model provided supersedes the previous one.

A2. Please clarify why there is a difference in what is reported in the company submission and estimated in the economic model for median overall survival.

Please see response to the previous question (A1).

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

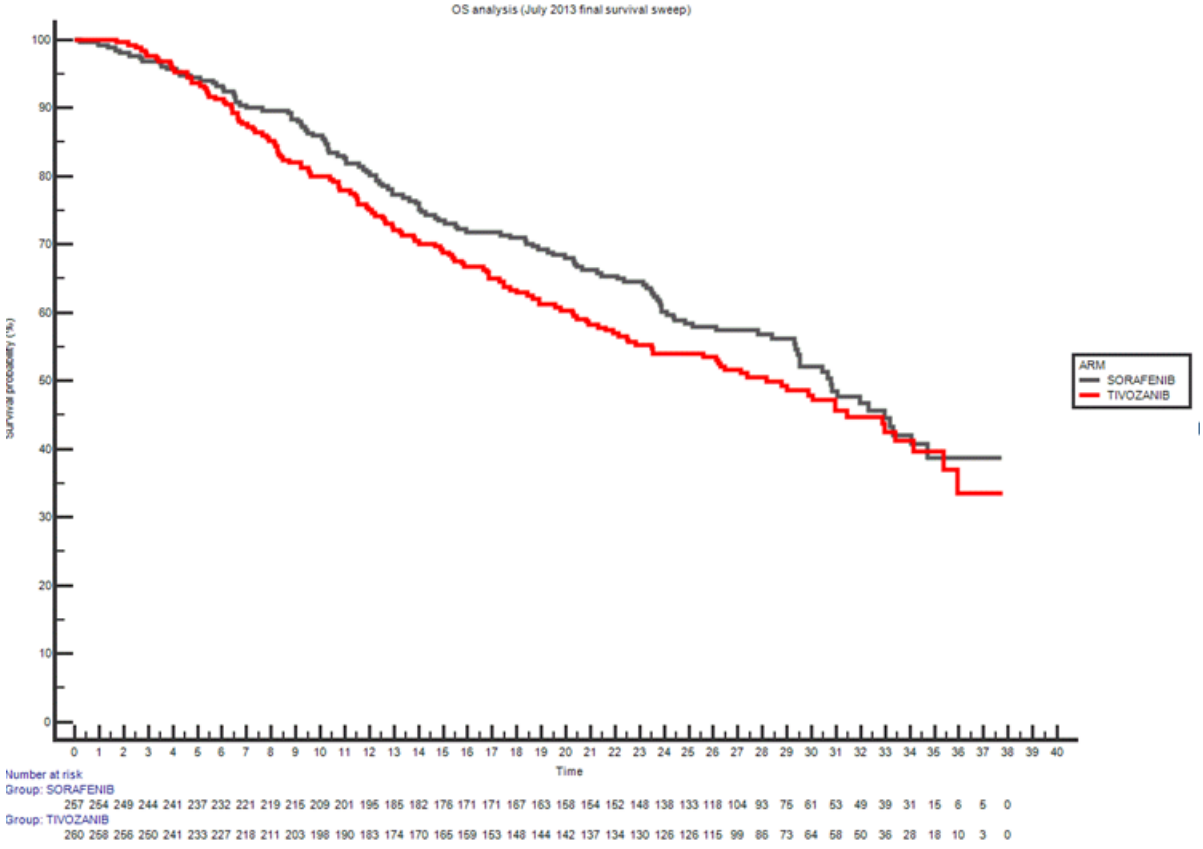
A3. Please clarify which data are correct and update the model as necessary, focusing on Kaplan Meier data for the treatment naive population, or provide justification as to why the original data used in the model is appropriate.

The data in the written submission are the correct ones and the model has been altered accordingly

A4. Please provide the numbers at risk for overall survival for the treatment naive population based on the response to question 2 c. In addition please clarify why the numbers at risk provided in Figure 7 of the company submission for tivozanib between month 17-21 drop and then increase from month 22 onwards.

It appears that the numbers at risk quoted for OS in the CSR (figure 12, p118 of reference 19) are incorrect: figure 7 in our response was drawn directly from this source. We have re-analysed the primary data to yield an accurate "numbers at risk table" (see below). The estimates of median PFS remain unaltered at 28.2 months for tivozanib and 30.8 months for sorafenib for the overall population. We have also provided K-M curves for the treatment-naïve population (Figure 34).

Figure 33: Re-run OS analysis for total population with corrected numbers at risk

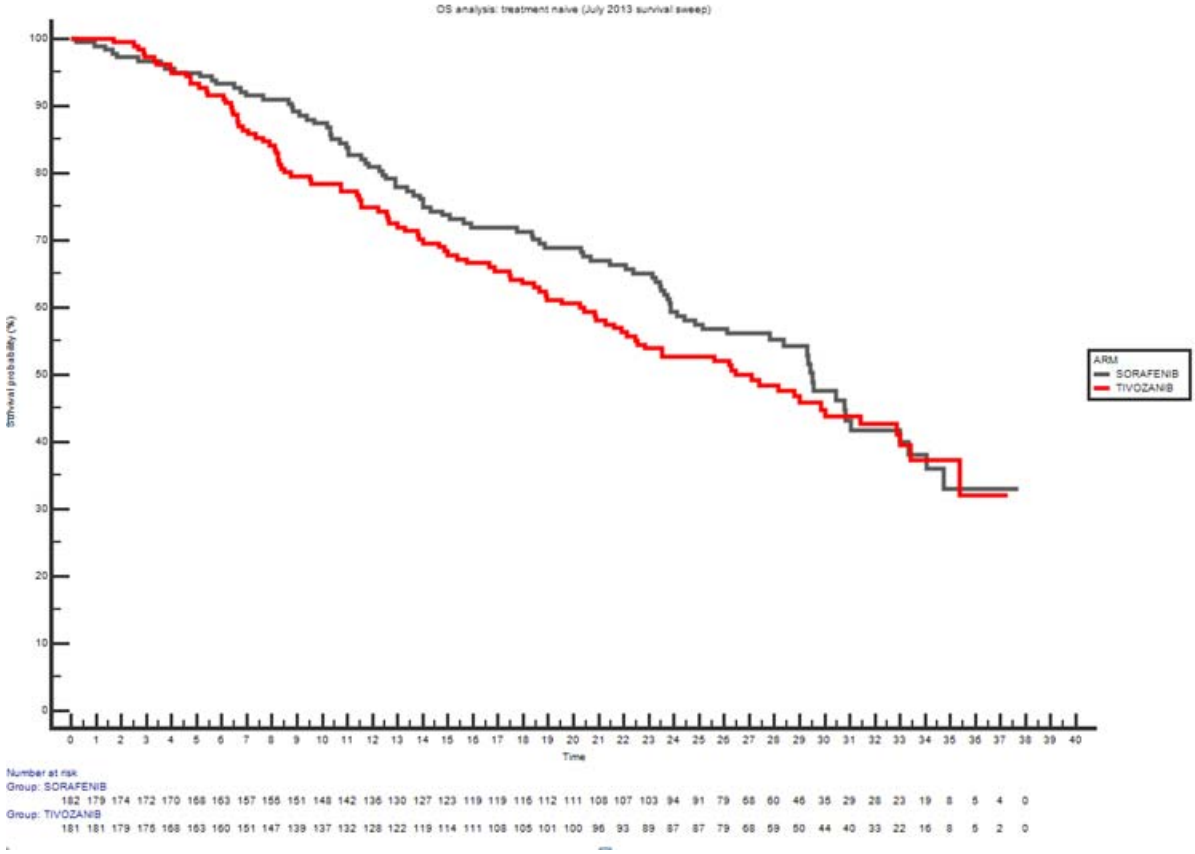


NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 34: OS analysis for treatment-naïve population



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

References

1. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. ScHARR, University of Sheffield; 2014.
2. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, NJ W. NICE DSU Technical Support Document 18: Methods for population-adjusted indirect comparisons in submissions to NICE2016 9th January 2017. Available from: http://www.nicedsu.org.uk/TSD18%20Population%20adjustment%20TSD%20-%20FINAL.pdf.
3. AVEO Pharmaceuticals I. Clinical study report protocol AV-951-09-301. A phase 3, randomized, controlled, multi center, open-label study to compare tivozanib (AV 951) to sorafenib in subjects with advanced renal cell carcinoma 2012.
4. Motzer R, Eisen T, Hutson TE, Szczylik C, Krygowski M, Strahs A, et al., editors. Overall survival results from a phase III study of tivozanib hydrochoride versus sorafenib in patients with renal cell carcinoma (poster). American Society of Clinical Oncology Genitourinary Symposium 2013; Orlando, Florida
5. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. ScHARR, University of Sheffield; 2011.
6. Ouwens MJ, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. Res Synth Methods. 2010;1(3-4):258-71.
7. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol. 2011;11:61.
8. Motzer R, Hutson TE, Reeves J, Hawkins R, Guo J, Nathan P, et al. Randomized, open-label, phase III trial of pazopanib versus sunitinib in first-line treatment of patients with Metastatic Renal Cell Carcinoma (MRCC): Results of the COMPARZ trial. Annals of Oncology.Conference:37th ESMO Congress Vienna Austria. Conference Start: 20120928 Conference End: 1002. Conference Publication: (var.pagings). 23 (pp ix13).
9. Dias S, Sutton AJ, Welton NJ, Ades AE. Embedding Evidence Synthesis in Probabilistic Cost-Effectiveness Analysis: Software Choices. NICE Decision Support Unit Technical Support Documents. London2012.

ESTIMATION OF OVERALL SURVIVAL ADJUSTING FOR CROSSING OVER USING IPCW METHOD – TIVO-1 TRIAL.

BACKGROUND AND RATIONALE

Tivozanib hydrochloride (Tivozanib) is a potent and selective VEGFR TKI with a relatively long half-life (approximately 4 days).12-14 Tivozanib inhibits phosphorylation of VEGFR1, -2, and -3 at Pico molar concentrations and inhibits other kinases such as c-KIT and platelet-derived growth factor receptor beta at 10 times higher concentrations, suggesting the potency and specificity of Tivozanib.

The TIVO-1 study was a randomized phase III open-label trial. Patients were randomly assigned 1:1 to either Tivozanib or Sorafenib as their initial targeted therapy. Random assignment of patients was stratified by geographic region, number of prior treatments for metastatic disease, and number of metastatic sites/organs involved.

The primary end point was progression-free survival (PFS). Secondary end points included overall survival, tumour response rate (Response Evaluation Criteria in Solid Tumours), and safety. A total of 517 patients were randomly assigned to Tivozanib (n = 260) or Sorafenib (n = 257). PFS was longer with Tivozanib than with Sorafenib in the overall population (median, 11.9 *v* 9.1 months; hazard ratio [HR], 0.797; 95% CI, 0.639 to 0.993; *P* = .042). The final overall survival (OS) analysis showed a trend toward longer survival on the Sorafenib arm than on the Tivozanib arm (median, 29.3 *v* 28.8 months; HR, 1.245; 95% CI, 0.954 to 1.624; *P* =.105). Adverse events (AEs) more common with Tivozanib than with Sorafenib were hypertension (44% *v* 34%) and dysphonia (21% *v* 5%). AEs more common with Sorafenib than with Tivozanib were hand-foot skin reaction (54% *v* 14%) and diarrhoea (33% *v* 23%).

A total of one hundred fifty-six patients (61%) who progressed on Sorafenib crossed over to receive Tivozanib. The likely effect of such cross-over was to increase the survival times for patients in the Sorafenib group relative to what would have been observed had Sorafenib patients not been allowed to cross-over. Because a treatment strategy of initial treatment with Sorafenib, followed by treatment with Tivozanib upon disease progression, the utility of the ITT analysis is therefore limited. An estimate of the treatment effect with Tivozanib on OS in a counterfactual setting where survival for patients receiving Tivozanib would be identical to those of patients randomized to Tivozanib arm in the TIVO-1 clinical trial whereas survival for those receiving Sorafenib would be identical to that of a hypothetical cohort of patients who received Sorafenib but who were ineligible to receive Tivozanib upon disease progression is required.

Several methods have been employed for analysing OS in randomized controlled trials in OS may be confounded by cross-over to active treatment. These include censoring patients who cross-over, or including a time-dependent covariate representing cross-over in a Cox proportional hazards regression analysis. However, these methods may be confounded by differences in between groups in time-dependent factors that are correlated with cross-over and survival. More recently, Inverse Probability of Censoring Weighed (IPCW) methods and Rank Preserving Structural Failure Time (RPSFT) methods have been employed to address this issue.

The objective of this analysis was to evaluate the effects of Tivozanib on OS among patients in the TIVO-1 trial controlling for the potential confounding effects of cross-over on survival. Survival outcomes, censoring, and cross-over in these patients summarized in **Table 1**.
Among patients in the TIVO-1 trial (260 patients randomized to Tivozanib and 257 patients randomized to Sorafenib), 147 patients randomized to Sorafenib (91.3%) crossed-over to Tivozanib after disease progression.

Table 1. Survival outcomes and cross-over of patients in the TIVO-1 trial

	Tivozanib	**Sorafenib**	**Total**
N (Total patients)	260	257	517
N (Censored)	127	214	341
N (Failure – dead)	133	43	176
N (Cross-over)	0	147	147

* A total of 161 patients randomised to Sorafenib crossed-over to other treatments. However, 147 of these patients have cross over to Tivozanib treatment (91.3%).

INVERSE PROBABILITY OF CENSORING WEIGHTED (IPCW) ANALYSIS
The IPCW method of analysing mortality to adjust for cross-over entails the following three general steps:

1- **Create Panel Data**: For Sorafenib patients, follow-up time from randomization until cross-over or end of follow-up (defined as death, withdrawal of consent, or end of study, whichever occurred first) was partitioned into intervals based on unique events time. For each of these intervals, time-dependent variables that might be predictive of cross-over and mortality (e.g. Number of week since diagnostics, and number of weeks since disease progression) were calculated.

2- **Calculate Stabilized Weights**: Using the panel data created in Step 1, for each Sorafenib patient *i* and interval (j), stabilized weights, $SW_i(j)$, were estimated. The denominator of the weights is the probability of remaining uncensored (i.e., not crossing over to Tivozanib) to the end of interval (j) given baseline and time-dependent confounders. The numerator of the weights is the probability of remaining uncensored (i.e., not crossing over to Tivozanib) to the end of interval (j) given only baseline confounders. Estimates were obtained by fitting pooled logistic models with censoring (cross-over) as the dependent variable.

3- **Run IPCW Cox Regression**: Adjusted Hazard Ratio (AHR) for OS was estimated using a weighted Cox proportional hazard regression model, where patients intervals were weighted by the stabilized weights calculated in Step 2. For all patients who were randomized to Tivozanib, the weight is equal to 1.0 (i.e., $SW_j = 1$). Sorafenib patients who crossed-over were censored (i.e., for Sorafenib patients who crossed over, intervals after cross-over have a weight of zero and are therefore dropped from the model).

Each of these steps is described in greater detail below.

Step 1: Create the Panel Data

A panel data set was created with multiple intervals per patient with each interval beginning with randomization and ending with cross-over to Tivozanib or trial censoring, defined as death, withdrawal of consent, or end of study, whichever occurred first. For each observation, baseline personal and disease characteristics, including age, gender, MSKCC risk category, time since initial diagnosis at baseline, Eastern Cooperative Oncology Group performance status (ECOG), and the number of metastatic disease sites were calculated. Time-dependent characteristics included time since disease progression and time since diagnostic as time dependent.

Who crossed over to Tivozanib were censored at the cross-over time, and post cross-over follow up time were excluded from the subsequent analysis. Out of 260 patients initially randomized to the Sorafenib arm, 161 patients had disease progression and 147 of these patients were IPCW-censored at the time of cross-over to Tivozanib after disease progression.

Among TIVO-1 patients, 29 had missing data on time since diagnosis covariate, 14 and 15 in Tivozanib and Sorafenib treatment groups, respectively. For these patients with missing information, we imputed the sample mean value in order to keep these patients for the survival analysis of Tivozanib relative to Sorafenib.

Step 2: Calculate Stabilized Weights

Using the panel data created in Step 1, for each Sorafenib patient *i* and interval *(j)*, an estimate of the stabilized weights $SW_i(j)$ was obtained where

$$SW(j) = \prod_{k=0}^{j} = \frac{P[C(k)_i | C(k-1)_i, X(0)_i]}{P[C(k)_i | C(k-1)_i, X(0)_i, Y(k)_i]}$$

$C(k)_i$ = an indicator function representing censoring/cross-over status at the end of interval *k* (1: censored or cross-over, 0: uncensored)

$X(0)_i$ = an array of patients characteristics measured at baseline

$Y(k)_i$ = an array of time-dependent patients characteristics measured at or prior to the beginning of interval k

$P[C(k)_i|C(k\text{-}1)_i, X(0)_i]$ = probability of remaining uncensored at end of interval *k* given uncensored at end of interval *k-1* and conditioned on baseline characteristics $X(0)_i$

$P[C(k)_i|C(k\text{-}1)_i, X(0)_i, Y(k)_i]$ = probability of remaining uncensored at end of interval *k* given uncensored at end of interval *k-1* and conditioned on baseline characteristics $X(0)_i$, and time-dependent patient characteristics $Y(k)_i$.

To estimate the numerator of the stabilized weights we fit a logistic regression (model 1) in which we modelled the probability of remaining uncensored at time (j) conditional on patient *i* baseline factors (age, sex, favourable/intermediate/poor MSKCC risk category, time since initial diagnosis in weeks, ECOG performance status, and the number of

metastatic disease sites). The dependent variable in the logistic model was a binary variable (1/0) indicating whether the patient had crossed over or not since last visit. We fit this model on all patient-intervals from randomization until cross-over to Tivozanib or trial censoring, defined as death, withdrawal of consent, or end of study, whichever occurred first.

To estimate the denominator of the stabilized weights we fit a logistic regression (model 2) in which modelled the probability of remaining uncensored conditional on the same baseline factors and patient *i* time-dependent covariates at time (j): Time since progression and time since diagnostic as time dependent variable were the only time dependent covariates. The choice of baseline and time-dependent covariates were based on prior knowledge from the literature and goodness-of-fit statistics. We fit this second model on all patient-intervals post-disease progression, i.e., from disease progression until cross-over to Tivozanib or trial censoring, defined as death, withdrawal of consent, or end of study, whichever occurred first. **Table 2** and **Table 3** present the results of the logistic regression models 1 and 2.

Table 2. Pooled logistic regression analysis on remaining uncensored conditioned on baseline factors in TIVO-1 trial (Sorafenib patients [N=257], all intervals [N=15758 intervals]) (Model 1)

Covariate	OR	95%CI		p
Age (Reference: < 65 years)	1.026	0.683	1.54	0.899
Male (Reference: Female)	0.8	0.561	1.162	0.251
MSKCC Score: Intermediate (Reference: Favourable)	1.35	0.962	1.92	0.081
MSKCC Score: Poor (Reference: Favourable)	3.5	0.453	27.132	0.229
ECOG Status (Reference: 0)	0.92	0.658	1.295	0.644
Number of Metastatic Disease Site (Continuous variable)	1.43	1	2.043	0.045
Weeks since Diagnosis (Continuous variable)	0.99	0.982	0.997	0.013

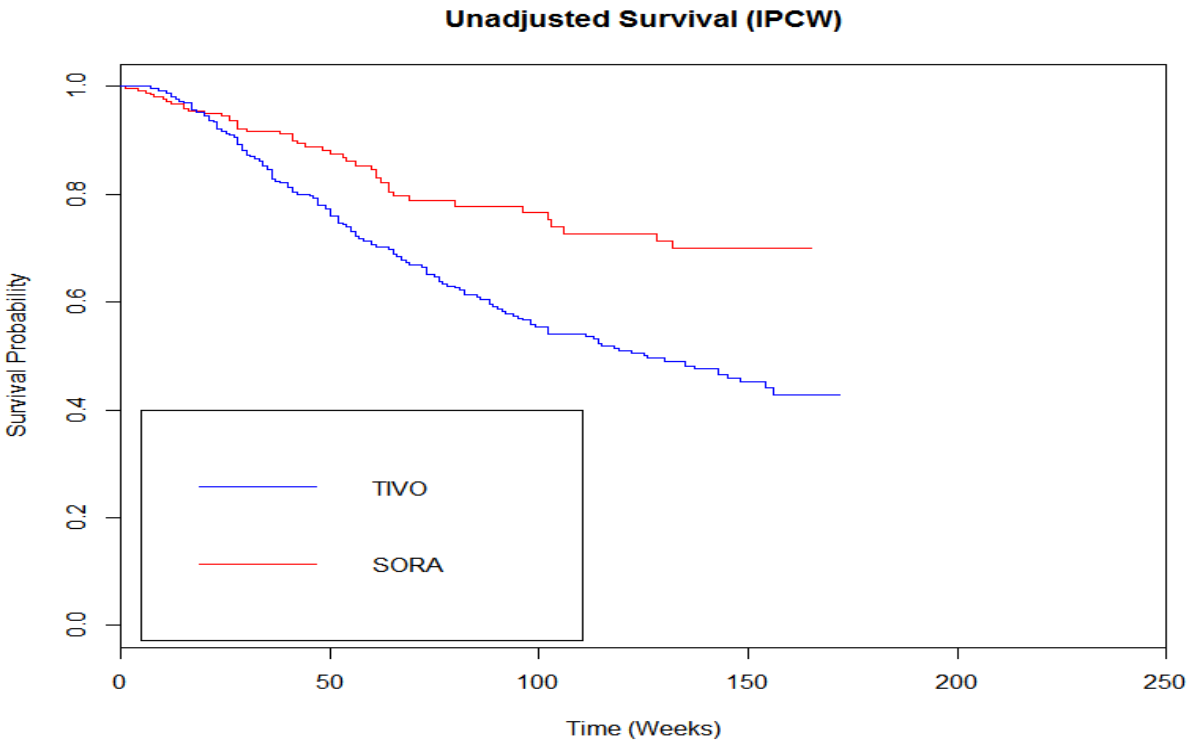
Table 3. Pooled logistic regression analysis on remaining uncensored given baseline and time-dependent factors in TIVO-1 trial (Sorafenib patients [N=147 patients], post-progression intervals [N=693 intervals]) (Model 2)

Covariate	OR	95%CI		p
Age (Reference: < 65 years)	1.141	0.781	1.666	0.494
Male (Reference: Female)	0.894	0.619	1.293	0.553
MSKCC Score: Intermediate (Reference: Favourable)	0.914	0.66	1.266	0.592
ECOG Status (Reference: 0)	0.535	0.388	0.737	<0.001
Number of Metastatic Disease Site (Continuous variable)	1.215	0.866	1.704	0.258
Weeks since Diagnosis (Continuous variable)	0.992	0.983	1.002	0.142
Weeks since Progression (Continuous variable)	0.785	0.72	0.856	<0.001
Weeks since Diagnosis – Time dependent (Continuous variable)	1.003	0.996	1.01	0.296

Step 3: IPCW Cox Proportional Hazards Regression (Censoring at Cross-Over)
In the final step, a time-dependent Cox proportional hazards model was estimated using time-varying stabilized weights, as calculated in Step 2, to compare the overall survival between Tivozanib and Sorafenib. In this model, a binary variable indicating the status (0=censored; 1=death) at each person-time was used as the censoring variable and number of days since randomization was used as the survival time variable. Patients randomized to Sorafenib who crossed over to Tivozanib were censored at the cross-over, and post cross-over time were excluded from the subsequent analysis (i.e., *SWi(j)*=0). All other person-time observations were weighted by the stabilized weights calculated in step 2. A binary indicator of randomization arm (Tivozanib relative to Sorafenib) was used in the IPCW.

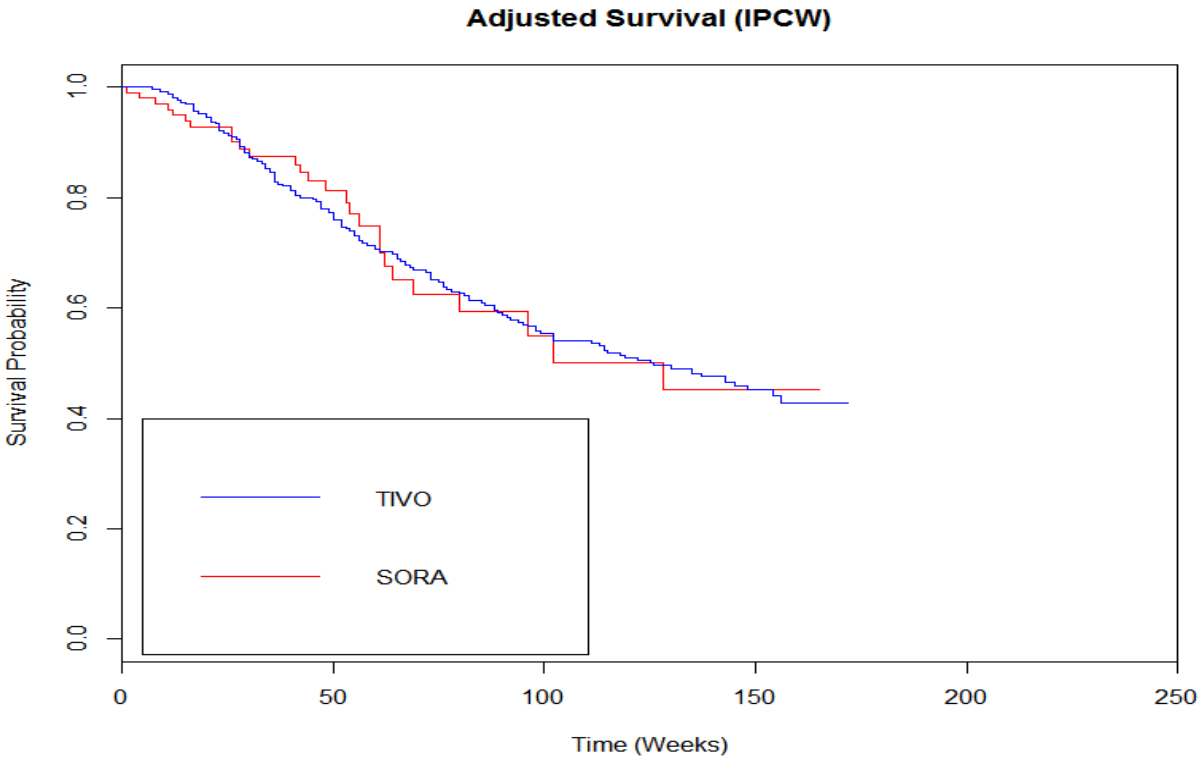
Figure 1 and 2 present the Kaplan-Meier curves for Overall Survival of the unadjusted and IPCW-adjusted models.

Figure 1. Kaplan-Meier curve: Unadjusted analysis for Overall Survival with crossover patients censored at the point of starting new therapy (Tivozanib: N=260; Sorafenib: N=257)



When performing a Cox proportional regression using the unadjusted dataset, the hazard ratio (HR) for OS - with Sorafenib patients censored when crossing over to Tivozanib – shows a better survival outcome in Sorafenib group compared with Tivozanib (HR: 2.046; 95%CI: 1.453-2.884; p-value<0.001).

Figure 2. Kaplan-Meier curve: IPCW-adjusted analysis for Overall Survival (Tivozanib: N=260; Sorafenib: N=257)



When performing a Cox proportional regression using the IPCW-adjusted dataset, the hazard ratio (HR) for OS - with Sorafenib patients censored when crossing over to Tivozanib – shows a similar survival outcome in Sorafenib group compared with Tivozanib (HR: 1.021; 95%CI: 0.671-1.553; p-value=0.923).

R code

```
library(Hmisc) ## Installing package to upload SAS data into R
library(SASxport) ## Installing package to upload SAS data into R
library(knitr)
library(dplyr)
library(tidyr)
library(broom)
library(gdata)
library(lmtest)
library(visreg)
library(lme4)
library(gridExtra)
library(ggplot2)
library(sas7bdat)
library(survival)
library(pglm)

##  Setting up the working directory
setwd("J:/Datasets/TIVO/301/Study_301_SDTM and Raw")

## Uploading the adeff and AE datasets
Data_VS <- read.sas7bdat("vs.sas7bdat")
Data_AE <- read.sas7bdat("ae.sas7bdat")
Data_Eff <- read.csv("adeff.csv")
Data_Cov <- read.csv("Baseline covariates TIVO.csv")

## Coercing data sets into tbl file
Data_VS <- tbl_df(Data_VS)
Data_AE <- tbl_df(Data_AE)
Data_Eff <- tbl_df(Data_Eff)
Data_Cov <- tbl_df(Data_Cov)

### Subsetting the ADEFF dataset
NData_Eff <- Data_Eff %>%
        select(USUBJID, ARM, RANDDT, DS01RS, DS01DT, CROSSFL, TRT02P, TR02SDT, TR02EDT,
            DLASTC01, DLASTC02, COMPDTC, ALLDTHDT, AGE, AGEGRP, SEX)%>%
        data.frame()

## Changing time variables format
NData_Eff$TR02SDT = strptime(as.character(NData_Eff$TR02SDT), format = "%d-%b-%y")
NData_Eff$RANDDT = strptime(as.character(NData_Eff$RANDDT), format = "%d-%b-%y")
NData_Eff$ALLDTHDT = strptime(as.character(NData_Eff$ALLDTHDT), format = "%d-%b-%y")
NData_Eff$DLASTC01 = strptime(as.character(NData_Eff$DLASTC01) , format = "%d-%b-%y")
NData_Eff$DLASTC02 = strptime(as.character(NData_Eff$DLASTC02), format = "%d-%b-%y")
NData_Eff$DS01DT = strptime(as.character(NData_Eff$DS01DT), format = "%d-%b-%y")

NData_Eff$TR02SDT <- format(NData_Eff$TR02SDT, "%Y-%m-%d")
NData_Eff$RANDDT <- format(NData_Eff$RANDDT, "%Y-%m-%d")
```

```
NData_Eff$ALLDTHDT <- format(NData_Eff$ALLDTHDT, "%Y-%m-%d")
NData_Eff$DLASTC01 <- format(NData_Eff$DLASTC01, "%Y-%m-%d")
NData_Eff$DLASTC02 <- format(NData_Eff$DLASTC02, "%Y-%m-%d")
NData_Eff$DS01DT <- format(NData_Eff$DS01DT, "%Y-%m-%d")

NData_Eff <- tbl_df(NData_Eff)

NData_Eff <- NData_Eff %>%
        mutate(CROSSFL = ifelse(ARM == "SORAFENIB" & TRT02P == "TIVOZANIB",  "Y", "N")) %>%
        mutate(time = ifelse(ARM == "SORAFENIB" & CROSSFL == "Y",
             difftime(TR02SDT, RANDDT, units ="weeks"), ifelse(!is.na(ALLDTHDT),
             difftime(ALLDTHDT, RANDDT, units ="weeks"), ifelse(is.na(ALLDTHDT) &
             CROSSFL == "N" & !is.na(DLASTC02), difftime(DLASTC02, RANDDT,
             units = "weeks"), difftime(DLASTC01, RANDDT, units = "weeks"))))) %>%
        mutate(TTP = as.numeric(ifelse(DS01RS == "Progressive Disease",
             round(difftime(DS01DT, RANDDT, units = "weeks"),0), ""))) %>%
        mutate(time = round(time,0)) %>%
        mutate(CROSSFL = ifelse(CROSSFL == "Y", 1, 0)) %>%
        mutate(Status = ifelse(CROSSFL == 1 | is.na(ALLDTHDT), 0, 1)) %>%
        mutate(Event_FL = ifelse(is.na(ALLDTHDT), 0, 1)) %>%
        select(USUBJID, ARM, time, Status, DS01RS, DS01DT, CROSSFL,TTP, SEX, AGEGRP, Event_FL)
%>%
        as.data.frame()
```

Assigning new names to variables

```
id <- 1:517
USUBJID <- NData_Eff$USUBJID
ARM <- NData_Eff$ARM
time <- NData_Eff$time
status  <- NData_Eff$CROSSFL
Censored <- NData_Eff$Status
DS01RS <- NData_Eff$DS01RS
DS01DT <- NData_Eff$DS01DT
TTP <- NData_Eff$TTP
SEX <- NData_Eff$SEX
AGEGRP <- NData_Eff$AGEGRP
Event_FL <- NData_Eff$Event_FL

Data_Base  <- data.frame(id, USUBJID, ARM, time, status, Censored, DS01RS, DS01DT, TTP, SEX,
AGEGRP, Event_FL)

Sub_Data_Cov <- subset(Data_Cov, select = -c(COUNTRYC, ARM))

NData_Base <- left_join(Data_Base, Sub_Data_Cov, by = "USUBJID") %>%
         mutate(Metastasis = as.factor(Metastasis), ECOG = as.factor(ECOG)) %>%
         data.frame()
```

Split data over all event and censoring times

```
NData_Long <- survSplit(NData_Base, cut = time, end ="time", start = "Tstart", event="status", id =
"id")

NData_Long_Cens <- survSplit(NData_Base, cut=time, end="time", start = "Tstart",
event="Censored", id = "id")
NData_Long_Cens <- NData_Long_Cens[order(NData_Long_Cens$id, NData_Long_Cens$time),]
Cens <- NData_Long_Cens$Censored
```

Dataset in the longitudinal format

```
NData_Long <- tbl_df(NData_Long) %>%
        arrange(id, time) %>%
        mutate(TSIDIAG = round(ifelse(is.na(TSIDIAG), mean(TSIDIAG, na.rm = TRUE), TSIDIAG)/7,0))
%>%
        mutate(TSD = TSIDIAG + time) %>%
        mutate(time2 = time^2) %>%
        mutate(TSP = as.numeric(ifelse(DS01RS == "Progressive Disease",time - TTP, ""))) %>%
        mutate(TSP2 = TSP^2) %>%
        mutate(Select = time - TTP) %>%
        mutate(Censored = Cens) %>%
        select(USUBJID, ARM, status, ECOG,  MSKCC, Metastasis, TSIDIAG, Tstart, time, SEX, AGEGRP,
            time2, TTP, TSP, TSP2, TSD, Select, DS01RS, Censored) %>%
        data.frame()
```

Subset date including only Sorafenib patients

```
Subdata <- NData_Long[which(NData_Long$ARM == "SORAFENIB"),]
```

pooled regression analysis using base case covariates in Sorafenib population

```
Reg_pglm1 <- pglm(status ~ AGEGRP + SEX + ECOG + MSKCC + Metastasis + TSIDIAG,
            data = Subdata, effect = "time", model = "pooling", family = binomial('logit'))
summary(Reg_pglm1)
```

Subsetting the dataset including only patients who progressed to Tivozanib

```
Subdata2 <- NData_Long[which(NData_Long$DS01RS == "Progressive Disease" & NData_Long$ARM
== "SORAFENIB"),]
Subdata2 <- Subdata2[which(Subdata2$Select > 0), ]
```

pooled regression analysis using time-dependent and baseline covariates

```
Reg_pglm2  <- pglm(status ~ AGEGRP + SEX + ECOG + MSKCC + Metastasis + TSIDIAG + TSP + TSD,
             data = Subdata2, effect = "time", model = "pooling", family = binomial('probit'))
summary(Reg_pglm2)

write.csv(NData_Long, "NData_Long.csv")
IPCW_Dataset <- read.csv("IPCW_Dataset.csv")
```

Unweighted Kaplan-meier curves

```
KM_UNWEIGHTED <- survfit(Surv(Tstart, time, Censored) ~ ARM, data = IPCW_Dataset)
plot(KM_UNWEIGHTED, col = c("red", "blue"), xlab="Time (Weeks)", ylab="Survival Probability",
main = "Unadjusted Survival (IPCW)", ylim=c(0, 1.0), xlim=c(0, 250), mark.time = FALSE)
legend(5, 0.4, legend = c("TIVO", "SORA"), col = c("blue", "red"), lty = 1)
```

Weigthed Kaplan-meier curves

```
KM_WEIGHTED <- survfit(Surv(Tstart, time, Censored) ~ ARM, data = IPCW_Dataset, weights =
SWEIGHT)
plot(KM_WEIGHTED, col = c("red", "blue"), xlab="Time (Weeks)", ylab="Survival Probability",
main = "Adjusted Survival (IPCW)", ylim=c(0, 1.0), xlim=c(0, 250), mark.time = FALSE)
legend(5, 0.4, legend = c("TIVO", "SORA"), col = c("blue", "red"), lty = 1)
```

Unweighted Cox regression

```
Cox_UNWEIGHTED <- coxph(Surv(Tstart, time, Censored) ~ ARM, data = IPCW_Dataset)
summary(Cox_UNWEIGHTED)
```

Weighted Cox regression

```
Cox_WEIGHTED <- coxph(Surv(Tstart, time, Censored) ~ ARM, data = IPCW_Dataset, weights =
SWEIGHT)
summary(Cox_WEIGHTED)
```

RANK PRESERVING STRUCTURAL FAILURE TIME METHOD (RPSFTM) IN NAÏVE PATIENTS POPULATION

I. Definition

The RPSFT method is based on an Accelerated Failure Time (AFT) model for time-varying treatment. This model uses a structural assumption: It relates each patient's observed failure time and treatment history to the failure time that would have been observed if patients in the Sorafenib arm had not switched to the Tivozanib arm.

II. Method

Let $T_i = T^{off}_i + T^{on}_i$ be the observed event time for subject i, where T^{off}_i and T^{on}_i are the time that the patient spent off and on Tivozanib arm, respectively. The T_i are related to the counter-factual or treatment-free event times U_i by the causal model:

$$U_i = T^{off}_i + T^{on}_i \exp(\psi_0)$$

Where $\exp(-\psi_0)$ is the acceleration factor associated with treatment and ψ_0 is the true causal parameter.

To estimate ψ we assume that the U_i are independent of randomised treatment groups (Tivozanib, Sorafenib), i.e. if the groups are similar with respect to all other characteristics except treatment, the average event times should be the same in each group if no patient were treated with Tivozanib. A g-estimation procedure is used to find the value of ψ such that U is independent of randomised treatment groups. For each value of ψ considered, the hypothesis $\psi_0 = \psi$ is tested by computing $U_i(\psi)$ and calculating the Log-rank and Wilcoxon statistics and their respective P-values as the test statistic. This is usually the same test statistic as for the intention-to-treat analysis.

The point estimate (ψ^*) is the value of ψ for which P-value $(\psi) = 1$ or as highest possible P-value. Confidence intervals for ψ^* were obtained by repeating the analysis on 500 bootstrap samples of the data. Unstratified and stratified estimates of ψ^* along with corresponding confidence intervals and p-values are reported for the Log-rank and Wilcoxon tests.

As well as assuming that the only difference between randomised groups is the treatment received, the RPSFTM also assumes a common treatment effect. The common treatment effect assumption states that the treatment effect is the same for all individuals (with respect to time spent on treatment) regardless of when treatment is received.

The censoring indicators of the observed event times are initially carried over to the counter-factual event times. However, the uninformative censoring on the *Ti* scale may be informative on the *Ui* scale. Suppose we have two individuals with the same *Ui*, one of whom receives the superior treatment. The individual receiving the superior treatment has their

Ui extended so that they are censored whilst the other individual may observe the event. Therefore, on the *Ui* scale, censoring is informative with respect to treatment group. To overcome this problem, the counter-factual event times are re-censored by the minimum *Ui* that could have been observed for each individual across their possible treatment changes.

Let *Ci* be the potential censoring time for an individual *i*. An individual is then re-censored at the minimum possible censoring time:

$D^*_i(\psi) = min\ (Ci, Ci \exp(\psi))$.

If $D^*_i(\psi) < Ui$, then *Ui* is replaced by D^*_i and the censoring indicator is replaced by 0. For treatment arms where switching does not occur, there can be no informative censoring and so re-censoring is not applied.

The RPSFT approach employed here consisted of the following steps:

1. Obtain an estimate of the effect of exposure to Tivozanib on survival time, ψ^*, as described above.

2. Estimate the HR for OS for randomization to Tivozanib vs. randomization to Sorafenib with no cross-over to Tivozanib by fitting a Cox proportional hazards regression model to the Tivozanib failure times as observed in the TIVO-1 trial and re-censored adjusted failure times for placebo patients based on the estimate of $\exp(\psi^*)$.

Four separate RPSFT analyses were performed. The stratified and unstratified Log-rank and Wilcoxon tests. The stratification was computed for patient baseline characteristics, including ECOG performance status (ECOG), Motzer risk category (MSKCC), and number of metastatic disease sites. The patient theoretical maximum follow-up time was defined by time from patient‘s randomization date to the final data cut-off date (July 10, 2013).

III. Log-rank and Wilcoxon tests (Unstratified analysis)

Results of the RPSFT analyses derived from the Log-rank and Wilcoxon tests are shown in Table 1, respectively. In the RPSFTM, the estimated values of the causal effect parameter (ψ_k) was performed using a grid search (Range -2 to 2).

Table 1. Estimated causal rate ratio (ψ^*) for OS for Tivozanib among naïve patients in TIVO-1 trial derived from the unstratified (Tivozanib: N=181; Sorafenib: N=182)

	Log-rank test	**Wilcoxon Test**
ψ^*	0.46	0.4
Standard error	0.623	0.627
95%CI	-0.78 to 1.66	-0.8 to 1.62
$\exp(\psi^*)$	1.584	1.491
95%CI	0.458 to 5.259	0.449 to 5.053

The causal effect estimates (ψ^*) reported in table 1 suggest that continuous treatment with Tivozanib decreases the survival time by a factor exp (-0.46) and exp (-0.4) in the Log-rank and Wilcoxon tests, respectively.

III.1 Estimation of the median OS using unstratified tests.

Kaplan Meier curves were estimated using the observed event times and the observed censoring indicators for each patient in Tivozanib arm. For patients in the Sorafenib arm, the adjusted event times $X_i(\psi^*)$ and censoring indicators $\Delta_i(\psi^*)$, were employed, with ψ^*, based on our point estimates.

Kaplan-Meier plots for the intention de treat analysis (ITT), the observed failure times for Tivozanib patients and adjusted re-censored failure times for Sorafenib patients are reported in Figures 1.A (ITT), 2.A (Unstratified Log-rank test) and 3.A (Unstratified Wilcoxon test).

Figure 1.A Kaplan-Meier plot using ITT analysis among naïve patients population in TIVO-1 trial (Tivozanib: N=181; Sorafenib: N=182)

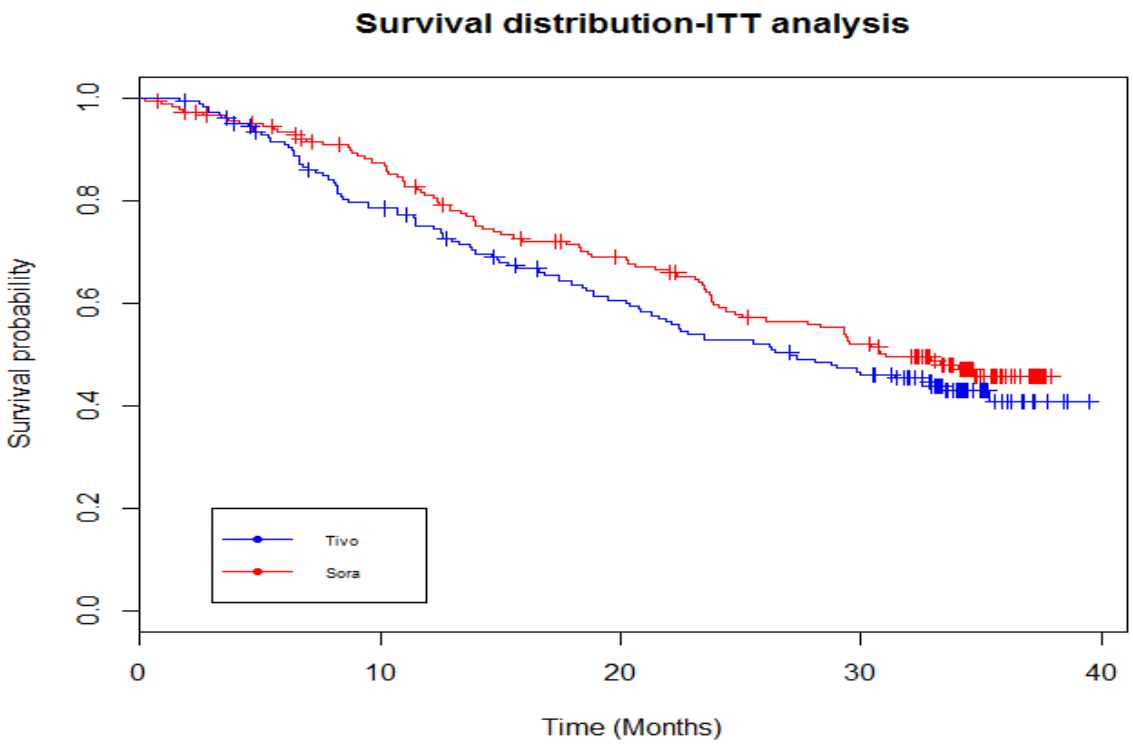


Figure 2.A Kaplan-Meier plot of observed survival times (Months) for Tivozanib patients and RPSFT adjusted and re-censored survival times for Sorafenib patients, treatment naïve population in TIVO-1 trial (Tivozanib: N=181; Sorafenib: N=182)

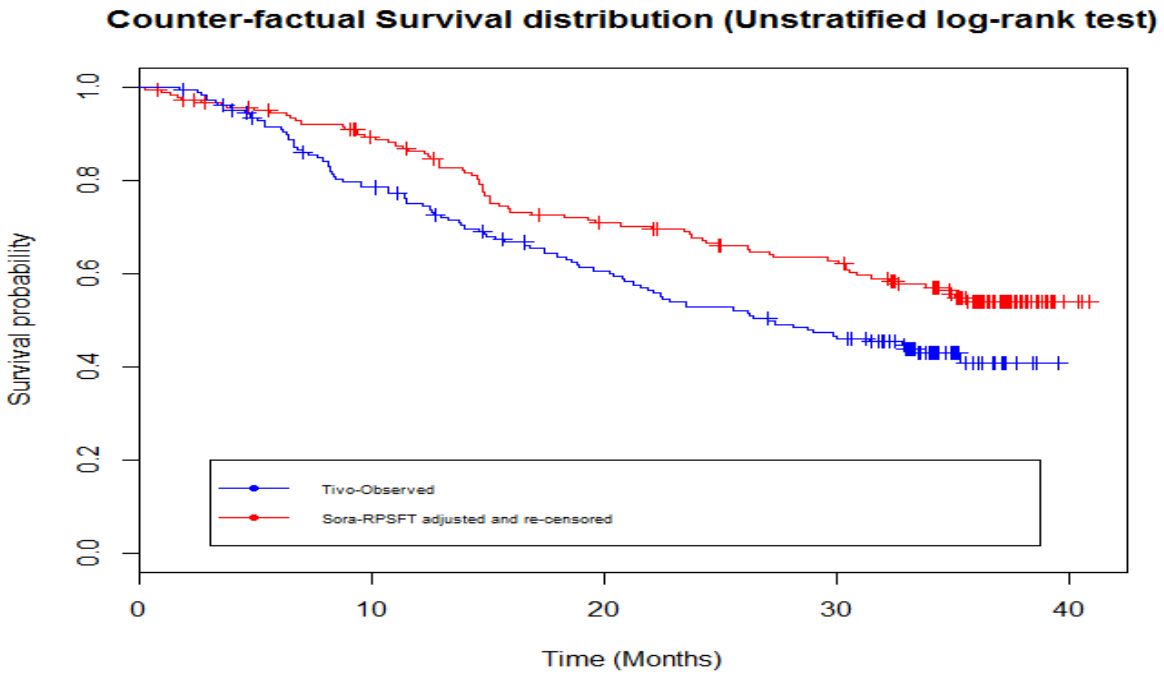
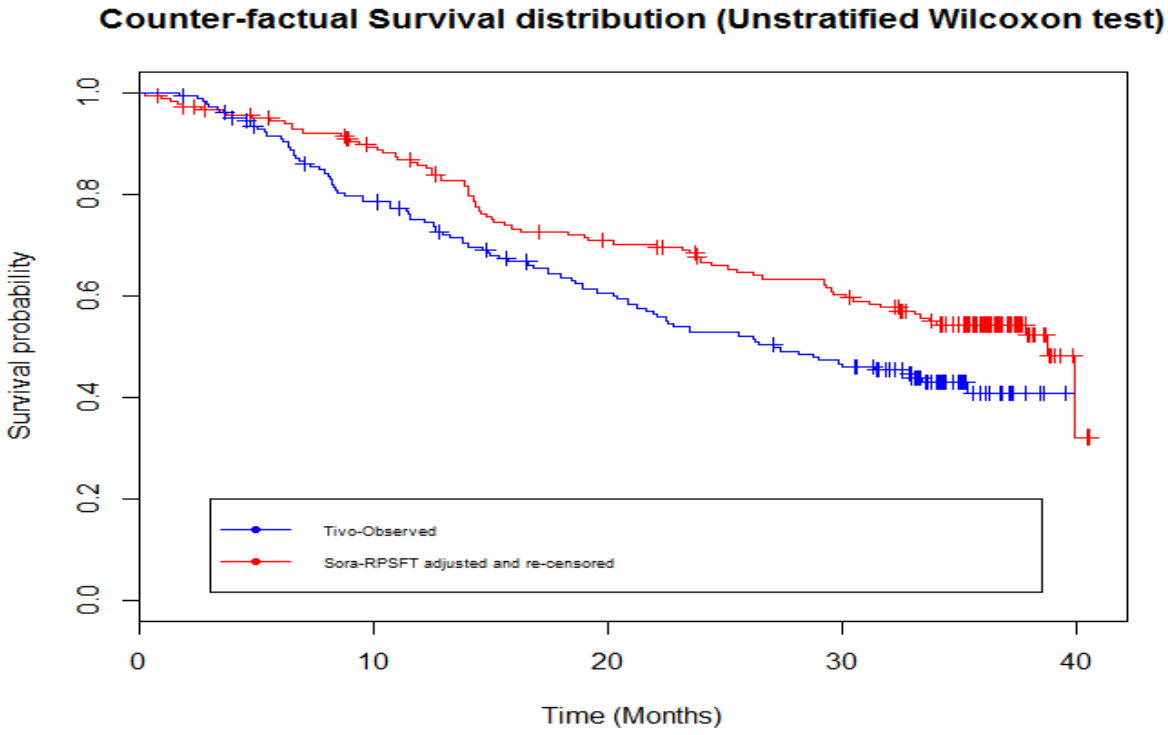


Figure 3.A Kaplan-Meier plot of observed survival times (Days) for Tivozanib patients and RPSFT adjusted and re-censored survival times for Sorafenib patients, treatment naïve population in TIVO-1 trial (Tivozanib: N=181; Sorafenib: N=182)



The median OS derived from the ITT analysis was 31 Months in Sorafenib group and 27.1 Months in Tivozanib group. In contrast, the counter-factual analysis (RPSFT) suggested different results for the median OS in Sorafenib group when using the Unstratified Log-rank test (Not reached) and Unstratified Wilcoxon test (38.7 Months), OS survival remaining equal in Tivozanib group for all analyses. This suggests that continuous treatment with Tivozanib is detrimental for the OS.

IV. Log-rank and Wilcoxon tests (Stratified analysis)

The stratified analysis was computed using three baseline characteristics as strata, which included ECOG performance status (ECOG), Motzer risk category (MSKCC), and number of metastatic disease sites.

The objective of stratification is to fix the level of the confounders and produce groups within which the confounder does not vary. Then evaluate the exposure-outcome association within each stratum of the confounder. So within each stratum, the confounder cannot confound because it does not vary across the exposure-outcome.

If there is difference between crude result and adjusted result (produced from strata), confounding is likely.

Table 2 below reports the results of the causal effect estimate derived from stratified analyses.

Table 2. Estimated causal rate ratio (ψ^*) for OS for Tivozanib - derived from the stratified analysis - among naïve patients in TIVO-1 trial (Tivozanib: N=181; Sorafenib: N=182)

	Stratified Log-rank test	**Stratified Wilcoxon Test**
ψ^*	0.05	0.05
Standard error	0.986	0.951
95%CI	-1.882 to 1.952	-1.813 to 1.913
exp(ψ^*)	1.05	1.05
95%CI	0.152 to 7.042	0.163 to 6.773

The results obtained from the stratified analysis suggest that a continuous treatment on Tivozanib has a neutral impact on OS. This completely cancels out the detrimental effect of continuous treatment with Tivozanib on OS showed by the unstratified analysis, proving that the disagreement between the crude result and the result produced from strata is down to the presence of an imbalance baseline characteristics between the treatment groups. This is also consistent with the IPCW analysis performed previously, where when adjusting for confounders, we obtained identical survival curves.

Kaplan-Meier plots of observed failure times for Tivozanib patients and adjusted re-censored failure times for Sorafenib patients are reported in Figures 1.B (Stratified Log-rank test) and 2.B (Stratified Wilcoxon test)

Figure 1.B Kaplan-Meier plot of observed survival times (Days) for Tivozanib patients and RPSFT adjusted and re-censored survival times for Sorafenib patients, among naïve patients in TIVO-1 trial (Tivozanib: N=181; Sorafenib: N=182)

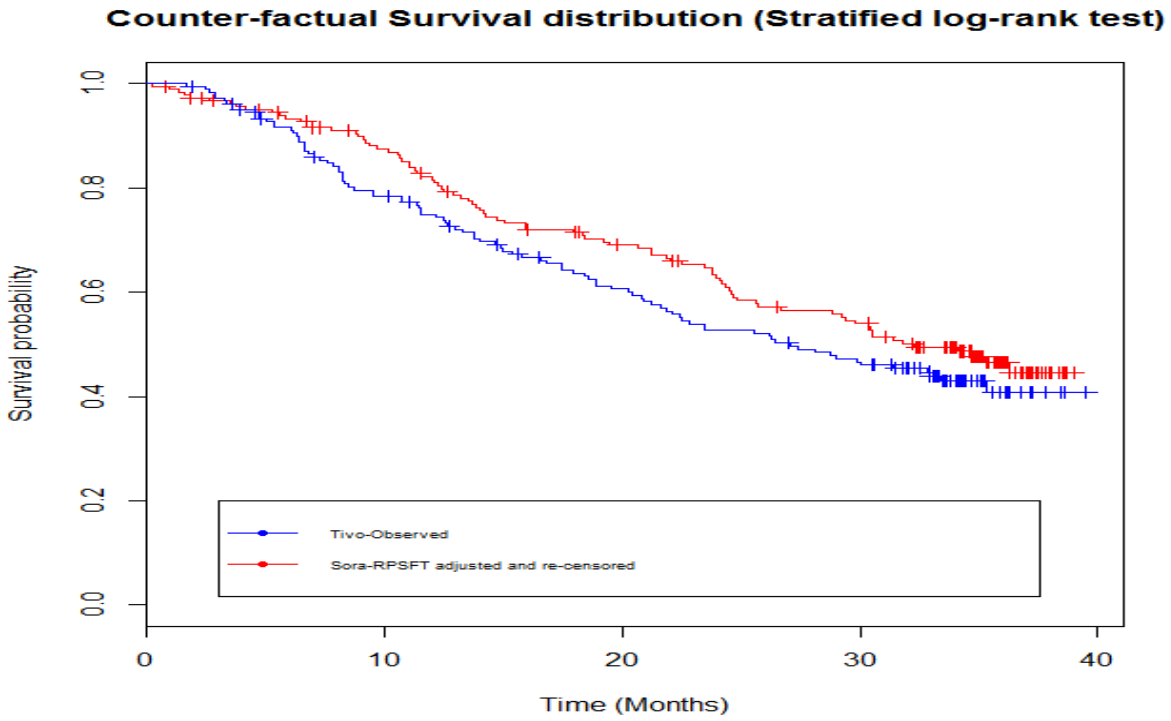
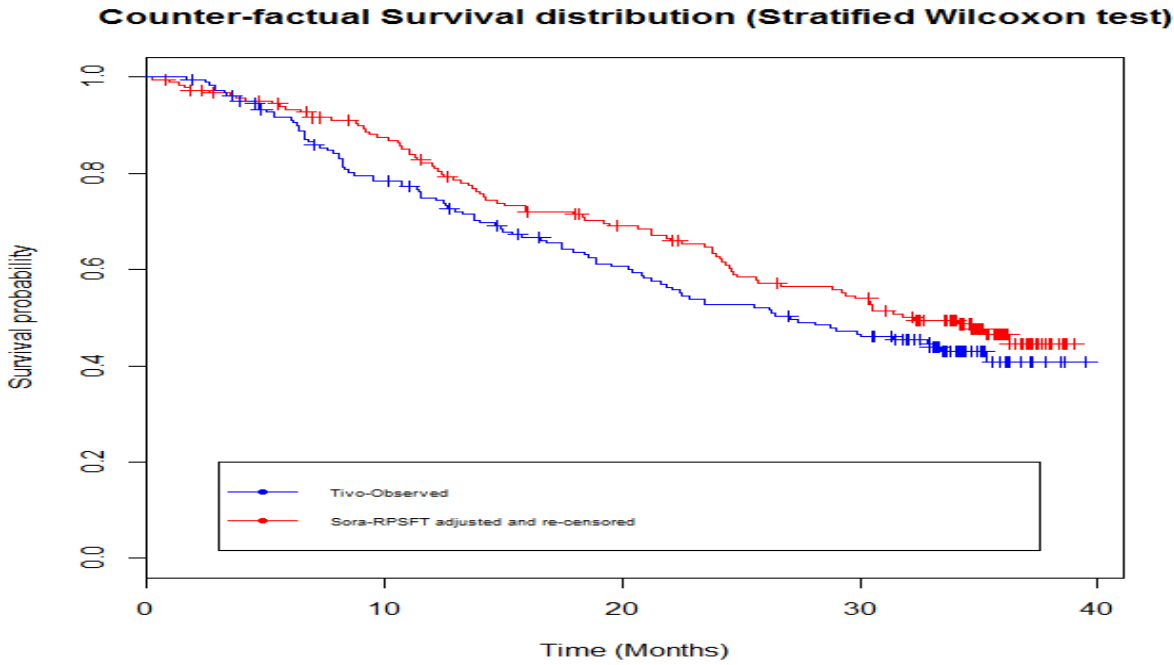


Figure 2.B Kaplan-Meier plot of observed survival times (Days) for Tivozanib patients and RPSFT adjusted and re-censored survival times for Sorafenib patients, among naïve patients in TIVO-1 trial (Tivozanib: N=181; Sorafenib: N=182)



The median OS was 32.3 Months in the Sorafenib group in both analyses. This result is similar to the ITT analysis and indicate that an adjustment on the confounders would normally yield similar OS between the treatment groups.

V. Discussion

The objective of this analysis was to estimate the effect of the treatment with Tivozanib vs. Sorafenib, measured in terms of a median OS in a setting where survival for patients receiving Tivozanib would be identical to those of patients randomized to Tivozanib in the TIVO-1 trial, whereas survival for those receiving Sorafenib would be identical to that for a hypothetical cohort of patients otherwise similar to those who received Sorafenib in the TIVO-1 trial, but who were ineligible to receive Tivozanib upon disease progression.

Limitations of these analyses should be noted. First, the RPSFT is suitable for placebo control trial, where patients from placebo group cross over to the active treatment group at disease progression. This was not the case in TIVO-1 trial, the implication is that if the sequential treatment with Sorafenib and then Tivozanib systematically yields a better or worst OS compared with Tivozanib alone, the common treatment effect assumption - states that the treatment effect is the same for all individuals (with respect to time spent on treatment) regardless of when treatment is received – would not hold.

Secondly, these analyses only controlled for cross-over from Sorafenib to Tivozanib and did not control for other anti-cancer therapy in the Sorafenib or Tivozanib groups. Among all patients in the TIVO-1 trial, 3.7% of Sorafenib patients and 13% of Tivozanib patients received post-study anti-cancer agents other than Tivozanib.

Thirdly, to estimate ψ we assume that the *Ui* are independent of randomised treatment groups (Tivozanib, Sorafenib), i.e. if the groups are similar with respect to all other characteristics except treatment, the average event times should be the same in each group if no patient were treated with Tivozanib. This assumption cannot hold for two reasons:

- ✓ Sorafenib is an active treatment, so if no patients is treated with Tivozanib, we could not expect to observe similar OS between the groups.

- ✓ As we proved above, the groups are not similar with respect to all the baseline characteristics, which would also introduce bias in our analysis.

R Code for RPSFT Analysis

```
library(Hmisc) #Installing package to upload SAS data into R
library(SASxport) #Installing package to upload SAS data into R
library(rpsftm)
library(tableone)
library(knitr)
library(dplyr)
library(tidyr)
library(ggplot2)
library(sas7bdat)
library(survival)
library(pglm)
library(scales)

#  Setting up the working directory
setwd("J:/Datasets/TIVO/301/Study_301_SDTM and Raw")

Data <- read.csv("adeff.csv")
Data <- Data[which(Data$NPTRT == 0),]
Data <- tbl_df(Data)
Data_Cov <- read.csv("Baseline covariates TIVO.csv")
Data_Cov <- Data_Cov[which(Data_Cov$NPTRT == 0),]
Data_Cov <- tbl_df(Data_Cov)
Sub_Data_Cov <- subset(Data_Cov, select = -c(COUNTRYC, ARM))

## Conerting time factors variables in POSIX format

## 1- RANDDT
Data$RANDDT<- as.Date(Data$RANDDT, "%d/%m/%Y") ## Randomization Date
Data$RANDDT<- as.POSIXlt(Data$RANDDT)
## 2- TR01SDT
Data$TR01SDT <- as.Date(Data$TR01SDT, "%d/%m/%Y") ## Start date for plan treatment
Data$TR01SDT <- as.POSIXlt(Data$TR01SDT)
## 3- TR01EDT
Data$TR01EDT <- as.Date(Data$TR01EDT, "%d/%m/%Y") ## End date for plan treatment
Data$TR01EDT <- as.POSIXlt(Data$TR01EDT)
## 4- TR02SDT
Data$TR02SDT <- as.Date(Data$TR02SDT, "%d/%m/%Y")  ## Start date for alternative
treatment(Tivo)
Data$TR02SDT <- as.POSIXlt(Data$TR02SDT)
## 5- TR02EDT
Data$TR02EDT <- as.Date(Data$TR02EDT, "%d/%m/%Y") ## End date for alternative treatment (Tivo)
Data$TR02EDT <- as.POSIXlt(Data$TR02EDT)
## 6- TTE_C
Data$DTH_D2<- as.numeric(Data$DTH_D2)

#"%d-%b-%y")  ## Time to Event or censoring
```

```
#Data$TTE_C<- as.POSIXlt(Data$TTE_C)

## 7- ALLDTHDT
#Data$ALLDTHDT<- as.Date(Data$ALLDTHDT, "%d-%b-%y")  ## Time to death
#Data$ALLDTHDT<- as.POSIXlt(Data$ALLDTHDT)
## 8- Cutoff date
CutoffD<- as.Date("2013-07-10")  ## Administrative cutoff date
CutoffD<- as.POSIXlt(CutoffD, "%Y-%m-%d")

## Creating new dataset's variables usable for the RPFST analysis

PID <- Data$USUBJID  ## Patients Identification
Z <- ifelse(Data$ARMN==2,0,1)  ## Treatment Assigment group (1=Tivozanib, 0=Sorafenib)
Futime<- (difftime(CutoffD, Data$RANDDT, units ="days"))/30.4375  ## Administrative follow up
time
TALT <- (ifelse(Data$ARMN == 2 & Data$CROSSFL == "Y", difftime(Data$TR02SDT,
          Data$RANDDT, units = "days"), 0))/30.4375 ## Time to receive alternative treatment (Tivo)
ALT <- ifelse(Data$CROSSFL == "Y",1,0)  ## Indicator to receive alternative therapy (Tivo)
T <- Data$DTH_M2
#difftime(Data$TTE_C, Data$RANDDT, units = "days") ## Follow up until death or censoring
Event <- Data$DTH_C2  ## Event indicator (Death)
ECOG <- Sub_Data_Cov$ECOG
MSKCC <- Sub_Data_Cov$MSKCC
Metastasis <-  Sub_Data_Cov$Metastasis
TSIDIAG <- Sub_Data_Cov$TSIDIAG

#SurvData <- data.frame(PID=PID, Time=T, Z=Z, Event=Event, TALT=TALT, ALT=ALT, Futime=Futime)

#SurvData <- Sub_Data_Cov %>%
        #mutate(PID = USUBJID) %>%
        #select(PID, ECOG, MSKCC, Metastasis, TSIDIAG)%>%
        #left_join(SurvData1,., by = "PID") %>%
        #mutate(TSIDIAG = ifelse(is.na(TSIDIAG), mean(TSIDIAG, na.rm = TRUE), TSIDIAG)) %>%
        #mutate(Futime = as.numeric(Futime)) %>%
        #mutate(Time = as.numeric(Time), Z = as.factor(Z)) %>%
        #data.frame()

#PID <- SurvData$PID
#Time <- SurvData$T
#Z <- SurvData$Z
#Event <- SurvData$Event
#TALT <- SurvData$TALT
#ALT <- SurvData$ALT
#Futime <- SurvData$Futime
# T_ON: Time on Tivo
# T_OFF: Time off Tivo
# psi: exp(psi) is the accelerate time factor after crossover
# C_psi= Censoing time if no Tivo
```

```
# U_psi: Overall event time if no treatment
# Event_psi: event indicator after recensoring (1=event, 0=censoring)
# X_psi:observed survival time if no Tivo
# X0_psi:observed survival time if no alternate to Tivo (Use for final analysis)
# Event0_psi:event indicator if no alternate therapy (Use for finaly analysis)

## New survival data time for counterfactual analysis

SurvData_01 <- as.data.frame(cbind(PID=PID, Time=T, Z=Z, Event=Event, TALT=TALT, ALT=ALT,
Futime=Futime,
                    ECOG = ECOG, MSKCC = MSKCC, Metastasis = Metastasis, TSIDIAG = TSIDIAG))

SurvData_01[1:10,]

## Bootstrapping
psi_LR_estimate <- rep(NA, 100)
psi_WC_estimate <- rep(NA, 100)
HRCoef <- rep(NA, 100)
SurvData_1 <- SurvData_01[which(SurvData_01$Z == 1),]
SurvData_2 <- SurvData_01[which(SurvData_01$Z == 0),]

for (i in 1:100){
SurvData_1 <- SurvData_1[sample(nrow(SurvData_1), size = 181, replace = TRUE),]
SurvData_2 <- SurvData_2[sample(nrow(SurvData_2), size = 182, replace = TRUE),]
SurvData <- rbind(SurvData_1, SurvData_2)

N <- dim(SurvData)[1]
AF <- seq(-2,2,0.01) # Accelerated factor

RPSFT <- function(SurvData, AF){

  PID <- SurvData[1]
  Time <- SurvData[2]
  Z <- SurvData[3]
  Event <- SurvData[4]
  TALT <- SurvData[5]
  ALT <- SurvData[6]
  Futime <- SurvData[7]
  ECOG <- SurvData[8]
  MSKCC <- SurvData[9]
  Metastasis <- SurvData[10]
  TSIDIAG <- SurvData[11]

  X0_AF <- Time
  Event0_AF <- Event

  T_ON <- NA
  T_OFF <- NA
```

```
 U_AF <- NA
 Event_AF <- NA

 if (Z==1){
  T_ON <- Time
  T_OFF <- 0
 }

 if (Z==0 & ALT==1){
  T_ON <- Time-TALT
  T_OFF <- TALT
 }

 if (Z==0 & ALT==0){
  T_ON <- 0
  T_OFF <- Time
 }

 U_AF <- T_OFF + AF*T_ON
 C_AF <- min(Futime, AF*Futime)

 if (Event==0){
  X_AF <- min(U_AF, C_AF)
  Event_AF <- 0
 }

 if (Event==1 & C_AF > U_AF){
  X_AF <- U_AF
  Event_AF <- 1
 }

 if (Event==1 & C_AF <= U_AF){
  X_AF <- C_AF
  Event_AF <- 0
 }

 if (Z==0 & ALT==1){
  X0_AF <- X_AF
  Event0_AF <- Event_AF
 }

  return (c(Z=Z, Futime=Futime, Time=Time, Event=Event, ALT=ALT, TALT=TALT, ECOG = ECOG,
MSKCC = MSKCC,
        Metastasis = Metastasis, TSIDIAG = TSIDIAG, T_ON=T_ON, T_OFF=T_OFF, U_AF=U_AF,
Event_AF=Event_AF,
        X_AF=X_AF,X0_AF=X0_AF, Event0_AF=Event0_AF, C_AF=C_AF))
}
```

```
exp_AF <- exp(AF)
length_AF <- length(AF)

#counterfactual survival time for both treatment arm and control arm
X_AF <- matrix(-1,nrow=N,ncol=length_AF)
U_AF <- matrix(-1,nrow=N,ncol=length_AF)
C_AF <- matrix(-1,nrow=N,ncol=length_AF)
Event_AF <- matrix(-1,nrow=N,ncol=length_AF)

chi_AF <- rep(-1,length_AF)
p_AF <- rep(-1,length_AF)

WCchi_AF <- rep(-1,length_AF)
WCp_AF <- rep(-1,length_AF)
#P_val_AF <- rep(-1, length_AF)

#counterfactual survival time used for final analysis (Adjust for patients who received alternate therapy/crossover only

X0_AF <- matrix(-1,nrow=N,ncol=length_AF)
Event0_AF <- matrix(-1,nrow=N,ncol=length_AF)

for (k in 1:length_AF){

 test_result <- apply(SurvData,1,RPSFT, AF=exp_AF[k])

 r_Z <- test_result[1,]
 r_futime <- test_result[2,]
 r_T <- test_result[3,]
 r_Event <- test_result[4,]
 r_ALT <- test_result[5,]
 r_TALT <- test_result[6,]
 r_ECOG <- test_result[7,]
 r_MSKCC <- test_result[8,]
 r_Metastasis <- test_result[9,]
 r_TSIDIAG <- test_result[10,]
 r_T_ON <- test_result[11,]
 r_T_OFF <- test_result[12,]
 r_U_AF <- test_result[13,]
 r_Event_AF <- test_result[14,]
 r_X_AF <- test_result[15,]
 r_X0_AF <- test_result[16,]
 r_Event0_AF <- test_result[17,]
 r_C_AF <- test_result[18,]


 index_Tivo <- which(r_Z==1)
```

```
 index_Sora <- which(r_Z==0)

 #Coxph <- coxph(Surv(r_X_AF, r_Event_AF) ~ r_Z + r_ECOG + r_MSKCC + r_Metastasis)
# P_val_AF[k] <- summary(Coxph)$coeff[1,5]

 logrankt_AF <- survdiff(Surv(r_X_AF, r_Event_AF) ~ r_Z +strata(r_ECOG, r_MSKCC, r_Metastasis))
 #logrankt_AF <- survdiff(Surv(r_X_AF, r_Event_AF) ~ r_Z)

 LRchi_AF <- logrankt_AF$chisq
 LR_AF <- 1 - pchisq(logrankt_AF$chisq, 1)

 Wilcoxon_AF <- survdiff(Surv(r_X_AF, r_Event_AF) ~ r_Z + strata(r_ECOG, r_MSKCC, r_Metastasis),
rho=1)
 #Wilcoxon_AF <- survdiff(Surv(r_X_AF, r_Event_AF) ~ r_Z, rho=1)

 Wilcoxonchi_AF <- Wilcoxon_AF$chisq
 Wilcoxonp_AF <- 1 - pchisq(Wilcoxon_AF$chisq, 1)

 X_AF[,k] <- r_X_AF
 U_AF[,k] <- r_U_AF
 C_AF[,k] <- r_C_AF
 Event_AF[,k] <- r_Event_AF


 X0_AF[,k]=r_X0_AF
 Event0_AF[,k]=r_Event0_AF

 chi_AF[k]=LRchi_AF
 p_AF[k]=LR_AF

 WCchi_AF[k]=Wilcoxonchi_AF
 WCp_AF[k]=Wilcoxonp_AF
}

Output <- (list(AF=AF, r_Z=r_Z, r_T_ON=r_T_ON, r_T_OFF=r_T_OFF, r_U_AF=r_U_AF, X_AF=X_AF,
C_AF=C_AF,
          Event_AF=Event_AF, X0_AF=X0_AF, Event0_AF=Event0_AF, chi_AF=chi_AF, p_AF=p_AF,
          WCchi_AF=WCchi_AF, WCp_AF=WCp_AF))
psi_LR_estimate[i] <- AF[which.min(chi_AF)]
psi_WC_estimate[i] <- AF[which.min(WCchi_AF)]

}
sd(psi_LR_estimate)

sd(psi_WC_estimate)
```

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

NICE TA 591 – results of additional analyses

Rationale

The Weibull distribution used in the original clarification response above was not the best fit for the patient level survival data from TIVO-1 (see B8). In fact, the log-normal distribution provided the best fit to the tivozanib and sorafenib PFS data. For the OS data, the log-normal and the Weibull provided the best fit to the tivozanib and sorafenib arms, respectively.

We originally planned to re-run the NMA using the log-normal distribution. However, on review of the distribution curves we decided to use an alternative method – the fractional polynomial method [Jansen, 2011]. This method does not rely on the proportional hazards assumption, it is therefore a suitable approach for our data given that the parametric hazard assumption does not hold for PFS in the TIVO-1 study.

Mixed treatment comparison: methods

The fractional polynomial method uses parametric survival functions which includes survival distributions such as Weibull or Gompertz together with more flexible fractional polynomials. Use of fractional polynomials allows for change of hazards over time and offers more freedom in distribution selection. With first or second order fractional polynomials the hazard functions of the interventions compared in a trial are modeled and the difference in the parameters of these fractional polynomials within a trial are considered the multidimensional treatment effect and synthesised (and indirectly compared) across studies. Therefore, with this approach the treatment effects are represented with multiple parameters rather than a single parameter or outcome [Jansen, 2011]. This method is described in detail in a paper by Jansen 2011 and was used in the recent ACD consultation - cabozantinib for previously treated advanced RCC [ID931]. It has also been successfully used to compare first-line treatments for RCC, reported in an abstract [Mihajlovic, 2015].

The deviance information criterion (DIC) is used to compare the goodness-of-fit of different fixed and random effects models with first and second order fractional polynomials with different powers. The model with the lowest DIC, is the model providing the 'best' fit to the data and is used in the base case. The lowest DIC in this analysis was the second-order fractional polynomial.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Table 1: Goodness-of-fit estimates for fixed effects fractional polynomial models for different powers P1 and P2: Overall Survival.

Power P1	Power P2	Dbar	Dhat	pD	DIC
-2	-	**851.253**	**838.089**	**13.165**	**864.418**
-1	-	876.164	862.514	13.65	889.814
-0.5	-	907.434	893.538	13.895	921.329
0	-	943.204	929.288	13.916	957.12
-2	-1	**835.061**	**815.808**	**19.253**	**854.314**

Table 2: Goodness-of-fit estimates for fixed effects fractional polynomial models for different powers P1 and P2: Progression Free Survival.

Power P1	Power P2	Dbar	Dhat	pD	DIC
-2	-	**960.183**	**946.642**	**13.541**	**973.724**
-1	-	1012.51	998.625	13.883	1026.39
-0.5	-	1089.43	1075.55	13.883	1103.31
0	-	1164.6	1150.77	13.827	1178.43
-2	-1	**919.32**	**905.807**	**13.513**	**932.832**

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 1: Fractional polynomial model vs original KM-curve for TIVO-1 study (PFS)

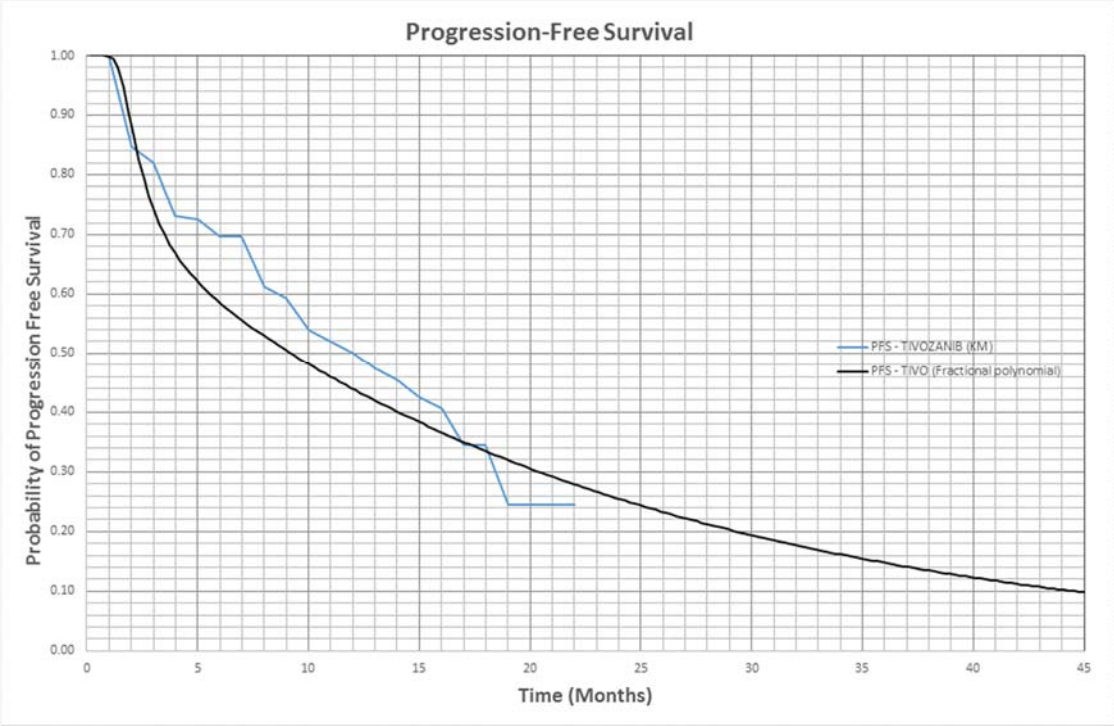
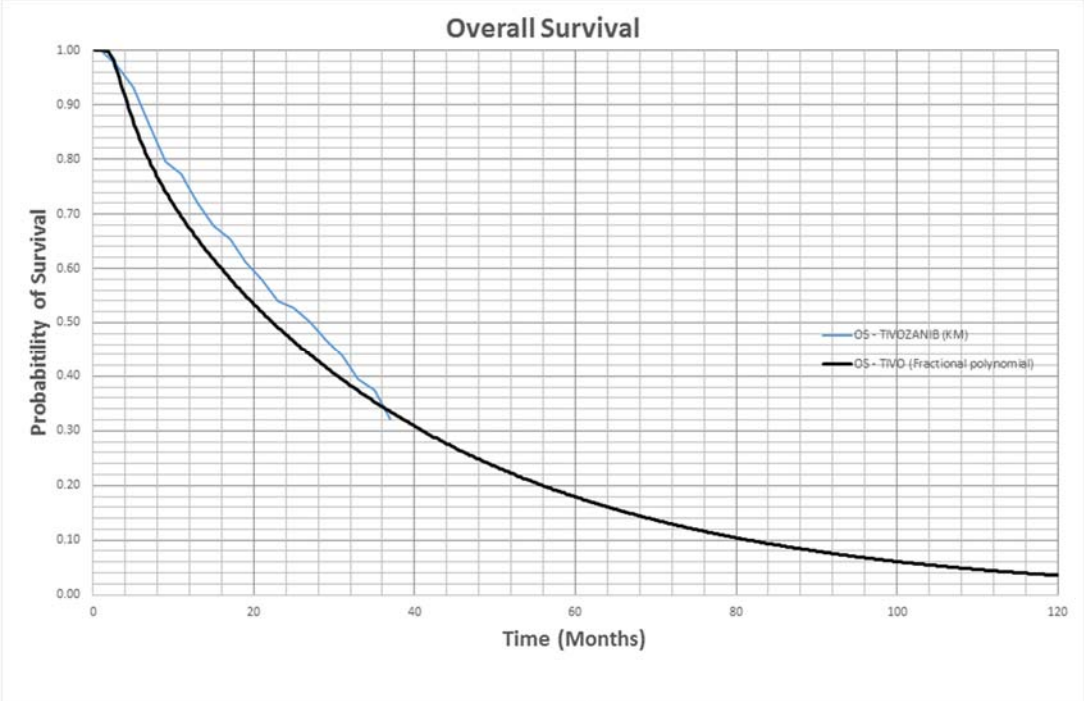


Figure 2: Fractional polynomial model vs original KM-curve for TIVO-1 study (OS)



NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Table 3: Summary of changes from original submission

	Approach in our original submission	**Revised approach as per clarification questions (base case)**
List price	Original submission [redacted] Revised submission without PAS: [redacted]	[redacted]
PAS	PAS applied	No PAS
TIVO-1 data	Two analyses: overall population and treatment-naïve patients	Treatment-naïve patients only
Efficacy data	From wide ITC incorporating both treatment naïve and pre-treated patients	From restricted ITC suggested by ERG in only treatment naïve patients (TIVO-1, SWITCH CROSS-J-RCC and COMPARZ)
Distribution used to parameterise survival curves for the NMA	Weibull	Fractional polynomial method
Adverse event data	From broad ITC data	From restricted ITC
Comparators	Interferon Sunitinib Pazopanib	Sunitinib Pazopanib
Scenario analyses (model)	Use of alternate utility for pre-progression and post-progression health states Reduction in post-progression treatment costs Efficacy estimates derived from all patients treated in trials No discounting of costs or benefits	As before with additionally: Lowest DIC (first order) used for efficacy data (lowest DIC for second order [best match] used in the base case) A second scenario analysis with CROSS-J-RCC excluded was planned owing to data concerns but insufficient time remained to implement

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Economic model: results

Results are presented for the base case result for a population of patients with no previous treatment with either immunotherapy or targeted therapy using tivozanib at list price ([redacted] per 21 day cycle). Costs used for the comparators (sunitinib and pazopanib) reflect established PAS prices.

Results of the revised model based on the restricted NMA network (TIVO-1, SWITCH, COMPARZ and CROSS-J-RCC) with the fractional polynomial distribution used to parameterise curves for the NMA are shown below.

Table 4: Base-case results: pairwise comparisons – tivozanib versus sunitinib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£70,476	1.757	
SUN	£105,566	2.425	
Increment (TIVO - SUN)	-£35,091	-0.668	£52,533 (SW Quadrant)
TIVO: Tivozanib, SUN: Sunitinib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 5: Base-case results: pairwise comparisons – tivozanib versus pazopanib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£70,476	1.757	
PAZO	£58,537	1.432	
Increment (TIVO - PAZ)	£11,938	0.325	£36,757
TIVO: Tivozanib, PAZ: Pazopanib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Table 6: Base-case results (list price for tivozanib) from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus pazopanib (QALYs)	ICER (£) incremental (QALYs)
Pazopanib	£58,537	2.076	1.432					
Tivozanib	£70,476	2.543	1.757	£11,938	0.467	0.325	£52,533	£52,533
Sunitinib	£105,566	3.586	2.425	£35,091	1.043	0.668	£47,361	£36,757
ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALYs: Quality-adjusted life years; IFN: Interferon								

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Disaggregated results of the base case incremental cost effectiveness analysis

Versus sunitinib

Table 7: Summary of QALY gain by health state (tivozanib versus sunitinib) (fractional polynomial analysis)

Health state	QALY tivozanib	QALY sunitinib	Increment	Absolute increment	% absolute increment
Pre-progression (no AEs)	0.953	0.879	0.074	0.074	9.1%
Pre-progression (with AEs)	0.034	0.076	-0.042	0.042	5.2%
Post-progression	0.770	1.469	-0.700	0.700	85.74%
Total	**1.757**	**2.425**	**-0.668**	**0.816**	**100.0%**
QALY: Quality-adjusted life year					

Table 8: Summary of costs by health state (tivozanib versus sunitinib) (fractional polynomial analysis)

Health state	Cost tivozanib	Cost sunitinib	Increment	Absolute increment	% absolute increment
Pre-progression	£34,714.5	£37,162	-£2,447.3	£2,447.3	7.0%
Post-progression	£35,761.1	£68,405	-£32,643.5	£32,643.5	93.0%
Total	**£70,475.6**	**£105,566**	**-£35,090.8**	**£35,090.8**	**100.0%**
QALY: Quality-adjusted life year					

Table 9: Summary of predicted resource use by category of cost – tivozanib versus sunitinib (fractional polynomial analysis)

Item	Cost tivozanib	Cost sunitinib	Increment	Absolute increment	% absolute increment
Medication cost (pre-progression)	£31,007.9	£33,523	-£2,515.5	£2,515.5	7.1%
Medication cost (post-progression)	£32,580.4	£62,189	-£29,608.2	£29,608.2	84.0%
Total medication cost	***£63,588.3***	***£95,712***			***91.1%***
Management cost (pre-progression)	£3,564.7	£3,478	£87.1	£87.1	0.2%
Management cost (post-progression)	£3,180.6	£6,216	-£3,035.4	£3,035.4	8.6%
AE cost	£142.0	£161	-£19.0	£19.0	0.1%
Total	**£70,475.6**	**£105,566**	**-£35,090.8**	**£35,265.1**	**100.0%**
AE: Adverse event					

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Versus pazopanib

Table 10: Summary of QALY gain by health state (tivozanib versus pazopanib) (fractional polynomial analysis)

Health state	QALY tivozanib	QALY pazopanib	Increment	Absolute increment	% absolute increment
Pre-progression (no AEs)	0.953	0.763	0.190	0.190	54.1%
Pre-progression (with AEs)	0.034	0.047	-0.013	0.013	3.7%
Post-progression	0.770	0.622	0.148	0.148	42.2%
Total	**1.757**	**1.432**	**0.325**	**0.351**	**100.0%**
QALY: Quality-adjusted life year					

Table 11: Summary of costs by health state (tivozanib versus pazopanib) (fractional polynomial analysis)

Health state	Cost tivozanib	Cost pazopanib	Increment	Absolute increment	% absolute increment
At list price					
Pre-progression	£34,714.5	£29,748	£4,966.3	£4,966.3	41.6%
Post-progression	£35,761.1	£28,789	£6,972.1	£6,972.1	58.4%
Total	**£70,475.6**	**£58,537**	**£11,938.5**	**£11,938.5**	**100.0%**
QALY: Quality-adjusted life year					

Table 12: Summary of predicted resource use by category of cost – tivozanib versus pazopanib (fractional polynomial analysis)

Item	Cost tivozanib	Cost pazopanib	Increment	Absolute increment	% absolute increment
At list price					
Medication cost (pre-progression)	£31,007.9	£26,705	£4,302.4	£4,302.4	36.0%
Medication cost (post-progression)	£32,580.4	£26,323	£6,257.6	£6,257.6	52.4%
Total medication cost	£63,588.3	£53,028			88.5%
Management cost (pre-progression)	£3,564.7	£2,937	£628.1	£628.1	5.3%
Management cost (post-progression)	£3,180.6	£2,466	£714.6	£714.6	6.0%
AE cost	£142.0	£106	£35.9	£35.9	0.3%
Total	**£70,475.6**	**£58,537.1**	**£11,938.5**	**£11,938.5**	**100.0%**
AE: Adverse event					

NICE National Institute for Health and Care Excellence

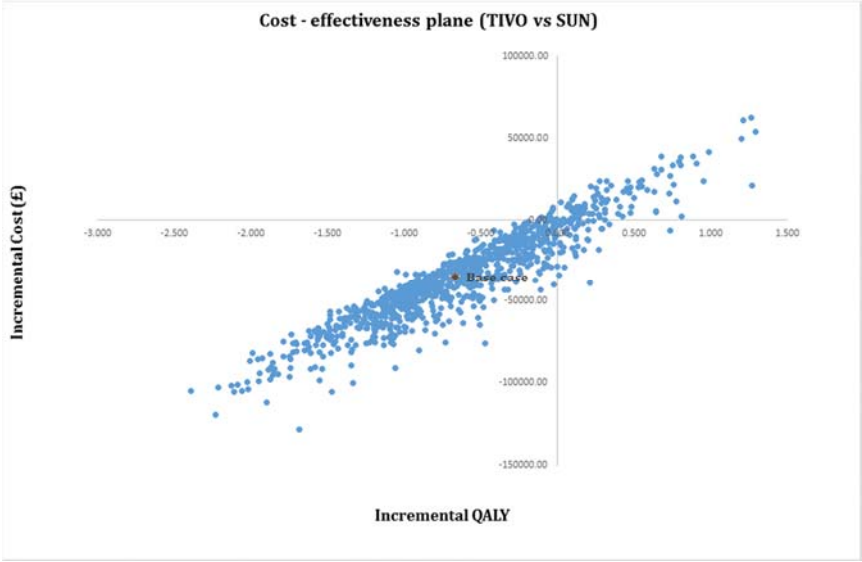
Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Probabilistic sensitivity analysis

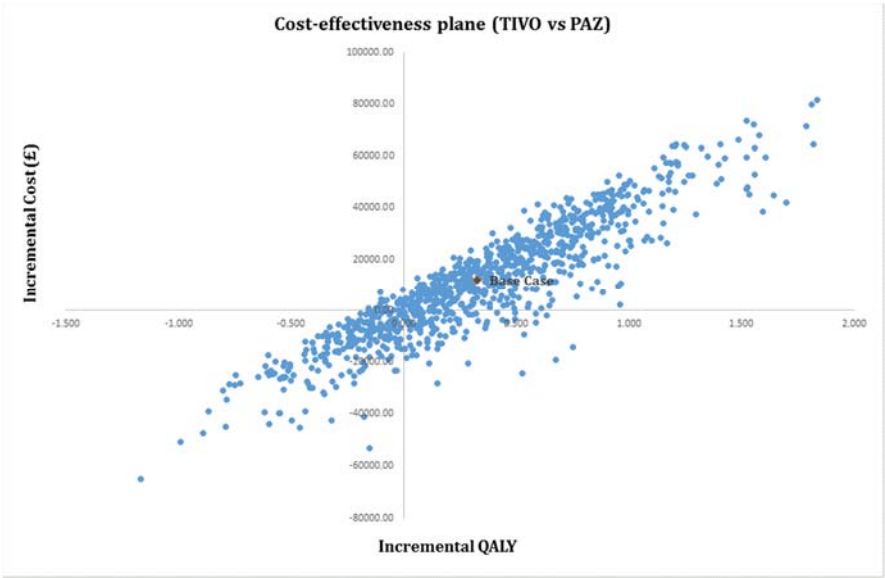
At a willingness to pay threshold of £30,000 per QALY there is a 89.6% probability that tivozanib will be cost effective versus sunitinib.

Figure 3: Cost effectiveness plane for tivozanib vs sunitinib



At a willingness to pay threshold of £30,000 per QALY there is a 43.3% probability that tivozanib will be cost effective versus pazopanib.

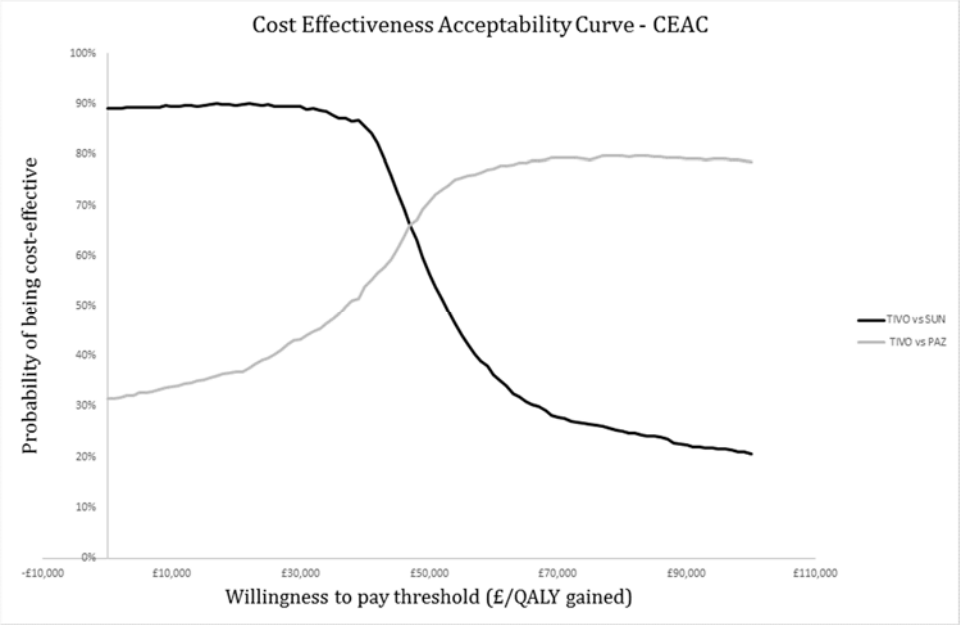
Figure 4: Cost effectiveness plane for tivozanib vs pazopanib



Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Figure 5: Cost effectiveness plane for tivozanib vs sunitinib and pazopanib



References

Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol 2011; 11: 61.
Mihajlovic J, Postma MJ. Network meta-analysis of survival data using fractional polynomials - an example with first line metastatic renal cell cancer treatments. Value Health 2015;18(7):A343.

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Winbugs code for NMA used in economic model

```
################################################################################
##### Second order fractional polynomial for OS (P1=-2, P2=-1)
################################################################################
#Winbugs code for second order fractional polynomial
#Fixed effects network meta-analysis model
Model{
for (i in 1:N){ # N number of datapoints in dataset
# time is expressed in months and transformed
#according powers of fractional polynomial P1 and P2
time_transf1[i]<-(equals(P1,0)*log(time[i]) + (1-
equals(P1,0))*pow(time[i],P1))
time_transf2[i]<-((1-equals(P2,P1))*(equals(P2,0)*log(time[i]) + (1-
equals(P2,0))*pow(time[i],P2)) +
equals(P2,P1)*(equals(P2,0)*log(time[i])*log(time[i]) + (1-
equals(P2,0))*pow(time[i],P2) *log(time[i])))
# likelihood
# hazard over interval [t,t+dt] expressed as deaths per person-month
# r is deaths in interval, n is number at risk, h is hazard
r[i]~ dbin(p[i],n[i])
p[i]<-1-exp(-h[i]*dt[i]) # cumulative hazard over interval [t,t+dt]
expressed as #deaths per person-month
# random effects model
# loop over datapoints
# s refers to study, t is intervention t, b is comparator
log(h[i])<-Beta[i,1]+ Beta[i,2]*time_transf1[i]+ Beta[i,3]* time_transf2[i]
Beta[i,1]<-mu[s[i],1]+delta[s[i],1]*(1-equals(t[i],b[i]))
Beta[i,2]<-mu[s[i],2]+delta[s[i],2]*(1-equals(t[i],b[i]))
Beta[i,3]<-mu[s[i],3]+delta[s[i],3]*(1-equals(t[i],b[i]))
}
# loop over studies
# NS is number of studies
# ts is intervention k, bs is comparator
for(m in 1:NS){
#delta[m,1:3]~dmnorm(md[m,1:3],omega[1:3,1:3])
delta[m,1]<-md[m,1]
delta[m,2]<-md[m,2]
delta[m,3]<-md[m,3]
md[m,1]<-d[ts[m],1]-d[bs[m],1]
md[m,2]<-d[ts[m],2]-d[bs[m],2]
md[m,3]<-d[ts[m],3]-d[bs[m],3]
}
# priors
# NT is number of treatments
d[1,1]<-0
d[1,2]<-0
d[1,3]<-0
for(j in 2:NT){
d[j,1:3] ~ dmnorm(mean[1:3],prec2[,])
}
for(k in 1:NS){
mu[k,1:3] ~ dmnorm(mean[1:3],prec2[,])
}
#omega[1:3, 1:3] ~ dwish(R[1:3,1:3],3)
# output SD and correlation based on estimated covariance matrix
#sigma.theta[1:3,1:3] <- inverse(omega[1:3,1:3])
#rho[1,2] <-sigma.theta[1,2]/sqrt(sigma.theta[1,1]*sigma.theta[2,2])
#rho[1,3] <-sigma.theta[1,3]/sqrt(sigma.theta[1,1]*sigma.theta[3,3])
#rho[2,3] <-sigma.theta[2,3]/sqrt(sigma.theta[2,2]*sigma.theta[3,3])
#sd[1]<-sqrt(sigma.theta[1,1])
#sd[2]<-sqrt(sigma.theta[2,2])
```

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

```
#sd[3]<-sqrt(sigma.theta[3,3])
# output hazard ratio for month 1 to 120
# NT is number of treatments, c is reference treatment, k is treatment of
#interest, l is month
for (c in 1:(NT-1)) {
for (j in (c+1):NT) {
for (l in 1:120) {
t1[c,j,l]<-(equals(P1,0)*log(l) + (1-equals(P1,0))*pow(l,P1))
t2[c,j,l]<-((1-equals(P2,P1))*(equals(P2,0)*log(l) + (1-
equals(P2,0))*pow(l,P2)) +equals(P2,P1)*(equals(P2,0)*log(l)*log(l) + (1-
equals(P2,0))*pow(l,P2)*log(l)))
log(hazard_ratio[c,j,l])<-d[j,1]-d[c,1]+(d[j,2]-d[c,2])*t1[c,j,l]+(d[j,3]-
d[c,3])*t2[c,j,l]
}}}
}
```

#Winbugs data set

```
list(N=202, NS=4, NT=4, mean=c(0,0,0), ts = c(2,2,3,4), bs = c(1,1,2,1), P1=-2, P2
=-1,
prec2 = structure(.Data = c(0.0001,0,0,0,0.0001,0,0,0,0.0001), .Dim = c(3,3)))

# initials 1
list(
#delta=structure(.Data(0,0,0,0,0,0,0,0), .Dim=c(4,2)),
d=structure(.Data=c(NA,NA,NA,0,0,0,0,0,0,0,0,0), .Dim = c(4,3)),
mu = structure(.Data=c(1,1,1,1,1,1,1,1,1,1,1,1), .Dim = c(4,3)))

# initials 2
list(
#delta=structure(.Data(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim=c(4,2)),
d=structure(.Data=c(NA,NA,NA,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim = c(4,3)),
mu = structure(.Data=c(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim =
c(4,3)))

# initials 3
list(
#delta=structure(.Data(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim=c(4,2)),
d=structure(.Data=c(NA,NA,NA,-1,1,-1,1,1,1,-1,1,-1), .Dim = c(4,3)),
mu = structure(.Data=c(-1,1,-1,-1,1,1,-1,1,1,-1,1,-1), .Dim = c(4,3)))
```

s[]	r[]	n[]	t[]	b[]	time[]	dt[]
1	0	63	1	1	1	2
1	1	62	1	1	3	2
1	0	62	1	1	5	2
1	2	59	1	1	7	2
1	0	59	1	1	9	2
1	6	53	1	1	11	2
1	2	51	1	1	13	2
1	3	47	1	1	15	2
1	2	45	1	1	17	2
1	5	39	1	1	19	2
1	0	38	1	1	21	2
1	1	36	1	1	23	2
1	3	33	1	1	25	2
1	1	32	1	1	27	2
1	2	29	1	1	29	2
1	1	28	1	1	31	2
1	3	24	1	1	33	2
1	1	23	1	1	35	2
1	0	23	1	1	37	2
1	1	21	1	1	39	2
1	1	19	1	1	41	2
1	0	19	1	1	43	2
1	0	19	1	1	45	2
1	0	16	1	1	47	2
1	0	16	1	1	49	2
1	0	15	1	1	51	2

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

1	1	12	1	1	53	2
1	1	9	1	1	55	2
1	0	7	1	1	57	2
1	0	5	1	1	59	2
1	0	57	2	1	1	2
1	0	57	2	1	3	2
1	2	55	2	1	5	2
1	1	54	2	1	7	2
1	2	52	2	1	9	2
1	1	51	2	1	11	2
1	5	46	2	1	13	2
1	2	44	2	1	15	2
1	3	41	2	1	17	2
1	3	37	2	1	19	2
1	2	35	2	1	21	2
1	1	34	2	1	23	2
1	1	33	2	1	25	2
1	0	33	2	1	27	2
1	0	32	2	1	29	2
1	1	30	2	1	31	2
1	3	27	2	1	33	2
1	0	26	2	1	35	2
1	0	26	2	1	37	2
1	2	23	2	1	39	2
1	0	23	2	1	41	2
1	2	20	2	1	43	2
1	1	18	2	1	45	2
1	0	17	2	1	47	2
1	0	17	2	1	49	2
1	0	15	2	1	51	2
1	0	14	2	1	53	2
1	1	11	2	1	55	2
1	0	9	2	1	57	2
1	0	7	2	1	59	2
2	0	182	1	1	1	2
2	8	169	1	1	3	2
2	10	148	1	1	5	2
2	8	137	1	1	7	2
2	6	127	1	1	9	2
2	8	118	1	1	11	2
2	7	109	1	1	13	2
2	3	105	1	1	15	2
2	4	95	1	1	17	2
2	3	84	1	1	19	2
2	3	76	1	1	21	2
2	4	68	1	1	23	2
2	4	60	1	1	25	2
2	4	50	1	1	27	2
2	0	42	1	1	29	2
2	1	35	1	1	31	2
2	2	29	1	1	33	2
2	1	25	1	1	35	2
2	3	21	1	1	37	2
2	1	18	1	1	39	2
2	0	16	1	1	41	2
2	2	11	1	1	43	2
2	0	9	1	1	45	2
2	0	8	1	1	47	2
2	0	7	1	1	49	2
2	1	180	2	1	1	2
2	11	162	2	1	3	2
2	9	147	2	1	5	2
2	9	135	2	1	7	2
2	6	125	2	1	9	2
2	6	116	2	1	11	2
2	6	106	2	1	13	2
2	7	95	2	1	15	2
2	1	92	2	1	17	2

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

2	5	84	2	1	19	2
2	3	77	2	1	21	2
2	2	67	2	1	23	2
2	1	59	2	1	25	2
2	4	49	2	1	27	2
2	1	40	2	1	29	2
2	2	34	2	1	31	2
2	0	31	2	1	33	2
2	0	29	2	1	35	2
2	3	23	2	1	37	2
2	1	19	2	1	39	2
2	0	17	2	1	41	2
2	0	14	2	1	43	2
2	0	12	2	1	45	2
2	0	10	2	1	47	2
2	0	8	2	1	49	2
3	3	546	2	2	1	2
3	16	515	2	2	3	2
3	29	478	2	2	5	2
3	24	450	2	2	7	2
3	28	421	2	2	9	2
3	30	389	2	2	11	2
3	22	367	2	2	13	2
3	18	348	2	2	15	2
3	17	330	2	2	17	2
3	12	314	2	2	19	2
3	16	297	2	2	21	2
3	7	288	2	2	23	2
3	10	272	2	2	25	2
3	13	249	2	2	27	2
3	12	229	2	2	29	2
3	11	214	2	2	31	2
3	5	206	2	2	33	2
3	14	186	2	2	35	2
3	5	176	2	2	37	2
3	11	161	2	2	39	2
3	7	137	2	2	41	2
3	8	112	2	2	43	2
3	3	92	2	2	45	2
3	9	67	2	2	47	2
3	1	45	2	2	49	2
3	0	28	2	2	51	2
3	3	16	2	2	53	2
3	1	8	2	2	55	2
3	0	557	3	2	1	2
3	19	531	3	2	3	2
3	25	501	3	2	5	2
3	21	474	3	2	7	2
3	18	452	3	2	9	2
3	25	425	3	2	11	2
3	33	391	3	2	13	2
3	15	375	3	2	15	2
3	22	353	3	2	17	2
3	18	333	3	2	19	2
3	25	305	3	2	21	2
3	7	293	3	2	23	2
3	12	276	3	2	25	2
3	7	258	3	2	27	2
3	25	225	3	2	29	2
3	0	221	3	2	31	2
3	5	214	3	2	33	2
3	2	205	3	2	35	2
3	10	189	3	2	37	2
3	11	174	3	2	39	2
3	6	161	3	2	41	2
3	8	130	3	2	43	2
3	4	99	3	2	45	2
3	7	65	3	2	47	2

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

3	2	50	3	2	49	2
3	1	28	3	2	51	2
3	2	20	3	2	53	2
3	2	14	3	2	55	2
4	2	179	1	1	1	2
4	4	172	1	1	3	2
4	3	168	1	1	5	2
4	6	157	1	1	7	2
4	4	151	1	1	9	2
4	9	142	1	1	11	2
4	10	130	1	1	13	2
4	7	123	1	1	15	2
4	3	119	1	1	17	2
4	5	112	1	1	19	2
4	3	108	1	1	21	2
4	3	103	1	1	23	2
4	12	91	1	1	25	2
4	2	68	1	1	27	2
4	2	46	1	1	29	2
4	8	29	1	1	31	2
4	2	23	1	1	33	2
4	3	8	1	1	35	2
4	0	181	4	1	1	2
4	5	175	4	1	3	2
4	7	163	4	1	5	2
4	12	151	4	1	7	2
4	12	139	4	1	9	2
4	4	132	4	1	11	2
4	9	122	4	1	13	2
4	7	114	4	1	15	2
4	4	108	4	1	17	2
4	7	101	4	1	19	2
4	5	96	4	1	21	2
4	7	89	4	1	23	2
4	2	87	4	1	25	2
4	4	68	4	1	27	2
4	4	50	4	1	29	2
4	3	40	4	1	31	2
4	3	22	4	1	33	2
4	1	8	4	1	35	2

END

```
################################################################################
#
####### Second order fractional polynomial for PFS (P1=-2, P2=-
1)
```

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

```
################################################################################
#
#Winbugs code for second order fractional polynomial
#Fixed effects network meta-analysis model
Model{
for (i in 1:N){ # N number of datapoints in dataset
# time is expressed in months and transformed
#according powers of fractional polynomial P1 and P2
time_transf1[i]<-(equals(P1,0)*log(time[i]) + (1-
equals(P1,0))*pow(time[i],P1))
time_transf2[i]<-((1-equals(P2,P1))*(equals(P2,0)*log(time[i]) + (1-
equals(P2,0))*pow(time[i],P2)) +
equals(P2,P1)*(equals(P2,0)*log(time[i])*log(time[i]) + (1-
equals(P2,0))*pow(time[i],P2) *log(time[i])))
# likelihood
# hazard over interval [t,t+dt] expressed as deaths per person-month
# r is deaths in interval, n is number at risk, h is hazard
r[i]~ dbin(p[i],n[i])
p[i]<-1-exp(-h[i]*dt[i]) # cumulative hazard over interval [t,t+dt]
expressed as #deaths per person-month
# random effects model
# loop over datapoints
# s refers to study, t is intervention t, b is comparator
log(h[i])<-Beta[i,1]+ Beta[i,2]*time_transf1[i]+ Beta[i,3]* time_transf2[i]
Beta[i,1]<-mu[s[i],1]+delta[s[i],1]*(1-equals(t[i],b[i]))
Beta[i,2]<-mu[s[i],2]+delta[s[i],2]*(1-equals(t[i],b[i]))
Beta[i,3]<-mu[s[i],3]+delta[s[i],3]*(1-equals(t[i],b[i]))
}
# loop over studies
# NS is number of studies
# ts is intervention k, bs is comparator
for(m in 1:NS){
#delta[m,1:3]~dmnorm(md[m,1:3],omega[1:3,1:3])
delta[m,1]<-md[m,1]
delta[m,2]<-md[m,2]
delta[m,3]<-md[m,3]
md[m,1]<-d[ts[m],1]-d[bs[m],1]
md[m,2]<-d[ts[m],2]-d[bs[m],2]
md[m,3]<-d[ts[m],3]-d[bs[m],3]
}
# priors
# NT is number of treatments
d[1,1]<-0
d[1,2]<-0
d[1,3]<-0
for(j in 2:NT){
d[j,1:3] ~ dmnorm(mean[1:3],prec2[,])
}
for(k in 1:NS){
mu[k,1:3] ~ dmnorm(mean[1:3],prec2[,])
}
#omega[1:3, 1:3] ~ dwish(R[1:3,1:3],3)
# output SD and correlation based on estimated covariance matrix
#sigma.theta[1:3,1:3] <- inverse(omega[1:3,1:3])
#rho[1,2] <-sigma.theta[1,2]/sqrt(sigma.theta[1,1]*sigma.theta[2,2])
#rho[1,3] <-sigma.theta[1,3]/sqrt(sigma.theta[1,1]*sigma.theta[3,3])
#rho[2,3] <-sigma.theta[2,3]/sqrt(sigma.theta[2,2]*sigma.theta[3,3])
#sd[1]<-sqrt(sigma.theta[1,1])
#sd[2]<-sqrt(sigma.theta[2,2])
#sd[3]<-sqrt(sigma.theta[3,3])
# output hazard ratio for month 1 to 120
# NT is number of treatments, c is reference treatment, k is treatment of
#interest, l is month
```

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

```
for (c in 1:(NT-1)) {
for (j in (c+1):NT) {
for (l in 1:120) {
t1[c,j,l]<-(equals(P1,0)*log(l) + (1-equals(P1,0))*pow(l,P1))
t2[c,j,l]<-((1-equals(P2,P1))*(equals(P2,0)*log(l) + (1-
equals(P2,0))*pow(l,P2)) +equals(P2,P1)*(equals(P2,0)*log(l)*log(l) + (1-
equals(P2,0))*pow(l,P2)*log(l)))
log(hazard_ratio[c,j,l])<-d[j,1]-d[c,1]+(d[j,2]-d[c,2])*t1[c,j,l]+(d[j,3]-
d[c,3])*t2[c,j,l]
}}}
}
```

#Winbugs data set

```
list(N=134, NS=4, NT=4, mean=c(0,0,0), ts = c(2,2,3,4), bs = c(1,1,2,1), P1=-2, P2
=-1,
prec2 = structure(.Data = c(0.0001,0,0,0,0.0001,0,0,0,0.0001), .Dim = c(3,3)))

# initials 1
list(
#delta=structure(.Data(0,0,0,0,0,0,0,0), .Dim=c(4,2)),
d=structure(.Data=c(NA,NA,NA,0,0,0,0,0,0,0,0,0), .Dim = c(4,3)),
mu = structure(.Data=c(1,1,1,1,1,1,1,1,1,1,1,1), .Dim = c(4,3)))

# initials 2
list(
#delta=structure(.Data(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim=c(4,2)),
d=structure(.Data=c(NA,NA,NA,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim = c(4,3)),
mu = structure(.Data=c(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim =
c(4,3)))

# initials 3
list(
#delta=structure(.Data(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim=c(4,2)),
d=structure(.Data=c(NA,NA,NA,-1,1,-1,1,1,1,-1,1,-1), .Dim = c(4,3)),
mu = structure(.Data=c(-1,1,-1,-1,1,1,-1,1,1,-1,1,-1), .Dim = c(4,3)))
```

s[]	r[]	n[]	t[]	b[]	time[]	dt[]
1	0	63	1	1	1	2
1	7	56	1	1	3	2
1	7	49	1	1	5	2
1	17	32	1	1	7	2
1	6	26	1	1	9	2
1	2	24	1	1	11	2
1	6	18	1	1	13	2
1	6	12	1	1	15	2
1	2	10	1	1	17	2
1	0	10	1	1	19	2
1	0	10	1	1	21	2
1	0	10	1	1	23	2
1	5	5	1	1	25	2
1	2	3	1	1	27	2
1	0	3	1	1	29	2
1	0	3	1	1	31	2
1	0	3	1	1	33	2
1	1	2	1	1	35	2
1	0	2	1	1	37	2
1	2	55	2	1	1	2
1	6	49	2	1	3	2
1	11	38	2	1	5	2
1	4	34	2	1	7	2
1	7	27	2	1	9	2
1	0	27	2	1	11	2
1	2	25	2	1	13	2
1	4	21	2	1	15	2
1	1	20	2	1	17	2
1	0	20	2	1	19	2
1	0	20	2	1	21	2
1	3	17	2	1	23	2

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

1	0	17	2	1	25	2
1	3	14	2	1	27	2
1	0	14	2	1	29	2
1	2	12	2	1	31	2
1	4	8	2	1	33	2
1	1	7	2	1	35	2
1	2	2	2	1	37	2
2	7	170	1	1	1	2
2	26	132	1	1	3	2
2	21	100	1	1	5	2
2	33	67	1	1	7	2
2	14	53	1	1	9	2
2	4	49	1	1	11	2
2	7	42	1	1	13	2
2	6	36	1	1	15	2
2	3	32	1	1	17	2
2	1	30	1	1	19	2
2	5	25	1	1	21	2
2	1	22	1	1	23	2
2	2	18	1	1	25	2
2	2	16	1	1	27	2
2	2	14	1	1	29	2
2	4	10	1	1	31	2
2	1	9	1	1	33	2
2	2	7	1	1	35	2
2	0	7	1	1	37	2
2	0	5	1	1	39	2
2	4	176	2	1	1	2
2	38	128	2	1	3	2
2	18	101	2	1	5	2
2	13	88	2	1	7	2
2	12	75	2	1	9	2
2	7	68	2	1	11	2
2	10	57	2	1	13	2
2	10	46	2	1	15	2
2	3	42	2	1	17	2
2	4	36	2	1	19	2
2	4	31	2	1	21	2
2	4	27	2	1	23	2
2	5	22	2	1	25	2
2	0	20	2	1	27	2
2	0	18	2	1	29	2
2	0	17	2	1	31	2
2	0	16	2	1	33	2
2	0	16	2	1	35	2
2	0	16	2	1	37	2
2	3	13	2	1	39	2
3	8	528	2	2	1	2
3	109	379	2	2	3	2
3	36	314	2	2	5	2
3	33	263	2	2	7	2
3	44	203	2	2	9	2
3	11	176	2	2	11	2
3	21	144	2	2	13	2
3	22	115	2	2	15	2
3	13	95	2	2	17	2
3	4	81	2	2	19	2
3	8	66	2	2	21	2
3	9	51	2	2	23	2
3	4	39	2	2	25	2
3	3	26	2	2	27	2
3	3	16	2	2	29	2
3	0	12	2	2	31	2
3	0	9	2	2	33	2
3	0	5	2	2	35	2
3	6	534	3	2	1	2
3	99	391	3	2	3	2
3	46	314	3	2	5	2

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

3	38	257	3	2	7	2
3	53	189	3	2	9	2
3	10	166	3	2	11	2
3	30	127	3	2	13	2
3	13	108	3	2	15	2
3	16	87	3	2	17	2
3	5	75	3	2	19	2
3	12	59	3	2	21	2
3	6	49	3	2	23	2
3	6	36	3	2	25	2
3	1	24	3	2	27	2
3	0	18	3	2	29	2
3	0	14	3	2	31	2
4	2	178	1	1	1	2
4	18	149	1	1	3	2
4	18	129	1	1	5	2
4	25	99	1	1	7	2
4	18	78	1	1	9	2
4	18	56	1	1	11	2
4	8	44	1	1	13	2
4	6	30	1	1	15	2
4	6	11	1	1	17	2
4	0	2	1	1	19	2
4	0	1	1	1	21	2
4	0	180	4	1	1	2
4	32	143	4	1	3	2
4	16	122	4	1	5	2
4	5	115	4	1	7	2
4	17	98	4	1	9	2
4	12	81	4	1	11	2
4	7	72	4	1	13	2
4	7	47	4	1	15	2
4	7	19	4	1	17	2
4	3	3	4	1	19	2
4	0	1	4	1	21	2

END

```
#############################################################################
####### First order fractional polynomial for OS (P1 =-2)
#############################################################################
#Winbugs code for second order fractional polynomial
#Fixed effects network meta-analysis model
Model{
for (i in 1:N){ # N number of datapoints in dataset
# time is expressed in months and transformed
#according powers of fractional polynomial P1 and P2
time_transf1[i]<-(equals(P1,0)*log(time[i]) + (1-equals(P1,0))*pow(time[i],P1))
# likelihood
# hazard over interval [t,t+dt] expressed as deaths per person-month
# r is deaths in interval, n is number at risk, h is hazard
r[i]~ dbin(p[i],n[i])
```

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

```
p[i]<-1-exp(-h[i]*dt[i]) # cumulative hazard over interval [t,t+dt] expressed as
deaths per
# person-month
# random effects model
# loop over datapoints
# s refers to study, t is intervention t, b is comparator
log(h[i])<-Beta[i,1]+ Beta[i,2]*time_transf1[i]
Beta[i,1]<-mu[s[i],1]+delta[s[i],1]*(1-equals(t[i],b[i]))
Beta[i,2]<-mu[s[i],2]+delta[s[i],2]*(1-equals(t[i],b[i]))
}
# loop over studies
# NS is number of studies
# ts is intervention k, bs is comparator
for(m in 1:NS){
#delta[m,1:3]~ dmnorm(md[m,1:3],omega[1:3,1:3])
delta[m,1]<-md[m,1]
delta[m,2]<-md[m,2]
md[m,1]<-d[ts[m],1]-d[bs[m],1]
md[m,2]<-d[ts[m],2]-d[bs[m],2]
}
# priors
# NT is number of treatments
d[1,1]<-0
d[1,2]<-0
for(j in 2:NT){
d[j,1:2] ~ dmnorm(mean[1:2],prec2[,])
}
for(k in 1:NS){
mu[k,1:2] ~ dmnorm(mean[1:2],prec2[,])
}
#omega[1:3, 1:3] ~ dwish(R[1:3,1:3],3)
# output SD and correlation based on estimated covariance matrix
#sigma.theta[1:3,1:3] <- inverse(omega[1:3,1:3])
#rho[1,2] <-sigma.theta[1,2]/sqrt(sigma.theta[1,1]*sigma.theta[2,2])
#rho[1,3] <-sigma.theta[1,3]/sqrt(sigma.theta[1,1]*sigma.theta[3,3])
#rho[2,3] <-sigma.theta[2,3]/sqrt(sigma.theta[2,2]*sigma.theta[3,3])
#sd[1]<-sqrt(sigma.theta[1,1])
#sd[2]<-sqrt(sigma.theta[2,2])
#sd[3]<-sqrt(sigma.theta[3,3])
# output hazard ratio for month 1 to 60
# NT is number of treatments, c is reference treatment, k is treatment of interest,
l is #month
for (c in 1:(NT-1)) {
for (j in (c+1):NT) {
for (l in 1:60) {
t1[c,j,l]<-(equals(P1,0)*log(l) + (1-equals(P1,0))*pow(l,P1))
#t2[c,j,l]<-((1-equals(P2,P1))*(equals(P2,0)*log(l) + (1-equals(P2,0))*pow(l,P2)) +
#equals(P2,P1)*(equals(P2,0)*log(l)*log(l) + (1-equals(P2,0))*pow(l,P2) *log(l)))
log(hazard_ratio[c,j,l])<-d[j,1]-d[c,1]+(d[j,2]-d[c,2])*t1[c,j,l]
#+(d[j,3]-d[c,3])*t2[c,j,l]
}}}
}
```

#Winbugs data set

```
list(N=202, NS=4, NT=4, mean=c(0,0), ts = c(2,2,3,4), bs = c(1,1,2,1), P1=-2,
prec2 = structure(.Data = c(0.0001,0,0,0.0001), .Dim = c(2,2)))

# initials 1
list(
#delta=structure(.Data(0,0,0,0,0,0,0,0), .Dim=c(4,2)),
d=structure(.Data=c(NA,NA,0,0,0,0,0,0), .Dim = c(4,2)),
mu = structure(.Data=c(1,1,1,1,1,1,1,1), .Dim = c(4,2)))

# initials 2
list(
#delta=structure(.Data(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim=c(4,2)),
d=structure(.Data=c(NA,NA,0.5,0.5,0.5,0.5,0.5,0.5), .Dim = c(4,2)),
mu = structure(.Data=c(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim = c(4,2)))

# initials 3
```

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

```
list(
#delta=structure(.Data(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim=c(4,2)),
d=structure(.Data=c(NA,NA,-1,1,-1,1,1,1), .Dim = c(4,2)),
mu = structure(.Data=c(-1,1,-1,-1,1,1,-1,1), .Dim = c(4,2)))
```

s[]	r[]	n[]	t[]	b[]	time[]	dt[]
1	0	63	1	1	1	2
1	1	62	1	1	3	2
1	0	62	1	1	5	2
1	2	59	1	1	7	2
1	0	59	1	1	9	2
1	6	53	1	1	11	2
1	2	51	1	1	13	2
1	3	47	1	1	15	2
1	2	45	1	1	17	2
1	5	39	1	1	19	2
1	0	38	1	1	21	2
1	1	36	1	1	23	2
1	3	33	1	1	25	2
1	1	32	1	1	27	2
1	2	29	1	1	29	2
1	1	28	1	1	31	2
1	3	24	1	1	33	2
1	1	23	1	1	35	2
1	0	23	1	1	37	2
1	1	21	1	1	39	2
1	1	19	1	1	41	2
1	0	19	1	1	43	2
1	0	19	1	1	45	2
1	0	16	1	1	47	2
1	0	16	1	1	49	2
1	0	15	1	1	51	2
1	1	12	1	1	53	2
1	1	9	1	1	55	2
1	0	7	1	1	57	2
1	0	5	1	1	59	2
1	0	57	2	1	1	2
1	0	57	2	1	3	2
1	2	55	2	1	5	2
1	1	54	2	1	7	2
1	2	52	2	1	9	2
1	1	51	2	1	11	2
1	5	46	2	1	13	2
1	2	44	2	1	15	2
1	3	41	2	1	17	2
1	3	37	2	1	19	2
1	2	35	2	1	21	2
1	1	34	2	1	23	2
1	1	33	2	1	25	2
1	0	33	2	1	27	2
1	0	32	2	1	29	2
1	1	30	2	1	31	2
1	3	27	2	1	33	2
1	0	26	2	1	35	2
1	0	26	2	1	37	2
1	2	23	2	1	39	2
1	0	23	2	1	41	2
1	2	20	2	1	43	2
1	1	18	2	1	45	2
1	0	17	2	1	47	2
1	0	17	2	1	49	2
1	0	15	2	1	51	2
1	0	14	2	1	53	2
1	1	11	2	1	55	2
1	0	9	2	1	57	2
1	0	7	2	1	59	2
2	0	182	1	1	1	2
2	8	169	1	1	3	2
2	10	148	1	1	5	2

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

2	8	137	1	1	7	2
2	6	127	1	1	9	2
2	8	118	1	1	11	2
2	7	109	1	1	13	2
2	3	105	1	1	15	2
2	4	95	1	1	17	2
2	3	84	1	1	19	2
2	3	76	1	1	21	2
2	4	68	1	1	23	2
2	4	60	1	1	25	2
2	4	50	1	1	27	2
2	0	42	1	1	29	2
2	1	35	1	1	31	2
2	2	29	1	1	33	2
2	1	25	1	1	35	2
2	3	21	1	1	37	2
2	1	18	1	1	39	2
2	0	16	1	1	41	2
2	2	11	1	1	43	2
2	0	9	1	1	45	2
2	0	8	1	1	47	2
2	0	7	1	1	49	2
2	1	180	2	1	1	2
2	11	162	2	1	3	2
2	9	147	2	1	5	2
2	9	135	2	1	7	2
2	6	125	2	1	9	2
2	6	116	2	1	11	2
2	6	106	2	1	13	2
2	7	95	2	1	15	2
2	1	92	2	1	17	2
2	5	84	2	1	19	2
2	3	77	2	1	21	2
2	2	67	2	1	23	2
2	1	59	2	1	25	2
2	4	49	2	1	27	2
2	1	40	2	1	29	2
2	2	34	2	1	31	2
2	0	31	2	1	33	2
2	0	29	2	1	35	2
2	3	23	2	1	37	2
2	1	19	2	1	39	2
2	0	17	2	1	41	2
2	0	14	2	1	43	2
2	0	12	2	1	45	2
2	0	10	2	1	47	2
2	0	8	2	1	49	2
3	3	546	2	2	1	2
3	16	515	2	2	3	2
3	29	478	2	2	5	2
3	24	450	2	2	7	2
3	28	421	2	2	9	2
3	30	389	2	2	11	2
3	22	367	2	2	13	2
3	18	348	2	2	15	2
3	17	330	2	2	17	2
3	12	314	2	2	19	2
3	16	297	2	2	21	2
3	7	288	2	2	23	2
3	10	272	2	2	25	2
3	13	249	2	2	27	2
3	12	229	2	2	29	2
3	11	214	2	2	31	2
3	5	206	2	2	33	2
3	14	186	2	2	35	2
3	5	176	2	2	37	2
3	11	161	2	2	39	2
3	7	137	2	2	41	2

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

3	8	112	2	2	43	2
3	3	92	2	2	45	2
3	9	67	2	2	47	2
3	1	45	2	2	49	2
3	0	28	2	2	51	2
3	3	16	2	2	53	2
3	1	8	2	2	55	2
3	0	557	3	2	1	2
3	19	531	3	2	3	2
3	25	501	3	2	5	2
3	21	474	3	2	7	2
3	18	452	3	2	9	2
3	25	425	3	2	11	2
3	33	391	3	2	13	2
3	15	375	3	2	15	2
3	22	353	3	2	17	2
3	18	333	3	2	19	2
3	25	305	3	2	21	2
3	7	293	3	2	23	2
3	12	276	3	2	25	2
3	7	258	3	2	27	2
3	25	225	3	2	29	2
3	0	221	3	2	31	2
3	5	214	3	2	33	2
3	2	205	3	2	35	2
3	10	189	3	2	37	2
3	11	174	3	2	39	2
3	6	161	3	2	41	2
3	8	130	3	2	43	2
3	4	99	3	2	45	2
3	7	65	3	2	47	2
3	2	50	3	2	49	2
3	1	28	3	2	51	2
3	2	20	3	2	53	2
3	2	14	3	2	55	2
4	2	179	1	1	1	2
4	4	172	1	1	3	2
4	3	168	1	1	5	2
4	6	157	1	1	7	2
4	4	151	1	1	9	2
4	9	142	1	1	11	2
4	10	130	1	1	13	2
4	7	123	1	1	15	2
4	3	119	1	1	17	2
4	5	112	1	1	19	2
4	3	108	1	1	21	2
4	3	103	1	1	23	2
4	12	91	1	1	25	2
4	2	68	1	1	27	2
4	2	46	1	1	29	2
4	8	29	1	1	31	2
4	2	23	1	1	33	2
4	3	8	1	1	35	2
4	0	181	4	1	1	2
4	5	175	4	1	3	2
4	7	163	4	1	5	2
4	12	151	4	1	7	2
4	12	139	4	1	9	2
4	4	132	4	1	11	2
4	9	122	4	1	13	2
4	7	114	4	1	15	2
4	4	108	4	1	17	2
4	7	101	4	1	19	2
4	5	96	4	1	21	2
4	7	89	4	1	23	2
4	2	87	4	1	25	2
4	4	68	4	1	27	2
4	4	50	4	1	29	2

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

4	3	40	4	1	31	2
4	3	22	4	1	33	2
4	1	8	4	1	35	2

END

```
################################################################################
####### First order fractional polynomial for PFS (P1 =-2)
################################################################################
#Winbugs code for second order fractional polynomial
#Fixed effects network meta-analysis model
Model{
for (i in 1:N){ # N number of datapoints in dataset
# time is expressed in months and transformed
#according powers of fractional polynomial P1 and P2
time_transf1[i]<-(equals(P1,0)*log(time[i]) + (1-equals(P1,0))*pow(time[i],P1))
# likelihood
# hazard over interval [t,t+dt] expressed as deaths per person-month
# r is deaths in interval, n is number at risk, h is hazard
r[i]~ dbin(p[i],n[i])
p[i]<-1-exp(-h[i]*dt[i]) # cumulative hazard over interval [t,t+dt] expressed as
deaths per
# person-month
# random effects model
# loop over datapoints
# s refers to study, t is intervention t, b is comparator
log(h[i])<-Beta[i,1]+ Beta[i,2]*time_transf1[i]
Beta[i,1]<-mu[s[i],1]+delta[s[i],1]*(1-equals(t[i],b[i]))
Beta[i,2]<-mu[s[i],2]+delta[s[i],2]*(1-equals(t[i],b[i]))
```

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

```
}
# loop over studies
# NS is number of studies
# ts is intervention k, bs is comparator
for(m in 1:NS){
#delta[m,1:3]~ dmnorm(md[m,1:3],omega[1:3,1:3])
delta[m,1]<-md[m,1]
delta[m,2]<-md[m,2]
md[m,1]<-d[ts[m],1]-d[bs[m],1]
md[m,2]<-d[ts[m],2]-d[bs[m],2]
}
# priors
# NT is number of treatments
d[1,1]<-0
d[1,2]<-0
for(j in 2:NT){
d[j,1:2] ~ dmnorm(mean[1:2],prec2[,])
}
for(k in 1:NS){
mu[k,1:2] ~ dmnorm(mean[1:2],prec2[,])
}
#omega[1:3, 1:3] ~ dwish(R[1:3,1:3],3)
# output SD and correlation based on estimated covariance matrix
#sigma.theta[1:3,1:3] <- inverse(omega[1:3,1:3])
#rho[1,2] <-sigma.theta[1,2]/sqrt(sigma.theta[1,1]*sigma.theta[2,2])
#rho[1,3] <-sigma.theta[1,3]/sqrt(sigma.theta[1,1]*sigma.theta[3,3])
#rho[2,3] <-sigma.theta[2,3]/sqrt(sigma.theta[2,2]*sigma.theta[3,3])
#sd[1]<-sqrt(sigma.theta[1,1])
#sd[2]<-sqrt(sigma.theta[2,2])
#sd[3]<-sqrt(sigma.theta[3,3])
# output hazard ratio for month 1 to 60
# NT is number of treatments, c is reference treatment, k is treatment of interest,
l is #month
#for (c in 1:(NT-1)) {
#for (j in (c+1):NT) {
#for (l in 1:60) {
#t1[c,j,l]<-(equals(P1,0)*log(l) + (1-equals(P1,0))*pow(l,P1))
#t2[c,j,l]<-((1-equals(P2,P1))*(equals(P2,0)*log(l) + (1-equals(P2,0))*pow(l,P2)) +
#equals(P2,P1)*(equals(P2,0)*log(l)*log(l) + (1-equals(P2,0))*pow(l,P2) *log(l)))
#log(hazard_ratio[c,j,l])<-d[j,1]-d[c,1]+(d[j,2]-d[c,2])*t1[c,j,l]+(d[j,3]-
#d[c,3])*t2[c,j,l]
#}}}
}
```

#Winbugs data set

```
list(N=134, NS=4, NT=4, mean=c(0,0), ts = c(2,2,3,4), bs = c(1,1,2,1), P1=-2,
prec2 = structure(.Data = c(0.0001,0,0,0.0001), .Dim = c(2,2)))

# initials 1
list(
#delta=structure(.Data(0,0,0,0,0,0,0,0), .Dim=c(4,2)),
d=structure(.Data=c(NA,NA,0,0,0,0,0,0), .Dim = c(4,2)),
mu = structure(.Data=c(1,1,1,1,1,1,1,1), .Dim = c(4,2)))

# initials 2
list(
#delta=structure(.Data(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim=c(4,2)),
d=structure(.Data=c(NA,NA,0.5,0.5,0.5,0.5,0.5,0.5), .Dim = c(4,2)),
mu = structure(.Data=c(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim = c(4,2)))

# initials 3
list(
#delta=structure(.Data(0.5,0.5,0.5,0.5,0.5,0.5,0.5,0.5), .Dim=c(4,2)),
d=structure(.Data=c(NA,NA,-1,1,-1,1,1,1), .Dim = c(4,2)),
mu = structure(.Data=c(-1,1,-1,-1,1,1,-1,1), .Dim = c(4,2)))
```

s[]	r[]	n[]	t[]	b[]	time[]	dt[]
1	0	63	1	1	1	2
1	7	56	1	1	3	2
1	7	49	1	1	5	2

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

1	17	32	1	1	7	2
1	6	26	1	1	9	2
1	2	24	1	1	11	2
1	6	18	1	1	13	2
1	6	12	1	1	15	2
1	2	10	1	1	17	2
1	0	10	1	1	19	2
1	0	10	1	1	21	2
1	0	10	1	1	23	2
1	5	5	1	1	25	2
1	2	3	1	1	27	2
1	0	3	1	1	29	2
1	0	3	1	1	31	2
1	0	3	1	1	33	2
1	1	2	1	1	35	2
1	0	2	1	1	37	2
1	2	55	2	1	1	2
1	6	49	2	1	3	2
1	11	38	2	1	5	2
1	4	34	2	1	7	2
1	7	27	2	1	9	2
1	0	27	2	1	11	2
1	2	25	2	1	13	2
1	4	21	2	1	15	2
1	1	20	2	1	17	2
1	0	20	2	1	19	2
1	0	20	2	1	21	2
1	3	17	2	1	23	2
1	0	17	2	1	25	2
1	3	14	2	1	27	2
1	0	14	2	1	29	2
1	2	12	2	1	31	2
1	4	8	2	1	33	2
1	1	7	2	1	35	2
1	2	2	2	1	37	2
2	7	170	1	1	1	2
2	26	132	1	1	3	2
2	21	100	1	1	5	2
2	33	67	1	1	7	2
2	14	53	1	1	9	2
2	4	49	1	1	11	2
2	7	42	1	1	13	2
2	6	36	1	1	15	2
2	3	32	1	1	17	2
2	1	30	1	1	19	2
2	5	25	1	1	21	2
2	1	22	1	1	23	2
2	2	18	1	1	25	2
2	2	16	1	1	27	2
2	2	14	1	1	29	2
2	4	10	1	1	31	2
2	1	9	1	1	33	2
2	2	7	1	1	35	2
2	0	7	1	1	37	2
2	0	5	1	1	39	2
2	4	176	2	1	1	2
2	38	128	2	1	3	2
2	18	101	2	1	5	2
2	13	88	2	1	7	2
2	12	75	2	1	9	2
2	7	68	2	1	11	2
2	10	57	2	1	13	2
2	10	46	2	1	15	2
2	3	42	2	1	17	2
2	4	36	2	1	19	2
2	4	31	2	1	21	2
2	4	27	2	1	23	2
2	5	22	2	1	25	2

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

2	0	20	2	1	27	2
2	0	18	2	1	29	2
2	0	17	2	1	31	2
2	0	16	2	1	33	2
2	0	16	2	1	35	2
2	0	16	2	1	37	2
2	3	13	2	1	39	2
3	8	528	2	2	1	2
3	109	379	2	2	3	2
3	36	314	2	2	5	2
3	33	263	2	2	7	2
3	44	203	2	2	9	2
3	11	176	2	2	11	2
3	21	144	2	2	13	2
3	22	115	2	2	15	2
3	13	95	2	2	17	2
3	4	81	2	2	19	2
3	8	66	2	2	21	2
3	9	51	2	2	23	2
3	4	39	2	2	25	2
3	3	26	2	2	27	2
3	3	16	2	2	29	2
3	0	12	2	2	31	2
3	0	9	2	2	33	2
3	0	5	2	2	35	2
3	6	534	3	2	1	2
3	99	391	3	2	3	2
3	46	314	3	2	5	2
3	38	257	3	2	7	2
3	53	189	3	2	9	2
3	10	166	3	2	11	2
3	30	127	3	2	13	2
3	13	108	3	2	15	2
3	16	87	3	2	17	2
3	5	75	3	2	19	2
3	12	59	3	2	21	2
3	6	49	3	2	23	2
3	6	36	3	2	25	2
3	1	24	3	2	27	2
3	0	18	3	2	29	2
3	0	14	3	2	31	2
4	2	178	1	1	1	2
4	18	149	1	1	3	2
4	18	129	1	1	5	2
4	25	99	1	1	7	2
4	18	78	1	1	9	2
4	18	56	1	1	11	2
4	8	44	1	1	13	2
4	6	30	1	1	15	2
4	6	11	1	1	17	2
4	0	2	1	1	19	2
4	0	1	1	1	21	2
4	0	180	4	1	1	2
4	32	143	4	1	3	2
4	16	122	4	1	5	2
4	5	115	4	1	7	2
4	17	98	4	1	9	2
4	12	81	4	1	11	2
4	7	72	4	1	13	2
4	7	47	4	1	15	2
4	7	19	4	1	17	2
4	3	3	4	1	19	2
4	0	1	4	1	21	2

END

NICE National Institute for Health and Care Excellence

Level 1A
City Tower
Manchester
M1 4BT
United Kingdom

+44 (0)300 323 0140

Scenario analyses from the updated economic model (fractional polynomial) (Information requested 8 June 2017)

Contents

List of tables

Base case results from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

Table 1: Base case results: pairwise comparisons – tivozanib versus sunitinib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£70,476	1.757	
SUN	£105,566	2.425	
Increment (TIVO - SUN)	-£35,091	-0.668	£52,533 (SW Quadrant)
TIVO: Tivozanib, SUN: Sunitinib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 2: Base case results: pairwise comparisons – tivozanib versus pazopanib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£70,476	1.757	
PAZO	£58,537	1.432	
Increment (TIVO - PAZ)	£11,938	0.325	£36,757
TIVO: Tivozanib, PAZ: Pazopanib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 3: Base case results (list price for tivozanib) from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus pazopanib (QALYs)	ICER (£) incremental (QALYs)
Pazopanib	£58,537	2.076	1.432					
Tivozanib	£70,476	2.543	1.757	£11,938	0.467	0.325	£52,533	£52,533
Sunitinib	£105,566	3.586	2.425	£35,091	1.043	0.668	£47,361	£36,757
ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALYs: Quality-adjusted life years; IFN: Interferon								

Scenario results: lowest DIC (first order) used for efficacy data (lowest DIC for second order [best match] used in the base case)

Table 4: Alternative scenario results: pairwise comparisons – tivozanib versus sunitinib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using first order fractional polynomial method (p1=-2)

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£61,839	1.596	
SUN	£88,543	2.047	
Increment (TIVO - SUN)	-£26,704	-0.451	£59,247 (SW Quadrant)
TIVO: Tivozanib, SUN: Sunitinib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 5: Alternative scenario: pairwise comparisons – tivozanib versus pazopanib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using first order fractional polynomial method (p1=-2)

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£61,839	1.596	
PAZO	£81,104	1.868	
Increment (TIVO - PAZ)	-£19,264	-0.272	£70,865
TIVO: Tivozanib, PAZ: Pazopanib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 6: Alternative scenario results (list price for tivozanib) from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using first order fractional polynomial method (p1=-2)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus pazopanib (QALYs)	ICER (£) incremental (QALYs)
Pazopanib	£81,104	2.784	1.868					
Tivozanib	£61,839	2.279	1.596	£19,264	0.505	0.272	£70,865	£70,865
Sunitinib	£88,543	3.023	2.047	£26,704	0.745	0.451	£41,559	£59,247
ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALYs: Quality-adjusted life years; IFN: Interferon								

Scenario results: no discounting of costs and benefits

Table 7: Alternative scenario results (No discounting of costs and benefits): pairwise comparisons – tivozanib versus sunitinib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£75,455	1.882	
SUN	£115,593	2.663	
Increment (TIVO - SUN)	-£40,138	-0.781	£51,379 (SW Quadrant)
TIVO: Tivozanib, SUN: Sunitinib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 8: Alternative scenario results (No discounting of costs and benefits): pairwise comparisons – tivozanib versus pazopanib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£75,455	1.882	
PAZO	£61,200	1.499	
Increment (TIVO - PAZ)	£14,256	0.383	£37,211
TIVO: Tivozanib, PAZ: Pazopanib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 9: Alternative scenario results (No discounting of costs and benefits - list price for tivozanib) from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus pazopanib (QALYs)	ICER (£) incremental (QALYs)
Pazopanib	£61,200	2.174	1.499					
Tivozanib	£75,455	2.728	1.882	£14,256	0.554	0.383	£37,211	£37,211
Sunitinib	£115,593	3.946	2.663	£40,138	1.217	0.781	£46,729	£51,379
ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALYs: Quality-adjusted life years; IFN: Interferon								

Scenario results: use of alternate utility for pre-progression and post-progression health states

Table 10: Alternative scenario results (Utilities from TA 169): pairwise comparisons – tivozanib versus sunitinib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£70,476	1.884	
SUN	£105,566	2.604	
Increment (TIVO - SUN)	-£35,091	-0.720	£48,728 (SW Quadrant)
TIVO: Tivozanib, SUN: Sunitinib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 11: Alternative scenario results (Utilities from TA 169): pairwise comparisons – tivozanib versus pazopanib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£70,476	1.884	
PAZO	£58,537	1.536	
Increment (TIVO - PAZ)	£11,938	0.348	£34,292
TIVO: Tivozanib, PAZ: Pazopanib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 12: Alternative scenario results (Utilities from TA 169 - list price for tivozanib) from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus pazopanib (QALYs)	ICER (£) incremental (QALYs)
Pazopanib	£58,537	2.076	1.536					
Tivozanib	£70,476	2.543	1.884	£11,938	0.467	0.348	£34,292	£34,292
Sunitinib	£105,566	3.586	2.604	£35,091	1.043	0.720	£44,035	£48,728
ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALYs: Quality-adjusted life years; IFN: Interferon								

Table 13: Alternative scenario results (Utilities from TA 215): pairwise comparisons – tivozanib versus sunitinib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£70,476	1.645	
SUN	£105,566	2.249	
Increment (TIVO - SUN)	-£35,091	-0.604	£58,060 (SW Quadrant)
TIVO: Tivozanib, SUN: Sunitinib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 14: Alternative scenario results (Utilities from TA 215): pairwise comparisons – tivozanib versus pazopanib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£70,476	1.645	
PAZO	£58,537	1.341	
Increment (TIVO - PAZ)	£11,938	0.304	£39,275
TIVO: Tivozanib, PAZ: Pazopanib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 15: Alternative scenario results (Utilities from TA 215 - list price for tivozanib) from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus pazopanib (QALYs)	ICER (£) incremental (QALYs)
Pazopanib	£58,537	2.076	1.341					
Tivozanib	£70,476	2.543	1.645	£11,938	0.467	0.304	£39,275	£39,275
Sunitinib	£105,566	3.586	2.249	£35,091	1.043	0.604	£51,794	£58,060
ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALYs: Quality-adjusted life years; IFN: Interferon								

Scenario results: change in post-progression treatment costs

Table 16: Alternative scenario results (Proportion of patients receiving second-line therapy with Axitinib is increased to 90%): pairwise comparisons – tivozanib versus sunitinib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	**QALYs**	**ICER (Cost per QALY gained)**
List price			
TIVO	£86,962	1.757	
SUN	£137,045	2.425	
Increment (TIVO - SUN)	-£50,083	-0.668	£74,977(SW Quadrant)
TIVO: Tivozanib, SUN: Sunitinib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 17: Alternative scenario results (Proportion of patients receiving second-line therapy with Axitinib is increased to 90%): pairwise comparisons – tivozanib versus pazopanib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	**QALYs**	**ICER (Cost per QALY gained)**
List price			
TIVO	£86,962	1.757	
PAZO	£71,851	1.432	
Increment (TIVO - PAZ)	£15,111	0.325	£46,526
TIVO: Tivozanib, PAZ: Pazopanib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 18: Alternative scenario results (Proportion of patients receiving second-line therapy with Axitinib is increased to 90%- list price for tivozanib) from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus pazopanib (QALYs)**	**ICER (£) incremental (QALYs)**
Pazopanib	£71,851	2.076	1.432					
Tivozanib	£86,962	2.543	1.757	£15,111	0.467	0.325	£46,526	£46,526
Sunitinib	£137,045	3.586	2.425	£50,083	1.043	0.668	£65,654	£74,977
ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALYs: Quality-adjusted life years; IFN: Interferon								

Table 19: Alternative scenario results (Mean cost of second-line treatment reduced by 50%): pairwise comparisons – tivozanib versus sunitinib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£54,185	1.757	
SUN	£74,472	2.425	
Increment (TIVO - SUN)	-£20,287	-0.668	£30,371 (SW Quadrant)
TIVO: Tivozanib, SUN: Sunitinib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 20: Alternative scenario results (Mean cost of second-line treatment reduced by 50%): pairwise comparisons – tivozanib versus pazopanib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	QALYs	ICER (Cost per QALY gained)
List price			
TIVO	£54,185	1.757	
PAZO	£45,376	1.432	
Increment (TIVO - PAZ)	£8,810	0.325	£27,124
TIVO: Tivozanib, PAZ: Pazopanib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 21: Alternative scenario results (Mean cost of second-line treatment reduced by 50% - list price for tivozanib) from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus pazopanib (QALYs)	ICER (£) incremental (QALYs)
Pazopanib	£45,375	2.076	1.432					
Tivozanib	£54,185	2.543	1.757	£8,810	0.467	0.325	£27,124	£27,124
Sunitinib	£74,472	3.586	2.425	£20,287	1.043	0.668	£29,302	£30,371
ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALYs: Quality-adjusted life years; IFN: Interferon								

Scenario results: efficacy estimates derived from all patients treated in trials

The efficacy data in this scenario uses our original NMA which includes data from all patients regardless of whether they were treatment naïve or had already received treatment. Please note that the original model submitted in our initial submission used an incorrect OS curve, we have now corrected this.

Table 22: Base-case results: pairwise comparisons – tivozanib versus sunitinib

	Costs	**QALYs**	**ICER (Cost per QALY gained)**
List price			
TIVO	£69,359	1.724	
SUN	£67,949	1.634	
Increment (TIVO - SUN)	£1,410	0.089	£15,756
TIVO: Tivozanib, SUN: Sunitinib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 23: Base-case results: pairwise comparisons – tivozanib versus pazopanib

	Costs	**QALYs**	**ICER (Cost per QALY gained)**
List price			
TIVO	£69,359	1.724	
PAZO	£68,387	1.704	
Increment (TIVO - PAZ)	£971	0.020	£49,152
TIVO: Tivozanib, PAZ: Pazopanib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 24: Base-case results (list price for tivozanib)

Technologies	**Total costs (£)**	**Total LYG**	**Total QALYs**	**Incremental costs (£)**	**Incremental LYG**	**Incremental QALYs**	**ICER (£) versus pazopanib (QALYs)**	**ICER (£) incremental (QALYs)**
Pazopanib	£67,949.30	2.338	1.634					
Tivozanib	£68,387.49	2.445	1.704	£971	0.027	0.020	£49,152	£49,152
Sunitinib	£69,359	2.472	1.724	£1,410	0.134	0.089	£15,733	£15,756
ICER: Incremental cost-effectiveness ratio; LYG: Life years gained; QALYs: Quality-adjusted life years; IFN: Interferon								

PSA results using base case scenario: pairwise comparisons from restricted NMA network

Table 25: PSA results using base case scenario: pairwise comparisons – tivozanib versus sunitinib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	**QALYs**	**ICER (Cost per QALY gained)**
List price			
Increment (TIVO - SUN)	-£34,950	-0.635	£55,039
TIVO: Tivozanib, SUN: Sunitinib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

Table 26: PSA results using base case scenario: pairwise comparisons – tivozanib versus pazopanib from restricted NMA network (TIVO-1, SWITCH, COMPARZ + CROSS-J-RCC) using fractional polynomial method

	Costs	**QALYs**	**ICER (Cost per QALY gained)**
List price			
Increment (TIVO - PAZ)	£10,528	0.326	£32,336
TIVO: Tivozanib, PAZ: Pazopanib, QALY: Quality-adjusted life year, ICER: Incremental cost effectiveness ratio			

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Tivozanib for treating renal cell carcinoma [ID591]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Kidney Cancer Support Network

Your position in the organisation: [redacted]

Brief description of the organisation:

(For example: who funds the organisation? How many members does the organisation have?)

Kidney Cancer Support Network (KCSN) was founded in 2006 by cancer patients/survivors Rose Woodward and Julia Black, who started by offering practical and bespoke support to individual patients for access to life-extending cancer drugs to treat metastatic kidney cancer.

Empowering patients to take an active role in their own health care, and, more generally, in decisions affecting the choice, provision and quality of cancer services throughout the UK, remains the top priority for KCSN. Over the years, KCSN has grown considerably, with a membership of over 900 kidney cancer patients and carers, and a further 600+ active and committed patients and carers on its confidential social networking sites. KCSN is unique; until recently it operated as a voluntary organisation, totally patient-led and managed by the patients and carers it represents. Although KCSN remains patient-led, the group is now a registered charity, which enables it raise the funds to better meet the growing needs of the kidney cancer community it represents.

KCSN is funded by grants from trusts/foundations/grant-making organisations and the pharmaceutical industry, in addition to donation from patients and fundraising events/activities carried out by the kidney cancer community in the UK.

We are asking for your collective view as an organisation and will be asking patient experts for their individual input separately. If you have the condition, or care for someone with the condition, you may wish to complete a patient expert questionnaire to give your individual views as well.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Kidney Cancer Support Network (KCSN) is a patient-led kidney cancer charity with the largest and most active patient and carer membership across the UK. As such, we feel we are in the strongest position to feedback how metastatic renal cell carcinoma (mRCC) affects the day-to-day lives of people living with this disease.

In 2014, there were more than 12,500 new cases of kidney cancer diagnosed in the UK (34 cases diagnosed every day) and kidney cancer is the seventh most common cancer affecting British people (2014). Kidney cancer accounts for 3% of all new UK cancer cases (2014). In

2014, nearly 4,500 people died from the disease and about 40% of kidney cancer patients will be diagnosed with late stage disease. In these cases, it is estimated that around only 10% of people will survive for five years or more (Cancer Research UK). It is difficult to remain positive in the face of figures like this.

Metastatic RCC is a devastating disease and is currently incurable. The majority of mRCC patients are forced to give up work because of the disease itself, and current treatments are very debilitating. This brings with it enormous financial pressures for the patient and their family (and additional costs to the state) and can precipitate psychological problems; depression, loss of confidence and self-worth. Patients may suffer constant pain from metastatic tumours in the brain, bones, lungs, liver, and other more rare sites. Patients with bone metastases are at risk of bone breaks and spinal cord compression. Metastases in the lungs can lead to breathlessness, and persistent coughing, while spread of the cancer to the brain can lead to severe and debilitating headaches, confusion and, in some cases, paralysis. Kidney function is often compromised and patients find daily living difficult, often needing periods of rest during the day. Patients diagnosed with hereditary kidney cancer or rare RCC subtypes currently have very limited treatment options.

Current first-line treatments offer an important, but sometimes short-lived period of stability, but not all patients respond to these treatments and most patients become refractory after a period of time. Biomarkers for the treatment of RCC are yet to be identified, and unfortunately clinicians are not able to predict which patients will respond to which drug. Therefore, selection of the most effective treatment for individual patients is accomplished by trial and error. Without a choice of treatment alternatives in the second-line and beyond, most patients will face disease progression, including worsening of symptoms, such as severe pain, fatigue and shortness-of-breath. Patients require choice in second- and third-line therapy to continue managing their disease, and to maintain quality of life.

Patients tell us that psychological support is very difficult to access, and many patients are prescribed anti-depressant drugs to help manage their mental as well as physical clinical situation. Sexual function is affected for both male and female patients, and family life suffers as a result. Kidney cancer cases are rising year-on-year and there is a strong unmet need for second- or third-line treatment with better overall survival rates than currently exist, especially for difficult-to-treat rare subtypes of RCC.

The impact of a terminal diagnosis on the family, as well as the patient, is also a major concern; these families need psychological and financial support during the most difficult time in their lives when a loved one has come to the end of their available treatment options and all that remains is palliative care.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

For most patients, the most important treatment outcome is no evidence of disease, i.e., a potential cure for their kidney cancer. The hope of achieving this outcome spurs patients on to continue to take current medication, despite significant toxicity, and to search for alternative, more effective treatments that can extend overall survival. Failing no evidence of disease, tumour shrinkage or disease stability would be the next best outcome for patients.

In addition to treatment outcomes, quality of life is also an important consideration for many patients. Most patients would prefer a treatment that allows them to continue to lead as normal a life as possible, and to contribute both socially and economically to their communities:

> *"The extra years, which the drugs give me, enable me to carry on working, using the accumulated knowledge and experience, gathered through my working life, for the benefit of the various ……. enterprises which I manage……..I'm making a hugely*

positive contribution to society, and the wider economy, and I wish to be able to carry on with this and more importantly to ensure that others, whatever their circumstances, will have the same opportunities".

"……has enabled me to enjoy every day, do 3 or 4 days voluntary work a week and to care for my elderly parents. The side effects for me have been milder than many people but the fear of diarrhoea striking all through the day makes travelling and working very difficult. I would like a treatment without digestive effects, little fatigue and control of growths……".

Although less serious than some of the side effect to current treatment, some patients find the changes to their appearance caused by current first-line treatments distressing: white, thinning hair, and pale skin make them feel nearer to death, and also singles people out as cancer patients. Some of the current treatments can also cause issues with the thyroid gland, blood pressure, and cholesterol levels.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

The current treatment pathway for mRCC is for surgery (either radical or partial nephrectomy), followed by either sunitinib or pazopanib in the first-line setting, and axitinib or everolimus in the second-line setting, all of which are oral medicines and have similar modes of action. Recently, nivolumab was recommended for use within NHS England for second- or third-line treatment of mRCC, and is the first third-line treatment in use by the NHS. Nivolumab is an immunotherapy (anti-PD-1), which is administered as a biweekly intravenous infusion, requiring outpatient hospital treatment (chemotherapy chair resources), and the associated travel time and expense for the patient and carer.

We have extracted the following details from statements submitted to the KCSN by patients living with mRCC. Using currently available drugs, many patients suffer with:

• Extreme fatigue

• Severe hand and foot syndrome which can leave patients unable to walk

• Intestinal problems (chronic diarrhoea)

• Pneumonitis requiring hospital treatment and cessation of treatment

• Severe mouth ulcers causing problems eating and drinking

• Nausea and vomiting, which can also cause problems taking the medication

• High blood pressure (hypertension)

• Hyperthyroidism

All the above side effects require additional medicines to help patients manage the drugs and/or tumour pain, which require opioid prescriptions. Costs for additional medicines to mitigate the side effects of these targeted therapies should be taken into account.

Other less serious side effects, which still affect the patient's quality of life, are loss of taste, loss of and change of hair colour, depression, loss of libido, and inability to drive. In some cases, treatment can affect a patient's quality of life to such an extent that clinicians recommend a dose reduction, and some patients are even advised to stop treatment as a result of severe side effects. Patients are aware that these treatments are life-extending drugs, but they continue to look for drugs with different modes of action, which can give improved overall survival with better quality of life.

The following statements from mRCC patients on axitinib and everolimus highlight the impact of these drugs on quality of life:

"….. my husband started on Axitinib. We had hoped this drug would work well but the treatment was stopped …. when my husband developed severe sepsis. ……. Axitinib caused severe side effects for my husband and at times he was unable to eat or walk. Axitinib caused diarrhoea, severe blistering to feet and mouth and we had to

seek help from a chiropodist to try and enable him to walk but even she couldn't help him. In all my husband lost 5 stone in weight during his time on TKIs."

"I was on pazopanib when my oncologist determined that it was starting to fail. At that point I was advised that everolimus was to be made available to me. Initially side effects were minimal, however about a month [sic] I started to get very bad mouth ulcers, which took a few weeks to clear up, fatigue and tiredness. Also experienced anaemia and had 2 blood transfusions. I suffered from nosebleeds, mainly when blowing my nose! Lung condition didn't help and was experiencing dry cough and breathlessness as well. Experienced lots of indigestion also had mild doses of feeling shaky and shivery. Ct scan showed that everolimus was struggling ……".

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

Clinicians in the UK should have the ability to choose the most effective treatments for individual patients from those available. Biomarkers for the treatment of RCC are yet to be identified, and unfortunately clinicians are not able to predict which patients will respond to which drug. Therefore, selection of the most effective treatment for individual patients is accomplished by trial and error. Without tivozanib, the clinician's choice of treatment is seriously compromised. Without treatment alternatives in the second-line and beyond, most patients will face disease progression, including worsening of symptoms, such as severe pain, fatigue and shortness-of-breath. Patients require choice in second- and third-line therapy to continue managing their disease, and to maintain quality of life.

The current second-line treatment options are not effective for everyone, and can be difficult to access. Axitinib, everolimus and nivolumab are the only second-line treatments available to patients in England on the NHS. Undue restrictions in accessing tivozanib would simply add unnecessary additional burden to patients with a terminal diagnosis. Choice in the second-line and beyond, and access to new innovative treatments remains paramount to managing the progression of this disease. Having a choice in second- and third-line treatment would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.

Please explain any advantages that patients or carers think this

treatment has over other NHS treatments in England.

Tivozanib is a potent, selective, long half-life inhibitor of all three vascular endothelial growth factor (VEGF) receptors (VEGF-1, VEGF-2 and VEGF-3) that is designed to optimise VEGF blockade while minimising side effects, resulting in a more tolerable treatment than is currently available for mRCC, especially in combination with other therapies.

The following statement from a patient currently taking tivozanib in the TIVO-3 trial highlights the tolerability of this drug:

> *"I have no problems taking the tablets each day. The side effects have been manageable and tolerable although I do find the 3rd week of treatment more difficult particularly with the effect on the skin of my hands. I really need the week off to recover and this is very important to me. It's been worthwhile taking the tablets and they are helping to control my cancer."*

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

None

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

Patients/carers have the following main concerns regarding current NHS treatments for mRCC in England:

- Current treatments do not cure mRCC: the disease can be controlled for, on average, 2 years with current first-line treatments, after which second-line treatments can extend life for another year or more. Patients need more choice in the second-line and beyond to effectively manage their disease and give them good quality life
- There are no biomarkers of response to treatment with current NHS treatments, and clinicians are unable to predict which patients will respond to which drug. This results

in patients being unnecessarily exposed to the side effects of current treatment without the benefits of the drug if they are found to be non-responders. Selection of the most effective treatment for individual patients is accomplished by trial-and-error.

- The toxicity of current treatments is a concern for patients, as described in section 3 above.
- Some of the side effects of current treatments, such as depression, loss of libido, inability to drive, hair and skin changes all have an impact on the psychological well-being and quality of life of patients, which negatively impacts family/social life and work life. Patients tell us that psychological support is very difficult to access, and many patients are prescribed anti-depressant drugs to help manage their mental health
- The impact of a terminal diagnosis on the family, as well as the patient, is also a major concern, both in terms of the psychological wellbeing of family members and the financial situation of the family if the patient is unable to return to work.

Please list any concerns patients or carers have about the treatment being appraised.

Tivozanib is currently only available to patients through participation in the TIVO-3 clinical trial, which started recruiting patients in the UK earlier this year. We have, therefore, been unable to determine any concerns patients or carers have about tivozanib.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

See comment above

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

None

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

None

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

☐ Yes x No

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in

the clinical trials.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

☐ Yes x No

If yes, please provide references to the relevant studies.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;
- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

Patients who have conditions that make it difficult to swallow tablets or gastrointestinal conditions that interfere with the absorption of the drug, for example ulcerative colitis.

9. Other issues

Do you consider the treatment to be innovative?

x Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

Tivozanib is a potent, selective, long half-life inhibitor of all three vascular endothelial growth factor (VEGF) receptors (VEGF-1, VEGF-2 and VEGF-3) that is designed to optimise VEGF blockade while minimising side effects, resulting in a more tolerable treatment than is currently available for mRCC, especially in combination with other therapies. The phase I/II TiNivo trial is investigating the efficacy and safety of tivozanib in combination with nivolumab for the treatment of mRCC, and recruited the first patient earlier this month (March 2017).

Are there any other issues that you would like the Appraisal Committee to consider?

Tivozanib is a potent and selective multiple kinase inhibitor against all three VEGF kinases, and has proven to be effective in extending progression free survival by nearly 3 months compared to sorafenib, with a tolerable side effect profile. Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including patient experience as well as overall survival, it is vital that innovative new drugs with different modes of action are made available to patients in order that they have the best care possible. If these drugs are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to the rest of Europe and North America.

A number of clinical trials of tivozanib have been conducted or are ongoing in recurrent and/or metastatic RCC patients in the UK. The patients who participated in these trials did so in the expectation that their data would enable other patients in the UK to benefit from this drug. If the government and the pharmaceutical industry cannot agree a price that allows the use of tivozanib within the NHS, we would have to question whether patients will continue to support future research by taking part in clinical trials. Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from new, innovative and clinically effective drugs if the precedent for these drugs is rejection by NICE.

We appreciate that tivozanib is expensive, and we urge NICE and the manufacturer to negotiate and find a way to make this new and innovative drug available to the patients who need it; failure to do so would be seen as professional inadequacy. NICE and the manufacturer need to think outside the box to negotiate an alternative funding scheme, for example, the government could pay for those cases where tivozanib is effective, and the manufacturer reimburse the NHS for those cases who do not respond to treatment. This will require more collaborative working with the manufacturer to negotiate an acceptable patient access scheme.

Current treatments have proven to shrink tumours and delay disease progression in some patients, but adding tivozanib as a choice in the second-line (and beyond) enables patients

and clinicians to have individualised treatment plans to better control this disease and maintain a high quality of life. It could also address the massive unmet need for treatment options in the third-line and beyond.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- Tivozanib is a potent, selective long half-life multiple kinase inhibitor against all three VEGF kinases that is designed to optimise VEGF blockade while minimising side effects
- Tivozanib seems to be well tolerated, as well as proven to be effective in extending progression free survival by nearly 3 months compared to sorafenib
- Adding tivozanib as a choice in the second-line (and beyond) enables patients and clinicians to individualise treatment plans to better control this disease and maintain a high quality of life
- Tivozanib addresses the massive unmet need for treatment options in the third-line and beyond
- A tolerable side effect profile renders tivozanib a useful candidate for combination with immunotherapy drugs, such as nivolumab, to further improve the overall survival of patients with recurrent or metastatic RCC.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer organisation submission (STA)

Tivozanib for treating renal cell carcinoma [ID591]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, and including health-related quality of life)
- the acceptability of different treatments and how they are given
- expectations about the risks and benefits of the treatment.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The length of your response should not normally exceed 10 pages.

1. About you and your organisation

Your name: [redacted]

Name of your organisation: Kidney Cancer UK

Your position in the organisation: [redacted]

Brief description of the organisation: We provide support to patients and families of people with kidney cancer, raise awareness, run campaigns, provide information and fund research into kidney cancer.

The organisation is funded by donations and each year we communicate with 3640 new patients.

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: We have no links with the tobacco industry

2. Living with the condition

What is it like to live with the condition or what do carers experience when caring for someone with the condition?

Different people will react to living with kidney cancer differently and the challenges they face greatly depend on the stage of their disease. Most people with kidney cancer will receive surgery at some point, which will require a period of recovery. There will be times when the patient and family/carers will be worried about the future and require information and guidance. Waiting for news, scans and procedures can be emotionally draining. Knowledge that there are a variety of treatment options available to them will give them some comfort. Dealing with side effects of drugs can be equally exhausting as the symptoms of the cancer, so finding the balance of treatment and quality of life that is right for each patient is important.

3. Current practice in treating the condition

Which treatment outcomes are important to patients or carers? (That is, what would patients or carers like treatment to achieve?) Which of these are most important? If possible, please explain why.

Treatment outcomes would most certainly include surviving kidney cancer and to be free of cancer for the foreseeable future. We understand that most drug treatments aim to extend the lives of people with kidney cancer and viewing

kidney cancer as a chronic disease that can be lived with would be a desirable outcome. Tolerable side effects of a treatment are important if kidney cancer is to be viewed as a chronic disease and patients are to have a good quality of life.

What is your organisation's experience of currently available NHS care and of specific treatments for the condition? How acceptable are these treatments and which are preferred and why?

The treatment and outcome are very much dependant on how early the kidney cancer has been caught. Ideally the tumour is of an early stage and is removed by surgery or cryotherapy and the patient enjoys a life after cancer. This would always be the preferred treatment. However, if the tumour has spread patients will rely on targeted therapies. Current drug treatments for kidney cancer are very limited in number and have plenty of side effects. Kidney Cancer UK feel that there are significant improvements that could be made in this area. A wider range of options with improved efficacy and fewer side effects. The most commonly used Tyrosine kinase inhibitors (sunitinib and pazopanib) act to extend life and in some cases they work very well and extend life for many years. For others, the extension of life is a matter of months. However, those months can be invaluable for individuals and their families.

The recent introduction of nivolumab (immunotherapy) as a NICE recommended 2nd line drug is very good news. We are awaiting reports back on how effective this drug is for patients and we are hopeful that in the future immunotherapies and combinations of treatments may give alternate options and even better results.

Giving alternate options for patients can be invaluable especially in an era where personalised medicine may be introduced. It may be found that tivozanib works for a set of patients where other treatments fail. A multitude of treatment options is always desirable.

4. What do patients or carers consider to be the advantages of the treatment being appraised?

Benefits of a treatment might include its effect on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (such as lifestyle and work)
- other people (for example, family, friends and employers)
- ease of use (for example, tablets rather than injection)
- where the treatment has to be used (for example, at home rather than in hospital)
- any other issues not listed above

Please list the benefits that patients or carers expect to gain from using the treatment being appraised.

An alternate Tyrosine kinase inhibitor (TKI) option is one of the biggest advantages of tivozanib. Tivozanib is a third line TKI which has shown high affinity for all 3 VEGF-R's. Recent phase 3 trials have shown that although overall survival was not significantly longer for patients on tivozanib than sorafenib the progression free survival was. Fewer people required to be swapped to other treatment options. Only 10% of patients received a next line VEGF-R therapy. Compared to 70% of patients in the sorafenib arm.

The dosing is similar to other TKI's which is an easy oral tablet to take at home continuously in a cycle of 3 weeks, followed by a week's break. This is of benefit to patients because it does not involve traveling to hospital to have the treatment administered.

Please explain any advantages that patients or carers think this treatment has over other NHS treatments in England.

Tivozanib is thought to have an acceptable side effect profile and when compared to sorafenib. Patients receiving sorafenib had higher overall rates of diarrhoea (32% vs 22%), hand-foot syndrome (54% vs 13%), and alopecia (21% vs 2%), compared with the tivozanib arm. The only side effect that is

worse is hypertension which is reported to be managed using hypertensives, Motzer et al, 2013.

If you know of any differences in opinion between patients or carers about the benefits of the treatment being appraised, please tell us about them.

I don't know of any differences in opinion.

5. What do patients and/or carers consider to be the disadvantages of the treatment being appraised?

Disadvantages of a treatment might include:

- aspects of the condition that the treatment cannot help with or might make worse
- difficulties in taking or using the treatment (for example, injection rather than tablets)
- side effects (for example, type or number of problems, how often, for how long, how severe. Please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- where the treatment has to be used (for example, in hospital rather than at home)
- impact on others (for example, family, friends and employers)
- financial impact on the patient and/or their family (for example, the cost of travel to hospital or paying a carer)
- any other issues not listed above

Please list any concerns patients or carers have about current NHS treatments in England.

I think patients and carers are concerned over the lack of options available to them.

Coping with the side effects of TKI's are a worry for patients and can affect their quality of life but I think most people with advanced kidney cancer are willing to take the treatment for the extension of life that it may bring. Any improvement in side effects is a positive.

TKI's such as tivozanib have a greater efficacy in some people and not others. However having a variety of TKI's to try is a significant advantage as a

different drug might work better and having more options gives hope and comfort to the patient.

Please list any concerns patients or carers have about the treatment being appraised.

I have not heard of any concerns that patients might have about tivozanib.

If you know of any differences in opinion between patients or carers about the disadvantages of the treatment being appraised, please tell us about them.

I don't know of any difference of opinion.

6. Patient population

Are there any groups of patients who might benefit more from the treatment than others? If so, please describe them and explain why.

Patients with advanced (stage 3 or 4) disease are likely to require TKI's to extend their life. People who have failed prior systemic treatment are likely to need another treatment option, which introducing tivozanib will provide.

Are there any groups of patients who might benefit less from the treatment than others? If so, please describe them and explain why.

Patients with early stage disease are less likely to require targeted therapy. People with hypertension may also struggle to manage the side effect profile of tivozanib.

7. Research evidence on patient or carer views of the treatment

Is your organisation familiar with the published research literature for the treatment?

Yes

If you answered 'no', please skip the rest of section 7 and move on to section 8.

Please comment on whether patients' experience of using the treatment as part of their routine NHS care reflects the experiences of patients in the clinical trials.

Tivozanib has not been used routinely within the NHS.

Do you think the clinical trials have captured outcomes that are important to patients? Are you aware of any limitations in how the treatment has been assessed in clinical trials?

The trial captured an overall improved side effect profile for tivozanib.

I know that the design of the study might have contributed to the lack of significance in the overall survival. More specifically the extension phase of the trial where treatments could be swapped if not successful may have contributed to the lack of tivozanib overall survival significance.

If the treatment being appraised is already available in the NHS, are there any side effects that were not apparent in the clinical trials but have emerged during routine NHS care?

Tivozanib is not currently available on the NHS

Are you aware of any relevant research on patient or carer views of the condition or existing treatments (for example, qualitative studies, surveys and polls)?

Yes

If yes, please provide references to the relevant studies.

The Kidney Cancer UK annual survey. However no one on the TIVO-1 trial completed our survey.

8. Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Protected characteristics are: age; being or becoming a transsexual person; being married or in a civil partnership; being pregnant or having a child; disability; race including colour, nationality, ethnic or national origin; religion, belief or lack of religion/belief; sex; sexual orientation.

Please let us know if you think that recommendations from this appraisal could have an adverse impact on any particular groups of people, such as:

- excluding from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment is/will be licensed;
- having a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the treatment;

- any adverse impact on people with a particular disability or disabilities.

Please let us know if you think that there are any potential equality issues that should be considered in this appraisal.

None known

Are there groups of patients who would have difficulties using the treatment or currently available treatments? Please tell us what evidence you think would help the Committee to identify and consider such impacts.

None known

9. Other issues

Do you consider the treatment to be innovative?

☐ Yes ☐ No

If yes, please explain what makes it significantly different from other treatments for the condition.

The treatment is thought to be more specific for all 3 VEGF receptors and provide effect with fewer side effects (apart from hypertension).

Are there any other issues that you would like the Appraisal Committee to consider?

I think that the number of different options available to people with advanced kidney cancer is very important. Having a variety of options provides hope and comfort.

10. Key messages

In no more than 5 bullet points, please summarise the key messages of your submission.

- People with advanced kidney cancer have very few treatment options and require a variety of drug choices.
- Tivozanib has an acceptable and improved side effect profile compared to other TKI's, which will improve people's quality of life.
- TKI's are continuing to improve and tivozanib has a greater affinity for all 3 VEGF receptors. Progression free survival was increased in the tivozanib group.
- Fewer people swapped to another treatment option once they had started on tivozanib.

- Different drugs work for different people. A particular group of people may respond really well to tivozanib where other TKI's and targeted therapies may not work for them.

Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)
Tivozanib for treating renal cell carcinoma [ID591]

Thank you for agreeing to make a submission on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your submission, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: NCRI-ACP-RCP-RCR

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry: None

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)
Tivozanib for treating renal cell carcinoma [ID591]

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?

Metastatic kidney cancer is treated by oncologists at specialist oncology centres.

Is there significant geographical variation in current practice?

No

Are there differences of opinion between professionals as to what current practice should be?

No significant differences between professionals

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

In the first line (untreated) setting, patients are treated with sunitinib or pazopanib. There is no directly comparable data available that compares efficacy or toxicity of tivozanib with either of these two agents within the same clinical trial. It is not therefore possible to directly make statements regarding advantages and disadvantages of tivozanib in the first line setting over standard care. The phase III study of sorafenib vs tivozanib which showed superiority of tivozanib was against a comparator (sorafenib) that is not used in the first line setting. In the second and subsequent lines of treatment in the UK sorafenib is not reimbursed although it is a standard of care in many other countries. The ongoing study of tivozanib vs sorafenib in 2nd and 3rd line treatment will not provide data in time for this STA.

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?

Although there are prognostic groups that can be identified there is no useful way of selecting patients who will or will not benefit from drug.

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

No

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

As above.

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)
Tivozanib for treating renal cell carcinoma [ID591]

N/A

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

No relevant UK guidelines.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

Three Tyrosine kinase inhibitors (TKIs) that inhibit the VEGF receptor are currently approved for the treatment of advanced RCC (sunitinib or pazopanib 1st line, axitinib in 2nd and subsequent lines). Cabozantinib is also a TKI and is undergoing an STA currently.

We know that many patients derive significant benefit from sequential use of TKIs and it is therefore highly likely that, if reimbursed tivozanib would confer benefit to a group of patients who were pre-treated with a first or second line TKI. There is not data available however to make a robust comparison between the efficacy of tivozanib and the other TKIs that are available in the UK.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

These drugs are used until evidence of significant disease progression.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

The study population in the TIVO-1 study is representative of the UK RCC population. The concerns are around study design, crossover rates and lack of a standard of care comparator in the first line setting.

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The adverse event profile of tivozanib is comparable with the AE profile seen with other drugs in this class.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Implementation issues

The NHS is required by the Department of Health to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)
Tivozanib for treating renal cell carcinoma [ID591]

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No additional resources required

Equality
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

No equality issues

NHS England submission on the NICE appraisal of tivozanib in the treatment of advanced/metastatic renal cell adenocarcinoma

1. The first line setting of systemic therapy for renal cell carcinoma (RCC) in NHS England has the options of either sunitinib or pazopanib. Further lines of treatment can involve axitinib or nivolumab or cabozantinib or everolimus. These 4 second line options have differing modes of action and hence NHS England considers them also to be potential options beyond 2nd line therapy if it is appropriate for patients to receive further treatment (ie if they remain fit for treatment and do not have clearly refractory disease).
2. Cytokine therapy as first line treatment is very rarely used and now only involves interleukin-2. Interferon therapy was never a great favourite and has not been used in England since sunitinib was approved by NICE in 2009.
3. NHS England notes that tivozanib has a positive CHMP opinion for use as 1st line treatment in advanced RCC patients who are naïve to treatment with VEGFR and mTOR pathway inhibitors following disease progression after one prior treatment with cytokine therapy for advanced RCC. The manufacturer was hoping for the positive CHMP opinion to apply to patients who are **either** untreated **or** following disease progression after one prior treatment with cytokine therapy. 70% of patients in the phase III tivozanib trial were classed as treatment naïve but previous therapy was not counted as being such if given as adjuvant treatment after nephrectomy and if such therapy was completed >6 months after nephrectomy. The wording of the CHMP opinion is such that a condition of tivozanib treatment within the marketing authorisation will be for a treatment modality to have been previously given but which no longer applies in England apart from to a tiny proportion of RCC patients treated with interleukin-2.
4. The tivozanib phase III trial was published in 2013 and hence the subsequent granting of a marketing authorisation in 2017 has taken a time that is much longer than usual for cancer drugs.
5. The tivozanib trial used sorafenib as the comparator for tivozanib. However, sorafenib is not used in RCC in England at all and was thus not in the NICE scope for the tivozanib appraisal. A randomised phase II trial which compared sorafenib with interferon showed similar progression-free survivals for both arms.
6. NHS England notes that the tivozanib trial patients were all of performance status 0 or 1 and there was a significant imbalance in performance status 0 patients which favoured the sorafenib arm.
7. NHS England also observes that the TIVO-1 protocol specified that patients had to have had a prior nephrectomy. More importantly, entry to the trial did not include an assessment of the fact that the advanced/metastatic disease was progressing. It is thus unknown as to whether the two arms were balanced in this regard.

8. As the trial design specified that cross-over was allowed to tivozanib from the sorafenib arm but not to sorafenib from the tivozanib arm, NHS England notes with concern that subsequent treatment rates differed according to which arm patients were randomised: 66% of patients in the sorafenib arm received a further TKI (nearly all tivozanib) whereas the figure for the tivozanib arm was much less at 21%. In addition and in the treatment naïve group in the trial, the only systemic therapy ever received was the randomised therapy in 70% of patients in the tivozanib arm and 32% in the sorafenib arm. This may have been as a consequence of the fact that 88% of patients recruited into this trial were from central/Eastern Europe. The subsequent treatments in the trial are thus very different to what occurs now in NHS practice, partly because the trial was performed (in renal cancer terms) a long time ago and partly because recruitment was so dominantly in one part of the world in which treatment options may have been limited.
9. NHS England notes that the median survival durations in the TIVO-1 trial were 29 months in both arms as shown in the J Clin Oncol paper. There were few patients at risk after 26 months at the time of this published analysis. The company's submission shows a later survival analysis in 2013 when the median OS was 28 months for the tivozanib arm and 30 months for the sorafenib arm.
10. NHS England notes that tivozanib is a reasonably well tolerated drug but is wary of any robust conclusion that it has fewer side-effects than sunitinib or pazopanib.
11. NHS England agrees with the ERG that the company is incorrect in modelling subsequent treatment in their economic model to be 60% axitinib and 40% BSC. These were fit patients that entered TIVO-1 and hence the ERG assumption is more realistic (50% axitinib, 30% nivolumab, 10% everolimus and 10% BSC). It is also wrong for the economic model to assume that axitinib is taken until death. NHS England notes the importance of the cost of post-progression treatments in the economic model.
12. In conclusion, tivozanib is a more selective VEGFR inhibitor and is better than sorafenib, a treatment that is not used in England and was not in scope. It is reasonably well tolerated. The trial has several problems in its design which add to the uncertainty generated from the network meta-analysis which is necessary because the comparator chosen in the trial is irrelevant to NHS practice in England. The wording in the CHMP opinion is also very important as it stipulates use of tivozanib in patients who are VEGF and mTOR inhibitor naïve but who have received prior cytokine therapy. Such a group of patients in England is very small indeed.

Prof Peter Clark

NHS England Chemotherapy Lead and National Clinical Lead for the Cancer Drugs Fund

July 2017

NICE National Institute for Health and Care Excellence

Clinical expert statement

Tivozanib for treating renal cell carcinoma [ID591]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this expert statement

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	**Dr Paul Nathan**
2. Name of organisation	**nominated by the NCRI-ACP-RCP-RCR**

NICE National Institute for Health and Care Excellence

3. Job title or position	**Consultant Medical Oncologist, Mount Vernon Cancer Centre**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? ☒ a specialist in the treatment of people with this condition? ☒ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	**x** yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☒ yes

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tivozanib for treating renal cell carcinoma [ID591]

Thank you for agreeing to give us a statement on your view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name:
Professor John Wagstaff

Name of your organisation
Swansea University and Abertawe Bro Morannwg University Health Board

Are you (tick all that apply):

- ✓a specialist in the treatment of people with the condition for which NICE is considering this technology?
- ✓a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- ✓an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

Links with, or funding from the tobacco industry - please declare any direct or indirect links to, and receipt of funding from the tobacco industry:

I do not have any links with or funding from the tobacco industry.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

The advantages and disadvantages of the technology

The current licensed and NICE approved first line therapy for patients with locally advanced (inoperable) and metastatic renal cell carcinoma are sunitinib and pazopanib. Interleukin-2 (a cytokine) is also an option but very few patients are eligible for this therapy. Interferon alpha (also a cytokine) is now very rarely used as a first line option for these patients.

Pazopanib and sunitinib were compared with one another in the COMPARZ trial (New Eng. J. Med. 2013; 369:722-731 & New Eng. J. Med. 2014; 370:1769-1770). The key outcomes are listed in the table below. Data from the TIVO 1 trial (J Clin. Oncol. 2013; 31:3791-3799) which compared tivozanib with sorafenib have also been included.

	Pazopanib	Sunitinib	Tivozanib	Sorafenib
Progression free survival (months)	8.4	9.5	12.7	9.1
Response rate (%)	31	29.1	33.1	23.3
Overall survival (months)	28.3	29.1	28.8	29.3
Discontinuation due to AEs (%)	24	20	4.0	5.0
Post study treatment (%)	55	54	26	65
Median duration of treatment (months)	8.0	7.6	12.0	9.5
Treatment delays (%)	44	49	19	43
Dose reductions (%)	44	51	19	36

Progression free survival (PFS) was the primary endpoint of both trials reported above. Tivozanib had numerically the longest PFS of all four drugs being approximately one third longer than the other three agents. Response rates for Pazopanib, sunitinib and tivozanib are similar at around 30%. Experts in the field generally accept that PFS is a good surrogate for overall survival (OS). In this case, however tivozanib was inferior to sorafenib. This is the reason that the US FDA did not approve tivozanib for first line use in the USA. The data were however confounded by the very high subsequent treatment rates for sorafenib (65%) compared with tivozanib (25%). This was largely due to the lack of availability of second and subsequent lines of treatment available in Easter Europe and Russia.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Post trial treatment rates for pazopanib and sunitinib in the COMPARZ trial were equilvalent. In conclusion my view is that the efficacy of pazopanib, sunitinib and tivozanib are at least equivalent with some evidence from PFS that tivozanib may be superior.

If efficacy is equivalent the choice of which drug to use in first line will depend on tolerability. In the COMPARZ and Pisces trials (*Journal of Clinical Oncology* 2014; 32:1412-1418) significantly more patients preferred pazopanib (70%) over sunitinib (22%); 8% expressed no preference ($P < .001$). Both treatment dose reductions and delays were higher for pazopanib (44 & 44%) than for tivozanib (19 & 19%). Treatment duration was also longer for tivozanib (12.0 months) compared with pazopanib (8.0 months). Discontinuation due adverse events was also lower with tivozanib (4.0%) compared with pazopanib (24%). All of these data suggest that tivozanib may be a better tolerated treatment than pazopanib. The only way to be sure of this would be to conduct a patient preference trial similar to the PISCES trial referenced above. AVEO, the sponsor of tivozanib in the USA, were intending to conduct such a study prior to the FDA declining to give them a licence. I would strongly recommend that such a trial be mandated.

Equality and Diversity

I do not believe that there are any impediments to access to this drug based on equality and diversity

Any additional sources of evidence

I know of no additional evidence largely because tivozanib has not be used extensively in England and Wales. I am currently principle investigator in Swansea for the TIVO 3 trial which is comparing tivozanib with sorafenib as second or third line therapy. My initial experience of using this drug fits with the tolerability seen in the TIVO trial.

Implementation issues

I note that the the full European licence indication is: "first line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR and mTOR pathway inhibitor-naïve **following disease progression after one prior treatment with cytokine therapy for advanced RCC**." If this is the case then there will be very little uptake of the drug because only a handful of patients in England and Wales receive a first line cytokine in the form of interleukin-2. If NICE approve the drug for first line in treatment naive patients it would replace either pazopanib or sunitinib. This means that its usage would not require extra resource in the NHS in England and Wales.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Patient/carer expert statement (STA)

Renal cell carcinoma (advanced) - tivozanib

[ID591]

Thank you for agreeing to give us your views on this treatment that is being appraised by NICE and how it could be used in the NHS. Patients, carers and patient organisations can provide a unique perspective on conditions and their treatment that is not typically available from other sources. We are interested in hearing about:

- the experience of having the condition or caring for someone with the condition
- the experience of receiving NHS care for the condition
- the experience of having specific treatments for the condition
- the outcomes of treatment that are important to patients or carers (which might differ from those measured in clinical studies, including health-related quality of life)
- preferences for different treatments and how they are given
- expectations about the risks and benefits of the treatment.

We have already asked your nominating organisation to provide an organisation's view. We are asking you to give your views as an individual whether you are:

- a patient
- a carer (who may be voicing views for a patient who is unable to) or
- somebody who works or volunteers for a patient organisation.

To help you give your views, we have provided a questionnaire. You do not have to answer every question — the questions are there as prompts to guide you. The response area will expand as you type. The length of your response should not normally exceed 10 pages.

1. About you

Your name: Lucy Willingale
Name of your nominating organisation: KCUK
Do you know if your nominating organisation has submitted a statement?

☐X Yes ☐ No

Do you wish to agree with your nominating organisation's statement?

☐X Yes ☐ No

(We would encourage you to complete this form even if you agree with your nominating organisation's statement.)

Are you:

- a patient with the condition?

☐ Yes ☐X No

- a carer of a patient with the condition?

☐ Yes ☐X No

- a patient organisation employee or volunteer?

☐X Yes ☐ No

Do you have experience of the treatment being appraised?

☐X Yes ☐ No

If you wrote the organisation submission and do not have anything to add, tick here X☐ (If you tick this box, the rest of this form will be deleted after submission.)

Tivozanib for treating renal cell carcinoma [ID591]

STA REPORT

This report was commissioned by the NIHR HTA Programme as project number 16/56/14

BMJ Technology Assessment Group

Tivozanib for treating renal cell carcinoma

Produced by: BMJ Technology Assessment Group (BMJ-TAG)

Authors: Steven J Edwards, Head of Health Technology Assessment, BMJ-TAG, London

Kayleigh Kew, Health Technology Assessment Analyst, BMJ-TAG, London

Tracey Jhita, Health Economics Manager, BMJ-TAG, London

Samantha Barton, Senior Health Technology Assessment Analyst, BMJ-TAG, London

Fatima Salih, Health Economist, BMJ-TAG, London

Natalie Masento, Associate Health Technology Assessment Analyst, BMJ-TAG, London

Correspondence to: Steven J Edwards, BMJ-TAG, BMJ, BMA House, Tavistock Square, London, WC1H 9JP.

Date completed: 19/06/2017

Source of funding: This report was commissioned by the NIHR HTA Programme as project number 16/56/14

Declared competing interests of the authors:
Description of any pecuniary relationship with sponsors, both personal and of the TAR Centre. If there are none, please state 'none'.

Acknowledgements:
The ERG would like to thank Dr Penny Kechagioglou (Consultant Clinical Oncologist, University Hospitals Coventry and Warwickshire NHS Trust), for providing clinical advice throughout the project; and Dr Naveed Sarwar (Consultant Medical Oncologist, Imperial College Healthcare NHS Trust) and Dr Lisa Pickering (Consultant Medical Oncologist, St George's University Hospitals NHS Trust) for providing feedback on the clinical sections of the report.

Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR HTA Programme. Any errors are the responsibility of the authors.

This report should be referenced as follows: Edwards SJ, Kew KM, Jhita T, Barton S, Salih F, Masento N. Tivozanib for treating renal cell carcinoma: A Single Technology Appraisal. BMJ Technology Assessment Group, 2017.

Declared competing interests of the authors:
No competing interests were declared which affect the impartiality of this report. BMJ Technology Assessment Group (BMJ-TAG) and the editorial team of The BMJ work independently to one another. The views and opinions expressed in this report are those of the BMJ-TAG.

Contributions of authors:

Steven J Edwards	Critical appraisal of the company's submission; validated the statistical analyses; provided feedback on all versions of the report. Guarantor of the report.
Kayleigh M Kew	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and drafted clinical sections of the report.
Tracey Jhita	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Samantha Barton	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; and drafted clinical sections of the report.
Fatima Salih	Critical appraisal of the company's submission; critical appraisal of the economic model; cross checking of company's search strategies; critical appraisal of the economic evidence; carried out the economic analyses; and drafted the economic sections
Natalie Masento	Critical appraisal of the company's submission; critical appraisal of the clinical evidence; validated the company's search strategies and quality assessments; and drafted the clinical sections.

All authors read and commented on draft versions of the ERG report.

TABLE OF CONTENTS

LIST OF BOXES

LIST OF TABLES

LIST OF FIGURES

TABLE OF ABBREVIATIONS

Abbreviation	In full
AE	Adverse events
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
BSC	Best supportive care
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CR	Complete response
CrI	Credible interval
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTSQ	Cancer Therapy Satisfaction Questionnaire
DIC	Deviance Information Criterion
DSU	Decision support unit
EAU	European Association of Urology
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EQ-5D	EuroQol-5 Dimensions
ERG	Evidence review group
ESMO	European Society for Medical Oncology
EU	European Union
FACT-G	Functional Assessment of Cancer Therapy-General
FCE	Finished consultant episodes
FDA	Food and Drug Administration
FE	Fixed effects
FKSI-19	FACT Kidney Symptom Index – 19
FKSI-DRS	FACT Kidney Symptom Index–Disease-Related Symptoms
FP	Fractional polynomial
GP	General practitioner
HFS	Hand-foot syndrome
HR	Hazard ratio
HRQoL	Health related quality of life
HSUV	Health-state utility value
ICER	Incremental cost-effectiveness ratio
IFN	Interferon
IL	Interleukin
IMDC	International Metastatic Renal Cancer Database Consortium
IPCW	Inverse Probability of Censoring Weighed
IRR	Independent radiology review
ISRCTN	International Standard Randomised Controlled Trial Number

ITT	Intention to treat
IVR/IWR	Interactive Voice Response/Interactive Web Response
KM	Kaplan Meier
KPS	Karnofsky performance status
MA	Marketing authorisation
MAIC	Matched adjusted indirect comparison
MCS	Mental Component summary
µg	Microgramme
mg	Milligramme
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
mTOR	Mammalian target of rapamycin
MU	Mega unit
NA	North America
nCC	Non-clear cell
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PCS	Physical Component summary
PD	Progressive disease
PFS	Progression-free survival
PH	Proportional hazards
PPS	Post-progression survival
PR	Partial response
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCC	Renal cell carcinoma
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RPSFT	Rank Preserving Structural Failure Time
RR	Relative risk
SB	Single blind
SD	Stable disease
SD	Standard deviation
SE	Standard error
SEER	Surveillance, Epidemiology and End Results
SmPC	Summary of Product Characteristics
SQLQ	Supplementary Quality of Life Questionnaire

STA	Single technology appraisal
SW	South-west
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TNM	Tumour node metastases
TRAE	Treatment-related adverse event
ULN	Upper limit of normal
VEGFR-TKI	Vascular endothelial growth factor receptor tyrosine kinase inhibitor
VEGFR	Vascular endothelial growth factor receptor
VHL	von Hippel-Landau
VTE	Venous thrombotic events
WHO ICTRP	World Health Organisation International Clinical Trials Registry Platform
WTP	Willingness-to-pay

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company (Fotivda®; EUSA Pharma Ltd) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of tivozanib in the treatment of renal cell carcinoma (RCC).

At the time of writing this report, marketing authorisation had not been granted for the use of tivozanib in RCC and the Committee for Medicinal Products for Human Use (CHMP) had not yet issued a positive opinion.

The clinical evidence presented in the company submission (CS) was based on the randomised controlled trial (RCT), TIVO-1, and its extension study (AV-951-09-902). The study recruited 517 patients with metastatic or recurrent RCC with a clear cell component, good performance status, and prior nephrectomy; 70% were treatment naïve and 30% had received one prior systemic therapy for metastatic RCC. The Evidence Review Group (ERG) agrees with the company's proposed positioning of tivozanib as a first-line treatment for people with recurrent or metastatic RCC, and considers those who were treatment-naïve in TIVO-1 relevant to the population outlined in the NICE final scope.

The final scope issued by NICE also indicated that people who had received prior treatment for metastatic RCC are of interest to the decision problem, but the scope did not specify type of prior therapy. In TIVO-1, those who were not treatment naive had received predominantly cytokines before being treated with tivozanib; this is in line with the proposed marketing authorisation of tivozanib, which outlines the eligible population for tivozanib as those who failed prior treatment with interferon-alpha (IFN-α) or interleukin-2 (IL-2). The ERG believes no relevant evidence was submitted for a pretreated population because cytokines, the most common prior treatment in TIVO-1, have been replaced as first-line treatment in UK clinical practice by pazopanib and sunitinib.

The ERG considers only pazopanib and sunitinib to be relevant comparators for the treatment-naïve population; the ERG's clinical experts confirm that cytokines are no longer a relevant comparator for those who are treatment naive and thus are not relevant for this decision problem.

All clinically relevant outcomes were reported in the CS, except for comparative effect estimates for health-related quality of life (HRQoL).

1.2 Summary of clinical effectiveness evidence submitted by the company

The direct evidence for tivozanib comprised TIVO-1 and the extension study, and two Phase II studies which were summarised as supplementary evidence. TIVO-1 was a parallel, open-label, Phase III trial which randomised 517 patients with metastatic or recurrent RCC to tivozanib or sorafenib. Patients who progressed on sorafenib in TIVO-1 were offered subsequent treatment with tivozanib in the extension study. The study is described as a one-way crossover because there was no provision of subsequent therapy for patients randomised to tivozanib. The study was generally of good methodological quality but was unblinded and the one-way crossover design makes overall survival (OS) difficult to interpret.

For the treatment-naïve population in TIVO-1, OS unadjusted for crossover favoured sorafenib (HR 1.23, 95% CI: 0.90 to 1.67) and progression-free survival (PFS) based on independent radiology review (IRR) favoured tivozanib by around 3 months (HR 0.76, 95% CI: 0.58 to 0.99; though proportional hazards do not hold). ORR, only available for the full population, favoured tivozanib at the main data cut (OR 1.623, 95% CI: 1.101 to 2.391, p=0.013), but not when the analysis included patients who remained on their as-randomised treatment in the extension study (OR 1.057, 95% CI: 0.744 to 1.572, p = 0.681). Compared with sorafenib, tivozanib was associated with lower rates of diarrhoea, hand-foot syndrome, alopecia, increased aspartate aminotransferase (AST), increased amylase, increased lipase and hypophosphataemia of any grade, and lower rates of Grade 3 diarrhoea, hand-foot syndrome, increased lipase and hypophosphatemia. Tivozanib was associated with higher rates of hypertension and dysphonia of any grade and more patients in the tivozanib group had fatal treatment-emergent adverse effects (TEAEs) than the sorafenib group (10.8% vs 5.8%).

The NICE final scope did not list sorafenib as a comparator of interest to the decision problem, and so the company estimated tivozanib's clinical effectiveness compared with pazopanib and sunitinib, which were specified comparators of interest for treatment-naïve RCC using network meta-analysis (NMA). The ERG had concerns that proportional hazards did not hold for PFS and OS, and that there was substantial clinical heterogeneity across the NMA that could be reduced by limiting the network to only the studies required to link tivozanib with pazopanib and sunitinib. Subsequently, the company submitted new analyses implementing a fractional polynomial NMA based on a simplified network structure (4 studies instead of 19), for OS and PFS.

The four studies required to link tivozanib with pazopanib and sunitinib for the treatment-naïve population are COMPARZ (pazopanib versus sunitinib), CROSS-J-RCC (sorafenib versus sunitinib), SWITCH (sorafenib versus sunitinib) and TIVO-1 (tivozanib versus pazopanib). Study baseline characteristics are comparable and were considered representative of a population who might be eligible for treatment with tivozanib in the UK; median age ranged from 59 to 67 and participants were more often male in line with prevalence in the population. Most or all patients had clear cell RCC (87 to 100%), prior nephrectomy (82 to 100%), intermediate prognostic status (with very few or none in the poor category), and two or more metastatic sites.

The ERG considers OS results from the company's FP-based NMA implausible because they show pazopanib to be much less effective than sunitinib, which contradicts the underlying head-to-head evidence from COMPARZ. Results from the OS FP-based NMA are likely to be confounded because the company did not include crossover-adjusted results for TIVO-1, and adjusted results were not available for CROSS-J-RCC and SWITCH.

The curves from the company's FP-based NMA suggest PFS with tivozanib may be similar to sunitinib and that both may have a slight benefit over pazopanib, though uncertainty around the estimates may outweigh the apparent differences. The company's results are consistent with head-to-head results from COMPARZ. The ERG notes several issues with the FP-based NMAs submitted by the company for OS and PFS and considered that various checks should be performed and additional analyses explored to reduce uncertainty in the results (see Section 1.5).

Odds ratios for response and adverse effects were generated using NMA of the number of patients experiencing an event in each treatment group. Due to time constraints at the clarification stage, the company was unable to update their response NMA to reflect the treatment-naïve population, and the available trial data does not support an NMA for HRQoL.

NMA results show lower incidence of Grade 3 or higher diarrhoea with tivozanib compared with sunitinib and pazopanib, but most results were not statistically significant. The ERG does not consider results from the NMAs to provide robust or consistent evidence to support the company's assertion that tivozanib has a favourable safety profile compared with pazopanib and sunitinib; the ERG considers the company's safety conclusions based on single-arm comparisons between studies to be unreliable.

1.3 Summary of cost-effectiveness evidence submitted by the company

The company submitted a *de novo* economic model developed using Microsoft Excel® that compared tivozanib against sunitinib, pazopanib and IFN-α. As described in Section 1.1, the company did not consider IFN-α, which is a cytokine, a relevant comparator by the company based on the reasoning that cytokines are rarely used as first line treatment for advanced RCC in the UK, a view supported by the ERG's clinical experts. As such the main comparators of interest for the pairwise analyses are sunitinib and pazopanib. As mentioned previously, the population of the TIVO-1 trial consisted of patients who were untreated (hereafter referred to as treatment naïve) and those who had previously been treated with cytokines. To maintain the relevance of the analyses to the UK context, the company focused their analyses on the treatment naïve population because the patient population in the UK who would be pre-treated with cytokines is limited.

The structure of the economic model was based on a partitioned survival model comprising three health states: alive pre-progression, alive post-progression, and dead. All patients enter the model in the alive

pre-progression health state and could transition to alive post-progression or death at each of the one-week cycles. Once a patient enters the alive post-progression health state, they remain in this state until death. The model time horizon is 10 years, which is based on the company's estimation that most patients would have died by this time point. The cycle length of one-week was justified by the company as sufficiently long enough to capture differences in costs and effects between treatments.

Treatment effectiveness estimates for PFS and OS implemented in the model were obtained from a FP-based NMA using the simplified network summarised in Section 1.2. The company explored a range of first order FP-based NMAs and one second order FP-based NMA (P1= -2, P= -1) for the extrapolation of PFS and OS. The company selected the second order FP-based NMA (P1= -2, P= -1) as this was the model with the lowest Deviance Information Criterion (DIC) statistic, which is an indicator of good statistical fit to the underlying data. Parameter (β_n) estimates based on the selected FP were implemented in the model using survival functions to produce the treatment specific PFS and OS estimates for each cycle of the model for all treatments.

Time on treatment was modelled using parametric survival distributions for PFS, as specified by the marketing authorisations for the treatments modelled (Table 67, page 150 of the CS) and published papers for sunitinib and pazopanib to estimate acquisition costs of active treatment. The list price for tivozanib is [redacted]. The acquisition costs for sunitinib and pazopanib in the base case analysis incorporate nationally implemented patient access schemes. The company assumed the relative dose intensity for all treatments was 100%. Disease management costs in the model are based on monthly oncologist visits and computed tomography scans every 3 months.

Costs of progressive disease were based on 60% of patients receiving axitinib as second line therapy with associated monitoring costs and 40% of patients receiving best supportive care (BSC) which consists of monitoring visits with an oncologist. Patients are assumed to receive axitinib upon progression for the remaining duration of the model time horizon (10 years).

The health state utility values (HSUVs) used in the model are based on EuroQoL-5 Dimensions (EQ-5D) data collected in the TIVO-1 trial for the overall intention-to-treat (ITT) population. Mean utility values of 0.726 and 0.649 are assumed for patients in the model regardless of treatment arm prior to progression and after progression, respectively.

Odds ratios for key adverse events (AE), which were defined as Grade 3 or more for more than 5% of the treatment population, were generated based on the company's original OR NMA and applied to baseline incidence rates for tivozanib from the TIVO-1 trial to generate incidence of AEs for sunitinib and pazopanib. Key AEs included anaemia, asthenia/fatigue, hand-foot syndrome (HFS), hypertension and diarrhoea. Costs of AEs were based on weighted management costs for each type of AE. The

company applied a utility decrement attributable to adverse events to the mean utility value for PFS along with mean durations of AEs in the model to reflect the impact of these events on patients' quality of life.

A range of one-way sensitivity analyses and scenario analyses were performed, as well as a probabilistic sensitivity analysis to test the impact of uncertainty of all relevant parameters on the model results.

The results from the company's base case show that the incremental cost-effectiveness ratio (ICER) for tivozanib versus sunitinib is £52,533 (south west quadrant of the cost-effectiveness plane) and for tivozanib versus pazopanib is £36,757. The corrected base case ICERs based on the ERG's model corrections are £48,222 (south west quadrant of the cost-effectiveness plane) for tivozanib versus sunitinib and dominant for tivozanib versus pazopanib.

1.4 ERG commentary on the robustness of evidence submitted by the company

1.4.1 Strengths

Clinical

- The CS was based on TIVO-1, a well-conducted large multicentre randomised controlled trial. The ERG considers the study to be largely free of internal biases.

- The ERG considers the treatment-naïve population of TIVO-1 (70%) representative of treatment-naïve patients who might be eligible for treatment with tivozanib in the UK. Some characteristics (prior nephrectomy, ECOG score) suggest the population of TIVO-1, and other studies in the NMA, might have more favourable prognosis than the full population outlined in the NICE final scope.

- The outcomes in TIVO-1 matched those listed in the NICE final scope.

- NMAs were conducted to provide evidence for the comparators of interest, pazopanib and sunitinib, with details of the methods used being reported in a sufficiently transparent manner to enable replication.

- While there were shortcomings of the original NMAs, the company conducted a large amount of additional analyses during the clarification process to provide more meaningful results, particularly for OS and PFS.

Economic

The economic model was straight forward and easy to navigate. The ERG did not encounter any major difficulty validating the methodologies applied in the economic model.

1.4.2 Weaknesses and areas of uncertainty

Clinical

- The ERG considers there to be limitations in the company's search strategy and methods of review; there was no description of duplicate processes and a lack of transparency in the way eligibility criteria were applied.

- Results of two Phase II studies were submitted as supplementary non-randomised data, but a randomised preference study of tivozanib versus sunitinib was omitted, despite being listed as contributing to the safety data on which the summary of product characteristics (SmPC) is based.

- The design of TIVO-1 and the concurrent extension study made participant flow difficult to disentangle, and caused substantial uncertainty regarding OS. There were multiple data cuts across the two studies and several data inconsistencies were noted.

- The CS did not provide evidence relevant to a pretreated population because the 30% who were pretreated in TIVO-1 had received different treatments (primarily cytokines) than would be given in the UK.

- TIVO-1 results for OS are expected to be confounded by imbalance in subsequent targeted therapies, primarily due to one-way crossover from sorafenib to tivozanib: 66.3% of the sorafenib group received subsequent targeted therapies (63% received tivozanib) and 20.3% of the tivozanib group. The two trials providing the direct comparison of sorafenib and sunitinib are likely to be confounded by higher rates of crossover from sorafenib to sunitinib than from sunitinib to sorafenib in both trials.

- The company provided methods and results of two approaches to minimise the confounding effect of treatment crossover on OS in TIVO-1. The company did not provide alternative NMA results including the TIVO-1 adjusted results because only unadjusted results were available for the other studies in the NMA.

- Results for OS, including the ERG's preferred analysis presented in Section 1.5, should thus be interpreted with caution because the unadjusted results from direct comparisons are likely to be confounded by treatment crossover. TIVO-1 crossover-adjusted results may overestimate the

effectiveness of tivozanib because the analyses did not adjust for subsequent targeted therapy received in the tivozanib group (20.3%).

- The ERG's validation of the OS and PFS FP-based NMAs uncovered flaws in the results and the way in which data implemented in the economic model; the company's curves for OS were implausible given the underlying data and estimated survival at 10 years.

- A matched-adjusted indirect comparison (MAIC) matching the TIVO-1 tivozanib group to the COMPARZ trial, suggested to the company as an option at the clarification stage, may provide more reliable results for OS because it would not rely on the within-study comparison with sorafenib.

Economic

From the time the ERG received the CS until submission of its report, the ERG has evaluated three iterations of the economic model, with each version employing a different method to estimate treatment effectiveness: proportional hazards modelling, a parametric NMA and finally the FP-based NMA. ICERs generated varied markedly across the three models, with ICERs ranging from £19,480 to £71,104 (SW quadrant of the cost-effectiveness plane) for tivozanib versus sunitinib and £36,757 to £97,130 (SW quadrant of the cost-effectiveness plane) for tivozanib versus pazopanib. In the first instance, the company did not present a thorough curve fit exercise as recommended by the Decision Support Unit technical support document (DSU TSD) 14. The ERG considers that if the company had used the recommended Survival Model Selection Process Algorithm and completed the Survival Model Selection for Economic Evaluations Process (SMEEP) chart when preparing the CS, this would have revealed that their initial choice of modelling was inappropriate for the data being used and other methods, such as a parametric NMA and FP-based NMA, could have been explored more thoroughly. The ERG raised these issues during the clarification stage, and appreciates that the company had limited time to implement more appropriate methods.

The ERG received the company's revised economic model using the FP-based NMA two weeks before the ERG report was due to be submitted to NICE. Despite the limited time to review the model, the ERG discovered a fundamental flaw with the survival calculation the company used to generate the PFS and OS curves based on the parameters generated by the selected FP-based NMA. The company's calculation estimated the within period hazard rather than calculating the cumulative hazard within a model cycle, which would produce area under the curve estimates. The incorrect calculation resulted in implausible OS curves, rendering any estimates of cost-effectiveness produced by the model to be meaningless. The ERG considers that this error could have been spotted by the company and rectified if the curves produced by the model were visually inspected.

The ERG corrected the calculation, but found that the parameter estimates generated by the company produced OS curves that didn't pass face validity or clinical validity. Notably the relative effectiveness between pazopanib and sunitinib observed in the COMPARZ trial was not maintained in the results of the FP-based NMA and that the curves produced implausibly long tails that would not be seen in clinical practice. As such, the ERG attempted to reproduce the FP parameter estimates used in the economic model using the WinBUGS dataset supplied by the company. The ERG was unable to replicate the parameter estimates generated by the company but recognise the company had stated to NICE that they had some difficulty conducting the FP-based NMA. The ERG implemented its own FP-based NMA estimates in the model, which produced significantly different curves that, although better reflections of the underlying data, still produced implausibly long tails.

The company explored a range of first order FP-based NMAs and one second order FP-based NMA to select the best fitting curve for the extrapolation of PFS and OS for all treatments. The ERG considers that the company should have explored further second order FP-based NMAs as the nature of the second order FP means that it has greater flexibility and so is expected to produce better fitting curves compared with the first order. As only one second order FP-based NMA was considered (P1= -2, P2= -1), it is not definitive that this permutation of powers would be the best fit out of all the second order FP permutations available. The ERG explored a range of other second order FP-based NMAs and these are discussed further in Section 1.5.

It is important that the issue of confounding seen for OS in the TIVO-1 trial due to treatment crossover, as described above in the clinical weaknesses sub-section, should not be overlooked when interpreting the results of the analyses carried out by the ERG and the company. Any treatment effectiveness estimates produced either by the company or the ERG will be subject to a high degree of uncertainty as the company did not implement crossover adjusted data in the NMA and the ERG was unable to modify this in the exploratory analyses.

The following points relate to secondary issues in the economic model but are nonetheless relevant to highlight. In addition to calculation errors in the economic model, the ERG also identified inaccuracies in the context of the population used in the model. The company stated that they had used the treatment naïve population. However, the ERG discovered the following parameters which related to the ITT population, that is, including those who had received prior treatment:

- Underlying KM PFS and OS data obtained from the TIVO-1 trial for tivozanib used in the original model. The company admitted that this was an error and corrected this in their response to clarification questions.

- Incidence of TEAEs from TIVO-1 for tivozanib. The ERG obtained the treatment naïve rates from the company's OR NMA for AEs and implemented them in the ERG exploratory analyses discussed in Section 1.5.

- Utilities for the alive pre-progression and alive post-progression health states. However, this was a limitation of the data collected in the trial as it did not distinguish between patients who were treatment naïve or pre-treated with cytokines.

The ERG considers the company's approach to modelling subsequent therapies to be inappropriate. Subsequent therapy costs assumed in the model do not reflect the current treatment pathway for patients with recurrent or metastatic RCC. Currently in the NHS, patients can receive axitinib, nivolumab and everolimus if they progress after first line of therapy. However, the company assumes that 60% of patients receive axitinib after discontinuing treatment, with remaining patients receiving BSC. The ERG's clinical experts stated that based on the current treatment options available they would expect patients to be split across the three treatment options with only 10% of patients receiving BSC. Furthermore, the company assumes that the patients in the model who go on to receive axitinib, continue receiving it until they die, with the cost of axitinib making up more than 50% of total costs for all treatments, which the ERG considers does not reflect clinical reality. The ERG produced an alternative scenario modelling subsequent therapy and this is discussed further in Section 1.5.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG conducted a series of exploratory analyses to test the impact of changes in the data and assumptions used by the company on the ICER. The choice of scenarios was driven by key issues found by the ERG around the modelling of treatment effectiveness, adverse events and costs (particularly costs of subsequent therapies). The scenarios which had a substantial impact on the ICER were as follows:

- Implementation of the alternative second order FP-based NMA (P1= -2, P2= -1.5) for OS. This was found to be the best fitting curve out of the options assessed by the ERG based on face validity and clinical validity. This increased the magnitude of the ICER for tivozanib versus sunitinib (from £48,222 to £55,586) and changed the direction of the ICER for tivozanib versus pazopanib from dominant to under £50,000 (SW quadrant of the cost-effectiveness plane);

- Implementation of the alternative second order FP-based NMA curves. Two curves were selected by the ERG as having equal goodness of fit. These curves were the second order FP (P1= -3, P2= -3) and the second order FP (P1= -3, P2= -2.5). Both curves had a significant

impact on the ICER for tivozanib versus pazopanib, changing it from dominant to below £10,000;

- Assuming equal efficacy for PFS and OS using the company's preferred second order FP-based NMA option (P1= -2, P2= -1) but using the ERG's estimates. This scenario was a cost minimisation exercise and found that tivozanib dominates sunitinib and pazopanib, respectively. These results are primarily driven by statistically non-significant differences in AEs; and

- ERG's alternative modelling of subsequent therapy costs which assumes a subsequent therapy profile that includes axitinib, everolimus and nivolumab, which are all approved second line RCC treatments in the NHS. A one-off total weighted cost for subsequent therapy was then calculated based on proportions of patients receiving each treatment (informed by the ERG's clinical expert), mean duration, list price and RDI for each treatment. Costs for nivolumab included administration costs and wastage.

The results for the ERG scenario analysis should be interpreted with caution as the company's parameter estimates used to extrapolate OS and PFS could not be validated by the ERG and thus may not be correct.

The ERG considers that the company's base case is based on flawed assumptions and incorrect data and thus, produced a preferred base case to estimate more plausible ICERs for tivozanib versus sunitinib and pazopanib, respectively. The ERG's preferred base case incorporates the following changes and assumptions made to the corrected company base case ICER:

- Implementation of the alternative second order FP-based NMA (P1= -2, P2= -1.5) for OS;

- Implementation of the alternative second order FP-based NMA (P1= -3, P2= -2.5) for PFS. This curve was selected out of the two best fitting options available as it produces conservative estimates for PFS. Implementation of the alternative second order FP-based NMA (P1= -3, P2= -3) is explored in a scenario analysis around the ERG preferred base case;

- Alternative modelling of AEs, which include the following changes:

    - Use of treatment naïve AE incidence rates for tivozanib (from the TIVO-1 trial). In the company's revised base case, the incidence rates used relate to the overall ITT population which is incorrect as the ORs applied are for the treatment naïve population;

    - ERG estimates of AE ORs based on the simplified NMA;

- ERG clinical expert resource use assumptions for AEs and
- Removal of AE HSUV decrements.

- Inclusion of blood tests for PFS disease management costs;
- Inclusion of relative dose intensities for treatments; and
- ERG's alternative modelling of subsequent therapy costs.

Table A presents the cumulative impact of each change on the company's corrected base case ICER, resulting in the ERG preferred ICER. Two scenarios around the ERG base case were conducted. One exploring the use of the alternative PFS curve on the ERG preferred base case and the second was a cost minimisation scenario exploring the impact of assuming equal efficacy for both PFS and OS for all treatments. Results of the first scenario demonstrates that tivozanib is dominated by both sunitinib and pazopanib, thus the ICER is extremely sensitive to changes in the curve choice for PFS. The cost minimisation scenario estimates that when treatment effectiveness is equal for all treatments, tivozanib is more expensive than sunitinib (£6) and pazopanib (£1,087).

The estimates produced by the economic model for the ERG's preferred base case ICERs (and indeed all other analyses presented throughout Section 5) should be viewed with caution as there is a substantial amount of uncertainty surrounding the underlying data, particularly the survival data, used to populate the model. The ERG has attempted to be conservative in its assumptions to reduce the uncertainty, however, as crossover adjusted data for OS were not available for use in the analysis, the confounded estimates are likely to introduce significant bias in the results. As mentioned throughout the report, the ERG are unable to predict the direction and magnitude of the bias on the ICERs produced by the model.

Table A. Results of ERG's preferred base case

Results per patient	Tivozanib (1)	Sunitinib (2)	Pazopanib (3)	Incremental value	
				(1-2)	(1-3)
Corrected company base case					
Total costs (£)	£71,281	£99,073	£71,369	-£27,792	-£88
QALYs	1.84	2.42	1.78	-0.58	0.06
ICER				**£48,222 (SW quadrant)**	**Dominant**
Second order FP-based NMA (P1= -2, P2= -1.5) for OS					
Total costs (£)	£76,997	£91,154	£94,896	-£14,156	-£17,899
QALYs	1.97	2.23	2.34	-0.25	-0.36
ICER				**£55,586 (SW quadrant)**	**£49,094 (SW quadrant)**
ICER with all changes incorporated				**£55,586 (SW quadrant)**	**£49,094 (SW quadrant)**
Second order FP-based NMA (P1= -3, P2= -2.5) for PFS					

Total costs (£)	£71,556	£98,916	£71,328	-£27,361	£228
QALYs	1.83	2.41	1.79	-0.58	0.04
ICER				**£47,180 (SW quadrant)**	**£5,161**
ICER with all changes incorporated				**£53,144 (SW quadrant)**	**£46,763 (SW quadrant)**
Alternative modelling for AEs					
Total costs (£)	£71,225	£99,035	£71,351	-£27,810	-£125
QALYs	1.84	2.43	1.79	-0.58	0.05
ICER				**£47,640 (SW quadrant)**	**Dominant**
ICER with all changes incorporated				**£51,729 (SW quadrant)**	**£46,585 (SW quadrant)**
Inclusion of blood tests for PFS disease management costs					
Total costs (£)	£71,325	£99,113	£71,405	-£27,787	-£79
QALYs	1.84	2.42	1.78	-0.58	0.06
ICER				**£48,214 (SW quadrant)**	**Dominant**
ICER with all changes incorporated				**£51,717 (SW quadrant)**	**£46,576 (SW quadrant)**
Inclusion of relative dose intensities for treatments					
Total costs (£)	£69,587	£95,222	£68,045	-£25,634	£1,542
QALYs	1.84	2.42	1.78	-0.58	0.06
ICER				**£44,478 (SW quadrant)**	**£27,756**
ICER with all changes incorporated				**£43,981 (SW quadrant)**	**£41,583 (SW quadrant)**
Alternative modelling of subsequent therapy costs					
Total costs (£)	£46,821	£49,796	£45,011	-£2,975	£1,810
QALYs	1.84	2.42	1.78	-0.58	0.06
ICER				**£5,162 (SW quadrant)**	**£32,570**
ICER with all changes incorporated				**£1,624 (SW quadrant)**	**Dominated**
ERG's preferred base case ICER				**£1,624 (SW quadrant)**	**Dominated**

Abbreviations in table: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; FP, fractional polynomial; PFS, progression-free survival; OS, overall survival; SW, south-west; AE, adverse event.

2 BACKGROUND

2.1 Critique of company's description of underlying health problems

Section 3 of the company's submission (CS) provides an overview of the key aspects of renal cell carcinoma (RCC), including aetiology, the clinical pathway of care, and the impact on the quality of life (QoL) of people with the condition. The final scope issued by the National Institute for Health and Care Excellence (NICE)[1] for this Single Technology Appraisal (STA) indicates the population of interest to the decision problem to be adults with recurrent or metastatic RCC.

Overall, the Evidence Review Group (ERG) considers the CS to present a thorough, accurate overview of RCC (Box 1) and its management in UK practice. The ERG considers that greater detail on some aspects of RCC, particularly prognostic factors, would aid in understanding the challenges faced in treating the population that is the focus of this STA, and the discussion of clinical effectiveness of tivozanib. Thus, the ERG provides supplementary information where it considered appropriate.

All information presented in boxes in the ERG's report is taken directly from the CS, unless otherwise stated, and references have been renumbered.

Box 1. Overview of RCC (adapted and restructured from CS, pgs 36 and 37)

RCC encompasses a number of different types of tumours found in the kidney, each derived from the lining of the nephron. There are three main types: clear cell (70–80% of cases), papillary (10–15%) and chromophobe (3–5%) and several other rarer types.[2]

Patients may present with local or systemic symptoms, although most presentations are incidental and found on unrelated abdominal imaging. Local signs and symptoms include the classic triad of flank pain, gross haematuria and palpable abdominal mass, however, this is rare (6–10%) and correlates with aggressive histology and advanced disease.[3] Systemic symptoms can be due to metastases or paraneoplastic events related to secreted proteins, for example parathyroidhormone-related protein (causing hypercalcaemia), renin (causing hypertension), erythropoietin (causing an increase in red blood cells known as erythrocytosis) and fever or wasting syndromes.[2]

The American Joint Committee on Cancer (AJCC) tumour node metastases (TNM) system is used to grade RCC into stages I to IV. Locally advanced RCC, in which the tumour is either locally invasive and/or has spread to regional lymph nodes, is generally defined as stage III. Metastatic RCC, in which the tumour has spread beyond the regional lymph nodes to other parts of the body, is generally defined as stage IV.[3]

In many cases the disease is locally advanced or metastatic at the point of diagnosis. A quarter of RCC cases in England are diagnosed after presenting as an emergency. The proportion of patients presenting as an emergency rises with increasing age, reaching a peak in 85+ year-olds (50%).[4]

Indeed, of those patients recorded with a known stage at diagnosis in 2013 (71%), 18% presented with stage III (locally advanced disease) and 28% with stage IV (metastatic disease).[4] If we assume

that the distribution is similar in patients without a recorded stage at diagnosis then this equates to around 3,570 patients each year in England (46% of 7,760 patients with RCC). RCC is more common in men than in women with a ratio of 1:1.6.[4] RCC incidence also increases with age; in the UK between 2010 and 2012, three-quarters (76%) of cases were diagnosed in people aged 60 and over.[4] Risk factors for RCC include cigarette smoking (active and passive), obesity and hypertension, although most patients do not have an identifiable risk factor and the pathological mechanisms underlying the disease remain unclear.[2] Around 2-3% of cases are familial with an underlying genetic basis, the most common of which is VHL syndrome (1 in 36,000 births) which is associated with a number of tumours including clear cell RCC. Clear cell RCC in people with VHL syndrome is generally early in onset and multifocal. In contrast, in patients with non-inherited clear cell RCC onset tends to be late and unifocal. However, most patients with RCC will have somatic defects in the VHL gene.[2] At present there is no cure for patients with locally advanced or metastatic disease and prognosis in patients with late stage disease is generally poor, varying according to prognostic factors.
Abbreviations: CS, company submission; pgs, pages; RCC, renal cell carcinoma; VHL, von Hippel-Landau.

In their description of RCC (Box 1), the company outlines that stage of RCC is typically assessed using the American Joint Committee on Cancer (AJCC) tumour node metastases (TNM) system. The ERG notes that the TNM scale gives a detailed description of the characteristics of a cancer. Categorisation of a tumour is based on its size and extent (T), the number of nearby lymph codes with cancer (N) and whether the cancer has metastasised (M) to generate a "TNM" combination, for example, T1N0M0.[5] As the company alludes to, a simpler system for staging of a cancer involves grouping TNM combinations into less-detailed stages, from Stage 0 to Stage IV, where Stage 0 denotes presence of localised abnormal cells that might not be cancerous and Stage IV indicates metastatic disease (spreading to adrenal gland, metastatic involvement of regional lymph node(s), or distant metastases).[5] Stages I to III signify the presence of cancer, with increasing size and spread of tumour moving from a classification of Stage I to Stage III. Early stages of renal cancer (Stages I and II) can be asymptomatic, and the early stages of the disease are typically identified during abdominal investigations for unrelated symptoms: >50% of renal cancer are detected incidentally.[6] People presenting with symptoms characteristic of renal cancer, including blood in the urine, a lump or mass in the area of the kidney, and localised pain in the back, are typically diagnosed at more advanced stages (Stages III and IV) of the disease.[6]

As touched on by the company (Box 2), stage of renal cancer at diagnosis is a key prognostic factor. Those whose cancer has metastasised have a considerably poorer long-term prognosis, as illustrated by survival rates at five years by stage at diagnosis:[4]

- Stage I, 84% for men and 82% for women;

- Stage II, 92% for men and 73% for women;
- Stage III, 56% for men and 59% for women;
- Stage IV, 5% for men and 7% for women.

Box 2. Prognosis of RCC (adapted from CS, pg. 37)

At present there is no cure for patients with locally advanced or metastatic disease and prognosis in patients with late stage disease is generally poor, varying according to prognostic factors. OS in patients with metastatic disease is of the order of 8 months in patients with a poor prognosis according to the International Metastatic Renal Cancer Database Consortium (IMDC) model[a] rising to 3.6 years in those with a favourable prognosis.[3] Clinical studies in patients treated with sunitinib or pazopanib at first line have demonstrated OS of around 2 years (26.4 months with sunitinib in patients with metastatic disease[7] and 22.9 months with pazopanib in patients with advanced or metastatic disease[8]). In the COMPARZ study, which compared pazopanib with sunitinib, OS was 28.4 months and 29.3 months, respectively.[9] In the UK in 2014, there were 4,421 deaths from kidney cancer. Five-year survival for kidney cancer is 56%; however, survival rates vary considerably with age. Around three-quarters of people diagnosed aged 15–49 survive their disease for 5 years or more, compared with less than a third of people diagnosed aged 80 and over.[4]
[a] The International Metastatic Renal Cancer Database Consortium (IMDC) is used in metastatic disease and includes the following six prognostic risk factors: anaemia (haemoglobin <ULN), thrombocytosis (platelets >ULN), neutrophilia (neutrophils >ULN), Karnofsky performance status <80%, and <1 year from diagnosis to first-line targeted therapy. Favourable prognosis is defined as no prognostic factors, intermediate prognosis as 1-2 prognostic factors and poor prognosis as >3 factors.[10] Abbreviations: CS, company submission; pg., page; OS, overall survival; RCC, renal cell carcinoma; ULN, upper limit of normal.

In their submission, the company highlights life expectancy in those with locally advanced or metastatic disease is generally poor and varies with prognostic factors (Box 2), with no accompanying review in the overview of the health problem of the key risk factors influencing survival: a brief description of the International Metastatic Renal Cancer Database Consortium (IMDC) prognostic model is provided as a footnote. For information purposes when comparing populations from which evidence is derived on comparative clinical effectiveness of tivozanib, the ERG considers it useful to provide a brief overview of variables known to affect prognosis, and how the presence of a combination of risk factors is used to predict an individual's risk of disease progression and, hence, length of survival.

Five risk factors were initially identified as independent predictors of short survival in people with untreated metastatic RCC (Stage IV disease with presence of measurable lesions) about to receive interferon, collectively known as the Memorial Sloan Kettering Cancer Centre (MSKCC) model[11] (implemented in TIVO-1[12]):

- Karnofsky performance status <80%;

- Absence of prior nephrectomy (subsequently amended to "time from diagnosis to treatment of <1 year");
- Serum lactate dehydrogenase more than 1.5 times the upper limit of normal (ULN);
- Corrected serum calcium >10.0mg/dL;
- Anaemia (haemoglobin <ULN).

People with none of the adverse factors listed above were categorised as having a favourable prognosis (median overall survival [OS] more than 2 years), those with intermediate risk had one or two adverse factors (median OS of ~14 months) and those with three or more factors had a poor prognosis (median OS of 4.9 months).[11]

The MSKCC model was externally validated in people with untreated metastatic RCC (clinical or biopsy evidence of metastatic disease) and extended to include prior radiotherapy and number of individual organ metastatic sites involved (one organ versus two or more) as prognostic factors associated with shorter survival.[13]

As noted above, in their submission, the company refers to the IMDC model (Box 2), which identified prognostic factors in those with untreated metastatic RCC who went on to receive vascular endothelial growth factor (VEGF)-targeted therapy.[10] The IDMC scale includes the additional prognostic variables of neutrophilia (neutrophil count >ULN) and thrombocytosis (platelet count >ULN) and excludes serum lactate dehydrogenase more than 1.5 times ULN.

One component common to the scales used to determine prognosis is the Karnofsky performance scale (KPS), which is a tool used to assess the level to which a person's condition impedes their day-to-day functioning.[14] The KPS is based on a 100-point scale, in which the higher the score, the better a person's performance status.[14] A second scale widely used in oncology to assess a person's health status, and used in TIVO-1,[12] is that established by the Eastern Cooperative Oncology Group (ECOG).[15] ECOG is a 5-point scale and, in contrast to KPS, the higher the score the worse a person's health. The comparability of the scales has been assessed and a mapping of the categories in the two scales has been proposed (Table 1).[16] The ECOG and Karnofsky performance scales can be applied in all oncological conditions and are typically used to assess whether a person is physically well enough to receive chemotherapy, and whether dose adjustment is necessary. Performance status is a key indicator of how a person will respond to treatment.

Table 1. Proposed mapping of the Karnofsky and ECOG performance scales[16]

KPS score	KPS performance status	ECOG Score	ECOG performance status
100	Normal; no evidence of disease	0	Fully active, able to carry on all pre-disease performance without restriction
90	Minor signs or symptoms	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light house work, office work
80	Normal activity with effort: some signs or symptoms		
70	Cares for self; unable to carry on normal activity	2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
60	Occasional assistance required; capable of most self-care		
50	Requires assistance, frequent medical care	3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
40	Disabled; requires special care/assistance		
30	Severely disabled; hospitalization indicated	4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
20	Hospitalization necessary; requires active supportive care		
10	Moribund; progressing rapidly		
0	Dead	5	Dead

Abbreviations: ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky performance scale.

As commented by the company, people with late stage RCC experience the psychological burden of a diagnosis of an incurable condition (Box 3). Although prolongation of OS is the key goal of treatment, the impact of other factors, for example, treatment-related toxicity, on health-related (HR) QoL is also a consideration. The company provides an overview of the effect of RCC on HRQoL, as well as the economic burden associated with the condition (Box 3).

Box 3. Overview of the effect of RCC on QoL and the economic burden associated with RCC (adapted from CS, pg. 38)

Quality of life for those with RCC

Late stage RCC has a considerable impact on HRQOL. A UK-based study demonstrated that the decline in HRQOL is significantly greater in patients with progressive disease than in patients with stable disease.[17] The consequences of advanced disease can be unpleasant and include weight loss/lethargy, fever, night sweats, dysgeusia (taste distortion), anaemia, hypercalcaemia (which may cause constipation and confusion), pain and venous thromboembolism. In patients with metastatic disease, symptoms may arise from the metastatic site e.g. lung metastases may cause airway obstruction, bleeding and dysponea. Furthermore, in patients with metastatic disease the psychosocial impact of a diagnosis with an incurable cancer with a poor prognosis is considerable.[18] Newer targeted therapies demonstrate an improvement in HRQOL over older treatments for RCC such as IFN. Clinical evidence supports a strong association between tumour response and delay in tumour progression with HRQOL benefits experienced by patients receiving the new targeted

therapies.[18] Although the newer treatments have improved tolerability over older treatments, AEs of treatment also impact negatively on HRQOL.[17]

Quality of life for carers of those with RCC

Given that RCC is a relatively rare disease, there is a paucity of data on the impact of the disease on carers' QOL. At present there is no cure for patients with advanced and/or metastatic disease and the uncertainty around a diagnosis of an incurable cancer with a relatively short survival period in a loved one is likely to cause carers great concern and have a considerable impact on their QOL.

Economic burden associated with RCC

The impact of RCC on healthcare resources is considerable. In England, data from Hospital Episode Statistics (2014–2015) revealed that there were 17,309 finished consultant episodes (FCE) for C64 (Malignant neoplasm of kidney, except renal pelvis), 14,341 admissions and 63,133 FCE bed-days annually.[19]

The cost of managing AE can also be considerable even with newer targeted agents.[6, 10, 20] A study using the US Surveillance, Epidemiology and End Results (SEER) Medicare database revealed that total cost of care over 30 days was substantially higher among patients aged ≥65 years with metastatic RCC treated with sunitinib, sorafenib, bevacizumab or pazopanib experiencing grade 3 or 4 AEs than those not experiencing AE: a mean (95% confidence interval [CI]) difference of $12,410 ($9217–$16,522). Given that 60% of patients experienced grade 3 or 4 AEs in this study, the financial impact is considerable.[20]

Abbreviations: AE, adverse effect; CS, company submission; HRQOL, health-related quality of life; IFN, interferon; pg., page; QoL, quality of life; RCC, renal cell carcinoma.

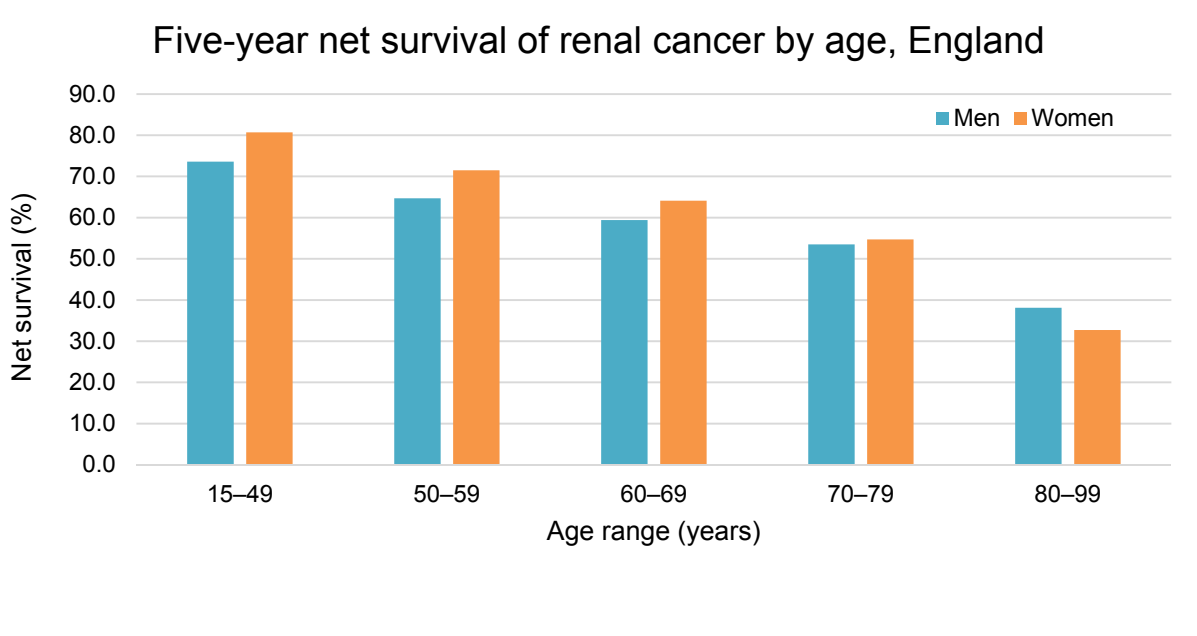
2.1.1 Epidemiology

Renal cancer was the seventh most common cancer in the UK in 2014, accounting for 3% of all new cases of cancer.[4] The company presented incidence data from the Office of National Statistics, reporting that there were 9,023 new cases of renal cancer in England in 2013.[21] The ERG notes that the data on the Office of National Statistics are for 2015, and exclude those with cancer of the renal pelvis, which has been included in other estimates of incidence of renal cancer. For example, Cancer Research UK reports that 10,517 new cases of renal cancer occurred in England in 2014, which also includes cancer of the renal pelvis and ureter.[4] RCC accounts for 86% of all renal cancers,[4] which equates to 9,045 new cases of RCC in England in 2014 and is similar to the number of new cases reported by the company. The ERG only mentions this potential discrepancy for completeness and in explanation of the calculation of the number of people potentially eligible for treatment with tivozanib in England presented in a subsequent section (Section 2.2.3).

In the UK, 50% people remain alive up to 10 years after being diagnosed with renal cancer (prevalence based on data from 2010–2011).[4] As noted by the company, survival of renal cancer varies considerably with age. Around three-quarters of people diagnosed with renal cancer who are aged 15–49 years

survive their disease for 5 years or more, compared with less than a third of people diagnosed who are aged 80 and over (Figure 1).[4]

Figure 1. Five-year net survival of renal cancer by age, England based on data from Cancer Research[4]



2.2 Critique of company's overview of current service provision

The company presents a comprehensive review of European guidance on the treatment of renal cancer, as well as an overview of the NICE pathway for renal cancer.[22] Here, the ERG focuses on guidance relevant to clinical practice in England and the wider UK. As the company reports, NICE has published seven Technology Appraisals (TAs) evaluating drug treatments for RCC, the recommendations of which are summarised in Table 2.

Table 2. Summary of exisiting TAs in RCC published by NICE (adapted from Table 9 in CS, pg. 41)

Line	Technology appraisal	Year	Title	Summary
First	TA169[23]	2009	Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma	Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic RCC who are suitable for immunotherapy and have an ECOG performance status of 0 or 1[a]
Mixed	TA178[24]	2009	Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma	Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic RCC. Sorafenib and sunitinib are not recommended as second-line treatment options for people with advanced and/or metastatic RCC

First	TA215[25]	2013	Pazopanib for the first-line treatment of advanced renal cell carcinoma	Pazopanib is recommended as a first-line treatment option for people with advanced RCC who have not received prior cytokine therapy and have an ECOG performance status of 0 or 1 and if the company provides pazopanib with a 12.5% discount on the list price as agreed in the PAS[a]
Second	TA333[26]	2015	Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment	Axitinib is recommended as an option for treating adults with advanced RCC after failure of treatment with a first-line TKI or a cytokine, only if the company provides axitinib with the discount agreed in the PAS
Second and above	TA417[27]	2016	Nivolumab for previously treated advanced renal cell carcinoma	Nivolumab is recommended, within its marketing authorisation, as an option for previously treated advanced RCC in adults, when the company provides nivolumab with the discount agreed in the PAS
Second and above	TA432[28]	2017	Everolimus for advanced renal cell carcinoma after previous treatment	Everolimus is recommended within its marketing authorisation as an option for treating advanced RCC that has progressed during or after treatment with VEGF-targeted therapy, only if the company provides it with the discount agreed in the PAS
Second and above	TA931[29]	2017	Cabozantinib for previously treated metastatic renal cell carcinoma	Cabozantinib is not recommended within its marketing authorisation for treating advanced RCC in adults after VEGF-targeted therapy [Note: information is taken from the Appraisal Consultation Document, which is used as the source throughout this document] **Note added by ERG: At the time of writing, NICE has yet to reach a final decision on the use of cabozantinib in RCC.**

[a] It should be noted that guidance for first-line sunitinib[23] and pazopanib[25] recommends first-line use in patients with an ECOG performance status of 0 or 1. Guidance for both agents states that when using ECOG performance status, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect ECOG performance status and make any adjustments they consider appropriate.

Abbreviations: CS, company submission; ECOG, Eastern Cooperative Oncology Group; NICE, National Institute for Health and Care Excellence; PAS, patient access scheme; pg., page; RCC, renal cell carcinoma; TA, technology appraisal; VEGF, vascular endothelial growth factor.

2.2.1 Management of renal cell carcinoma

For those diagnosed with early stage renal cancer (Stages I–III), as discussed by the company, the mainstay of treatment remains surgery, either partial or radical nephrectomy.[22] Surgery may also be considered for those with advanced or metastatic disease (Stage IV) if they are considered to be in good general health and able to recover from the operation. Data for the period 2004–2006 indicate that 60% of people diagnosed with renal cancer in that time period underwent surgery.[30] Those not having surgery may have been considered to be in too poor health to undergo the procedure.

Other interventional procedures available as an alternative to surgery for those with early stage disease are:[4]

- Freezing therapy (cryotherapy);

- radiofrequency ablation;
- radiotherapy;
- arterial embolisation.

Of those who undergo surgery, some will have a recurrence of their disease: reported recurrence rates of renal cancer after nephrectomy (either partial or radical) are between 20% and 30%.[31, 32] For those who are unable to undergo surgery and those whose disease recurs after surgery, available treatment options are drugs that target and block tumour growth pathways.

The company highlights that two new classes of targeted systemic therapy are available for the treatment of renal cancer. One class elicits an effect by blocking vascular endothelial growth factor (VEGF) receptors (VEGFRs) and the other through inhibiting the mechanistic target of rapamycin (mTOR) signalling pathway. Sunitinib, pazopanib, axitinib and tivozanib belong to the class of tyrosine kinase inhibitors (TKIs) that target VEGFRs thereby interrupting angiogenesis (formation of new blood vessels), whereas everolimus acts by blocking mTOR to interrupt aberrant cellular signalling that has led to uncontrolled cell growth and proliferation. As the company comments, uptake of TKIs and mTORs has been widespread, and the company considers that these treatments have superseded cytokines (interferons [IFNs] and interleukins [ILs]) in UK clinical practice for the first-line treatment of renal cancer. The ERG's clinical experts concur with the company on the place of cytokines in the treatment of RCC in England.

For first-line systemic therapy for RCC, NICE recommends sunitinib or pazopanib as treatment options in those with an ECOG performance score of 0 or 1 (Table 2).[22] For people with previously treated RCC, NICE recommended options are axitinib, nivolumab and everolimus, with accompanying caveats around prior treatment received (Table 2).[22] The appraisal process is ongoing for cabozantinib[29] and for lenvatinib in combination with everolimus[33] as second-line therapy for RCC.

The ERG's clinical expert highlighted that response to first systemic therapy influences treatment choice for subsequent lines. If a person's RCC did not progress on first-line TKI (i.e., sunitinib or pazopanib) for 1–2 years, they are more likely to have a good response to subsequent TKI (i.e., axitinib). However, if a person's disease progresses on first-line TKI within 6 months of starting treatment, they are likely to have a poor response to second-line TKI and everolimus might be considered for second-line therapy.

The company is proposing tivozanib as a treatment option for adults with advanced RCC who are VEGFR and mTOR pathway inhibitor-naïve and are untreated or have failed prior IFN-α or IL-2 based therapy. However, the company acknowledges that confirmation of previous treatment failure with prior

IFN-α or IL-2 was not required for enrolment into TIVO-1. The ERG's clinical expert fed back that differentiating between those failing treatment and those not would be important as failing prior treatment would influence treatment response to subsequent treatment and hence prognosis. In addition, the ERG notes that an inclusion criterion of TIVO-1 was that people have a prior nephrectomy. As prior nephrectomy is a recognised prognostic factor (discussed in Section 2.1), the ERG considers the patient population in TIVO-1 to have a better prognosis than a "mixed" population, where patients may or may not have had surgery.

Overall, the ERG considers the company's overview of current service provision to be an accurate, relevant representation of clinical practice in England for the treatment of RCC. After consultation with clinical experts, the ERG considers the company's proposed position of tivozanib as a first-line treatment for RCC in those who are VEGFR and mTOR pathway inhibitor-naïve and are untreated or have failed prior IFN-α or IL-2 based therapy to be mostly appropriate. Given that the clinical opinion is that cytokines are no longer used in UK clinical practice to treat RCC, and the subgroup of people having received prior IFN-α or IL-2 cannot be determined to have failed cytokine therapy, the ERG considers the population relevant to UK clinical practice to be those who are naïve to any systemic therapy.

2.2.2 Resources required to administer tivozanib

The company proposes that no additional resources or infrastructure will be required to implement tivozanib in the management of RCC in the National Health Service (NHS). The proposed Summary of Product Characteristics (SmPC) for tivozanib (presented within the CS) indicates that tivozanib is an oral treatment, to be taken once daily. Most of the other recommended first and second-line treatment options for RCC are also taken orally once daily,[34, 35] with the exception of axitinib,[35] which is administered orally but twice daily, and nivolumab,[36] which is given intravenously and infused over 60 minutes. The draft SmPC states that tivozanib be initiated by an oncologist with experience of managing patients with RCC.

The company reports that the most common adverse effect associated with tivozanib during the clinical trial programme was hypertension, which the company reports can be managed using standard antihypertensive medication or dose reduction, interruption or discontinuation. The ERG notes that hypertension is a recognised adverse effect of TKIs. In TIVO-1, 44% of people in the tivozanib group experienced hypertension (any grade). Reported incidences of hypertension (any grade) during treatment with TKIs for RCC and other malignancies range from 22% with sunitinib[37] to 40% with axitinib.[38] It has been noted that hypertension incidence is higher with more potent TKIs,[39] probably as a result of an on-target effect: an on-target effect is the effects of a drug resulting from the intended interaction with the target.[40]

Within the CS, the company presents a detailed description of the standard tests required for monitoring treatment with tivozanib (Box 4), highlighting that the tests are similar to those required for sunitinib and pazopanib and do not represent additional costs to the NHS. The company went on to comment that, "*Tivozanib use is unlikely to result in additional monitoring or hospital visits compared with sunitinib and pazopanib. Indeed, the adverse event (AE) profile with tivozanib seen in the pivotal TIVO-1 trial*[41] *suggests that patients receiving tivozanib may require fewer hospital visits than those receiving pazopanib or sunitinib*". The ERG's clinical expert agreed with the company's view, feeding back that implementing tivozanib would not require additional resource or infrastructure to that already in place for use of other TKIs and mTORs.

Box 4. Tests required before and during treatment with tivozanib (adapted from CS, pgs 33–34)

The tests required prior to initiation of tivozanib are as follows:

- Blood pressure: patients should have controlled blood pressure prior to initiation of tivozanib.
- Proteinuria: all patients should undergo dipstick urinalysis before starting treatment.
- Liver tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin).
- Thyroid function.

The monitoring requirements for tivozanib are as follows:

- Blood pressure: during treatment, patients should be monitored for hypertension and treated as needed with anti-hypertensive therapy according to standard medical practice.
- Cardiac failure: signs or symptoms of cardiac failure should be periodically monitored throughout treatment with tivozanib.
- Proteinuria: should be monitored periodically throughout treatment. In clinical practice this will generally be at each cycle.
- Liver tests: should be monitored periodically throughout treatment. Unlike with pazapanib33 there is no specific liver toxicity signal necessitating explicit monitoring with tivozanib.
- Gastrointestinal perforation/fistula: symptoms of gastrointestinal perforation/fistula should be monitored during treatment.
- Thyroid function: should be monitored periodically throughout treatment.

2.2.3 Estimated number of people eligible for treatment with tivozanib

The company presents a detailed breakdown of how they have reached an estimate of 2,967 people with RCC who would be eligible for treatment with tivozanib annually in England (Table 3). The ERG's clinical experts fed back that the approach taken and assumptions made by the company are reasonable. The ERG's experts went on to comment that it is difficult to determine accurately the number of people eligible for treatment but that the company's estimate is a realistic approximation of those likely to be

treated annually with tivozanib in England. As noted in 2.1.1, the ERG noted a potential error in the company's estimate of the number of new cases of renal cancer in England in 2015. To illustrate the minimal impact of this potential error on the number of people likely to be eligible for treatment with tivozanib, the ERG presents revised data based on statistics for 2014 from Cancer Research alongside the company's original estimates (Table 3).

Table 3. Number of patients suitable for treatment with tivozanib (adapted from CS, Table 8, pg. 40)

	Company's original estimate	**ERG's updated estimate based on data for 2014[4]**	**Company's data source**
Number of people with new kidney cancer diagnoses in England	9,023[a]	10,517	Office for National Statistics[42]
86% of kidney cancer patients have RCC	7,760	9,045	Cancer Research[4]
44% of RCC patients have advanced or metastatic disease at presentation	3,414	3,980	National Cancer Registration and Analysis Service[43]
Of the remaining 56% who present with localised disease, 33% will relapse following surgical treatment	1,434	1,671	Cohen & McGovern;[44] cited in NICE TA169[23]
Total patients in England with advanced or metastatic RCC	4,848	5,651	Sum of previous two rows (i.e., 3,414 + 1,434)
68% of patients have an ECOG score of 0-1 and are eligible for first-line treatment with VEGFR-TKI	3,297	3,843	Elson *et al*;[45] cited in NICE TA169[23]
90% of eligible patients currently receive treatment with first-line VEGFR-TKI	2,967 (32.9% of all new kidney cancer cases)	3,459 (32.9% of all new kidney cancer cases)	Personal communication Dr Robert Jones

[a] As discussed in Section 2.1.1, this number excludes those with cancer of the renal pelvis.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

3 CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

The company submission (CS) included a summary of the final decision problem issued by the National Institute for Health and Care Excellence (NICE)[1] together with the rationale for deviations from the decision problem (reproduced in Table 4).

Table 4. Summary of the decision problem as outlined in the company's submission (adapted from CS, Table 1, pgs 13–16)

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	Adults with recurrent or metastatic RCC	Adults with recurrent or metastatic RCC	N/A
Intervention	Tivozanib	Tivozanib	N/A
Comparator(s)	Untreated disease: •Sunitinib •Pazopanib •Immunotherapy (interferon-α, interleukin-2) Previously treated disease: •Axitinib •Nivolumab •Everolimus •Cabozantinib •Best supportive care	Untreated disease: •Sunitinib •Pazopanib •Immunotherapy (interferon-α, interleukin-2)	**ERG summary, full version provided in Box 5.** The company states that there were insufficient data to provide reliable estimates via MTC for a previously treated population, and that it is not relevant because pazopanib and sunitinib[23, 25] (i.e. TKIs) have replaced cytokines as first-line treatment of recurrent or metastatic RCC in England, and that tivozanib will not be licensed for people who have received prior VEGFR-targeted therapy.
Outcomes	•OS •PFS •Response rates •AE of treatment •HRQoL	•OS •PFS •Response rates •AE of treatment	HRQOL data for tivozanib versus sorafenib from the pivotal clinical trial (TIVO-1) are presented. There are insufficient data for independent analysis of HRQOL and the MTC cannot give reliable estimates.
Economic analysis	The reference case stipulates that the cost-effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost-effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any patient access schemes for the intervention and	As per the scope: With regard to time horizon, we believe that a 10-year horizon is the most appropriate one to use in this case, in that it approximates to lifetime. Survival duration in advanced RCC is relatively limited, with a median overall survival duration of around 3 years. Individual patients, however, may survive for considerably longer, perhaps up to 10 years.	N/A

	comparator technologies should be taken into account.		
Subgroups to be considered	N/A	N/A	N/A
Special considerations, including issues related to equity or equality	N/A	N/A	N/A
Abbreviations: AE, adverse effects; HRQOL, health-related quality of life; MTC, mixed treatment comparison (referred to as NMA [network meta-analysis] by the ERG); N/A, not applicable; NHS, national health service; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptors			

3.1 Population

Evidence provided in the CS on clinical effectiveness of tivozanib is based primarily on data from the TIVO-1 trial and the associated extension study.[12, 41, 46] The CS also presents supplementary non-randomised evidence for tivozanib from a Phase II discontinuation study (AV-951-07-201)[47] and a Phase II biomarker study (AV-951-10-202)[48] but data from these studies do not inform the direct or indirect estimates of clinical and cost-effectiveness. As such, the Evidence Review Group (ERG) critique of the decision problem focuses on TIVO-1. All studies evaluating tivozanib and included in the CS are summarised in Table 5.

Table 5. Tivozanib studies in the company submission

Study number	Name	Description
AV-951-09-301	TIVO-1[12, 41, 46]	Phase III open-label RCT comparing tivozanib (n=260) with sorafenib (N=257) for patients with RCC (adults, measurable recurrent or metastatic disease, prior nephrectomy, clear cell component, ECOG 0 or 1, treatment naïve or no more than one prior systemic therapy, no prior VEGF or mTOR). Data included in clinical and cost-effectiveness analyses.
AV-951-09-902	TIVO-1 extension study[46]	One-way crossover, open-label extension for patients in TIVO-1 study. Patients who progressed on sorafenib in TIVO-1 were offered tivozanib. Patients who had not progressed on tivozanib or sorafenib had continued access to the drugs. There was no provision of subsequent therapy for patients who progressed on tivozanib. Data included in clinical and cost-effectiveness analyses.
AV-951-07-201	Phase II discontinuation study[47, 49]	16 weeks open-label tivozanib for patients with RCC (adults, measurable recurrent or metastatic disease or primary RCC not amenable to surgery) followed by: •12 weeks tivozanib for patients with ≥ 25% tumour shrinkage (N=78) •Discontinuation for patients with ≥ 25% tumour growth (N=50) •Randomisation to 12 weeks tivozanib or placebo for patients with < 25% tumour change since baseline (N=118) Study recruited adults with confirmed measurable recurrent or metastatic RCC or primary RCC not amenable to surgery. Data not included in clinical and cost-effectiveness analyses.
AV-951-10-202	Phase II biomarker study[48, 50]	Study to evaluate biomarkers and their correlation with the effectiveness and toxicity of tivozanib for patients with RCC (adults, unresectable locally recurrent or metastatic disease, prior nephrectomy, treatment naïve or one prior systemic therapy, no prior VEGFR- or mTOR-targeted therapy). Also designed to estimate PFS at 6 months. Study terminated.

		Data not included in clinical and cost-effectiveness analyses.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; mTOR, mammalian target of rapamycin; PFS, progression-free survival; RCC, renal cell carcinoma; RCT, randomised controlled trial; VEGFR, vascular endothelial growth factor

TIVO-1 (AV-951-09-301) was designed to evaluate the efficacy and safety of tivozanib compared with sorafenib for patients with recurrent or metastatic renal cell carcinoma (RCC), which matches the population outlined in the NICE final scope.[1] However, the ERG notes that the inclusion criteria of TIVO-1 specified that people have:

- RCC of a clear cell histology;
- previous nephrectomy;
- an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 (i.e. be fully active or restricted only in physically strenuous activity);[15]
- measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.

Inclusion criteria regarding prior nephrectomy and clear cell histology were based on more favourable results observed in patients with these characteristics in the preceding Phase II discontinuation study, AV-951-07-201. Therefore, the ERG considers that there is potential for the population enrolled in TIVO-1 to have generally better prognosis than the full population defined in the scope (see Section 2.1), though the population was similar to the populations of the trials included in the NMA (Section 4.3).

TIVO-1 enrolled 517 patients, primarily from Central or Eastern Europe (457/517; 88%); only four patients were enrolled in the UK (Leicester and Cambridge). Information about prior therapy of those who were not treatment naïve suggests that cytokines are the most common first-line therapy received prior to enrolment in TIVO-1 (CS page 67). As discussed in Section 3.1.2 and Box 5, the ERG considers that cytokine therapies are no longer used in UK clinical practice as first-line treatment for RCC. In addition, the number and type of subsequent therapies received after progression in TIVO-1 (CS Table 16, page 66) is unlikely to represent current clinical practice in the National Health Service (NHS); recruitment for the study took place in 2010 at a time when vascular endothelial growth factor tyrosine kinase inhibitors (VEGFR-TKIs) were less established, and there may not have been widespread access to them in the geographical locations where most patients were treated. Patients were eligible for inclusion if they were naïve to treatments targeting the VEGFR and mammalian target of rapamycin (mTOR) pathways, and had received no more than one prior treatment with immunotherapy (including the cytokines interferon-α [IFN-α] and interleukin-2 [IL-2] therapy, hereafter referred to as cytokines), chemotherapy, or hormonal therapy for metastatic RCC.

The NICE final scope[1] outlines that treatment naïve people and those having received prior treatment are distinct populations of interest to the decision problem. The CS presents studies recruiting a treatment-naïve population separately in one set of analyses (in which the treatment naïve subpopulation of TIVO-1 is used), and together with studies of pretreated patients in another set of analyses (in which the TIVO-1 mixed ITT population is used). As set out in the final scope,[1] the ERG has assessed separately the treatment-naïve TIVO-1 subpopulation (untreated disease) and mixed naïve and pretreated population with regard to the decision problem and applicability to patients in England.

3.1.1 Untreated disease

In TIVO-1, 70% of those randomised to receive tivozanib (181/260) and 70% of those randomised to receive sorafenib (181/257) had untreated disease, that is, were naïve to treatment with immunotherapy (including cytokines), chemotherapy, hormonal therapy, and newer targeted therapies (mTOR and VEGFR-TKIs) for metastatic RCC. Results for these treatment-naïve patients are provided in the submission and baseline characteristics for the subpopulation were presented at the 2013 American Society of Clinical Oncology (ASCO) conference.[51] Baseline characteristics for the TIVO-1 treatment-naïve subpopulation are reproduced in Section 4.2.2 alongside characteristics for the mixed ITT population (Table 11). The ERG's clinical experts considered the characteristics of the TIVO-1 population to be generalizable to the population in the UK likely to be eligible for treatment with tivozanib, despite only 4 people being recruited from the UK.

3.1.2 Previously treated disease

In TIVO-1, 30% in both groups had previously treated recurrent or metastatic RCC, primarily with IFN-α (more than 90%, CS page 67). Current first-line treatment in the UK is a VEGFR-TKI (pazopanib or sunitinib) which were exclusionary in TIVO-1, and prior treatments that were permitted (cytokines, chemotherapy, hormonal therapy) are not representative of the current treatment pathway in the NHS (see Table 4). As such, treatments currently available for RCC in the UK are unlikely to be representative of those received by patients enrolling in TIVO-1. While other treatments recommended by NICE for patients with RCC have referenced cytokines as possible prior therapy,[26] we agree with the company that people in the UK likely to be eligible for tivozanib are unlikely to have received prior cytokine therapy. The ERG does not consider the cytokine-pretreated subpopulation of TIVO-1 (or the associated network meta-analysis [NMA], discussed in Section 4.3) to be applicable to patients at first or second-line treatment for metastatic RCC in the NHS. People who had previously received VEGFR-TKIs (including pazopanib and sunitinib) were not eligible for TIVO-1 and the proposed marketing authorisation states that tivozanib is for patients who are VEGFR and mTOR pathway inhibitor-naïve. The CS does not provide any evidence for a population who have received prior VEGFR-TKI or mTOR therapy, which the ERG considers appropriate to the proposed license.

In summary, the ERG considers the treatment-naïve subpopulation of TIVO-1 to be representative of people with treatment-naïve, recurrent or metastatic RCC in England. The inclusion criteria of TIVO-1 mean the evidence submitted is primarily applicable to people with clear cell RCC, good performance status (ECOG score of 0 or 1) and who have had prior nephrectomy, and hence may have better prognosis than the full population covered by the NICE final scope.[1] The CS does not provide evidence that is relevant to patients in England who have already received treatment because first-line treatments given in the NHS are unlikely to overlap with those received by patients in TIVO-1.

3.2 Intervention

Tivozanib (Fotivda®) is a VEGFR-TKI that potently inhibits VEGF receptors 1, 2, and 3.[52] Therapies belonging to the VEGFR-TKI class target growth proteins (tyrosine kinases) of tumour cells and their associated blood supply. The VEGFR-TKI mode of action has been shown to inhibit angiogenesis (formation of new blood vessels) which can suppress tumour growth and metastatic progression.[52] Tivozanib is proposed to be more potent and selective than other available drugs in the VEGFR-TKI class.[53]

At the time of writing the ERG report, tivozanib was awaiting marketing authorisation from the European Medicines Agency (EMA) and, thus, no European Public Assessment Report (EPAR) was available for review. The CS states that tivozanib was submitted to the Committee for Human Medicinal Products (CHMP) in March 2016 and a decision is anticipated in May 2017. The company confirmed that tivozanib is not subject to any other health technology assessment in the UK.

The ERG notes that the US Food and Drug Administration (FDA) did not approve tivozanib for people with RCC based on evidence from the TIVO-1 trial submitted in 2013. The CS states the following in reference to the FDA's decision:

"They [the FDA] did not approve tivozanib in this indication, since they felt the results of the study were unclear as to whether the benefit-to-risk evaluation was favourable. Although there was a significant benefit for tivozanib in terms of PFS, the primary outcome, there was a non-significant decrease in OS [overall survival] versus the comparator (sorafenib).

At the time of the FDA submission no analysis of crossover was available. We have carried out an analysis adjusted for crossover which confirms that the difference in OS reflects imbalance in access to next-line targeted therapies." [CS, page 31–32]

In the absence of an EPAR, the ERG has based its description of the intervention and the extent to which it covers the NICE final scope[1] on Section 2 of the CS and the Draft Summary of Product Characteristics (SmPC)[54] provided in the CS appendices. The proposed indication for tivozanib is for

the treatment of adults with advanced RCC who are VEGFR and mTOR pathway inhibitor-naïve and are either untreated or who have failed prior therapy with IFN- or IL-2.[54]

Tivozanib is taken in four-week cycles once a day as a 1,340µg hard capsule. A four- week cycle comprises three weeks on treatment and a one week rest period. Tivozanib is also available in 840µg hard capsules for patients who require a dose reduction due to adverse effects. The draft SmPC states that this treatment schedule should be maintained if clinical benefit is observed or until unacceptable toxicity occurs. Prescribing information for tivozanib is summarised in Table 6, reproduced from the CS (Table 7, pg. 33).

The daily dose of 1.5mg (1,500µg) described in TIVO-1 is different to the dose of 1,340µg stated in the CS draft SmPC. The company states that the dose given in the TIVO-1 was the same as the proposed licensed dose, and that the discrepancy is a result of CHMP guidelines to state only the amount of active substance in the SmPC, with the difference of 160µg made up by excipients (CS footnote, page 34). The four-week cycle used in TIVO-1 is the same as that described in the draft SmPC. Protocols for dose reduction, interruption and study drug discontinuation due to adverse events in TIVO-1, and how these compare to other studies in the NMA, are discussed in Section 4.2.4.6.

Table 6. Tivozanib prescribing information and costs (adapted from CS, Table 7, pg. 33)

	Cost	Source
Pharmaceutical formulation	Hard capsule	Draft SmPC
Acquisition cost (excluding VAT)	[redacted]	EUSA Pharma Please note that the cost of tivozanib has not yet been confirmed and is confidential
Method of administration	Oral	Draft SmPC
Doses	1,340µg; 890µg in patients requiring dose reduction	Draft SmPC
Dosing frequency	Once daily	Draft SmPC
Average length of a course of treatment	Until disease progression or unacceptable toxicity	Draft SmPC
Average cost of a course of treatment	[redacted]	Based on cost per month x median PFS in TIVO-1(11.9 months)[41] Calculated as 13 x price
Anticipated average interval between courses of treatment	Given for 3 weeks in a 4-week cycle	Draft SmPC
Anticipated number of repeat courses of treatments	N/A	Draft SmPC
Dose adjustments	Dose adjustments may be required to manage side effects or in patients with hepatic impairment.	Draft SmPC

	Dose reduction is recommended for uncontrolled hypertension, cardiac failure, proteinuria and troublesome HFS. Dose interruption or discontinuation is recommended in patients with severe/persistent hypertension or HFS and may be required for the management of cardiac failure. Patients with grade 2 or 3 proteinuria may benefit from temporary discontinuation, in those with grade 4 proteinuria tivozanib should be discontinued. Temporary discontinuation is recommended in patients undergoing major surgical procedures.	
Anticipated care setting	Secondary care, medication taken in the patient's home	Draft SPC
Abbreviations: HFS, hand-foot syndrome; PFS, progression-free survival; SmPC, summary of product characteristics; VAT, value added tax		

Contraindications to tivozanib listed in the draft SmPC are hypersensitivity to the active substance or excipients and coadministration with herbal preparations containing St. John's wort (*Hypericum perforatum*) due to the risk of reduced plasma levels and reduced time to reach steady-state of tivozanib.[54] The draft SmPC states that tivozanib should not be used during pregnancy or breastfeeding and should be used with caution in patients undergoing dialysis or at risk of, or with a history of, the following conditions: arterial thrombotic events (e.g. myocardial infarction or stroke), venous thrombotic events and bleeding, QT interval prolongation, and gastrointestinal perforation/fistula. Tivozanib is not recommended for patients with severe hepatic impairment and for those with mild to moderate hepatic impairment, the dose should be reduced to alternate days and patients should be monitored closely.[54]

The CS presents information from the draft SmPC about adverse events that may require dose reduction, interruption or discontinuation of tivozanib. These include hypertension, cardiac failure, proteinuria, bleeding, hand-foot syndrome, QT interval prolongation, gastrointestinal perforation and fistula, wound healing complications, and hypothyroidism. The ERG's clinical experts consider the safety considerations listed in the draft SmPC for tivozanib to be broadly comparable to those of other VEGFR-TKIs.

3.3 Comparators

3.3.1 Untreated disease

The NICE final scope[1] lists sunitinib, pazopanib and immunotherapy (IFN-α and IL-2) as the relevant comparators for patients with untreated recurrent or metastatic RCC. In line with the CS, the ERG uses the term cytokines in this report rather than immunotherapy.

The ERG and its clinical experts agree that the VEGFR-TKIs pazopanib and sunitinib are the two relevant comparators for a treatment naïve population likely to be eligible for treatment with tivozanib in England[23, 25]; both drugs are recommended by NICE as first-line treatment for advanced and metastatic RCC. The ERG note that the company includes cytokines as a comparator in the NMA in

line with the NICE final scope,[1] but agree with the company that cytokine therapies are not a relevant comparator for the treatment-naïve population because they have been replaced by VEGFR-TKIs as standard first-line treatment (CS page 13 to 16, reproduced in Box 5 below).

3.3.2 Previously treated disease

The NICE final scope[1] lists axitinib, nivolumab, everolimus, cabozantinib and best supportive care as comparators for RCC patients with previously treated disease. The company do not present evidence for a pretreated population because first-line treatment in England is with a VEGFR-TKI, which was an exclusion criteria for the TIVO-1 (see Section 3.1.2). The ERG's clinical experts agree that axitinib, nivolumab, everolimus, cabozantinib and best supportive care are not relevant comparators for tivozanib given the evidence submitted by the company and the proposed marketing authorisation.

Box 5. Company's explanation of comparators not covered in the CS in relation to the final scope issued by NICE (adapted from CS, Table 1, pgs 13–16)

Tivozanib was not compared in patients with previously treated disease because there are insufficient data for independent analysis of tivozanib and other vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) in pre-treated patients and the mixed treatment comparison (MTC) cannot give reliable estimates.

Furthermore, we believe that tivozanib will not be used in clinical practice in patients with previously treated disease.

The VEGFR-TKIs pazopanib and sunitinib are recommended by NICE as first-line treatment options for advanced and metastatic disease.[23, 25] VEGFR-TKIs have replaced cytokines to become the standard of care at first-line and evidence provided to NICE by clinical experts in the course of several recent Technology Appraisals (axitinib[26] and nivolumab[27]) supports this view. Clinical experts in the axitinib appraisal which was issued in February 2015 suggested that <1% of patients would receive cytokines as first-line treatment[26]. Clinical opinion elicited for the nivolumab appraisal issued 21 months later in November 2016[27] reinforced this view *…The committee heard from the clinical experts that most people in the NHS with newly diagnosed advanced renal cell carcinoma would be offered one of two tyrosine kinase inhibitors; either pazopanib or sunitinib, as recommended in NICE's technology appraisal guidance…*

Supportive real world data comes from the RECCORD registry which gathered UK data on the use of targeted therapies in locally advanced or metastatic RCC from seven UK hospitals (five in England) from March 2009 to October 2012. Anonymised data was collected through an online registry and data was included on 415 patients.[55] Sunitinib and pazopanib accounted for 90.3% of all first-line treatments, cytokines for 1% and everolimus, sorafenib, temsirolimus for the balance. Expert opinion from the UK confirms this approach, we are aware of only one hospital in the UK (The Christie, Manchester) which routinely uses cytokines first-line in a highly selected subgroup of patients who receive high dose IL-2. We understand that around 20 patients per year receive treatment in this way (Dr Robert Jones, Personal Communication).

Axitinib is recommended by NICE as an option for treating adults with advanced RCC after failure of treatment with a first-line VEGFR-TKI or a cytokine (immunotherapy).[26] Nivolumab is licensed as monotherapy for the treatment of advanced RCC after prior therapy in adults[56] and is recommended by NICE in that population.[27] We believe that that axitinib and nivolumab are not relevant comparators since tivozanib will not be licensed in patients pre-treated with VEGFR-TKI or mammalian target of rapamycin (mTOR) inhibitors and very few people in UK clinical practice will receive cytokines first line and be eligible for treatment with tivozanib, axitinib or nivolumab at second line. The Everolimus is recommended by NICE for second-line treatment.[28] It is licensed for treatment of patients with advanced RCC, whose disease has progressed on or after treatment with VEGF-targeted therapy.[57] Treatment of patients previously treated with VEGFR pathway inhibitors is outside the proposed product licence for tivozanib. Cabozantinib is not recommended by NICE for previously treated RCC.[29] It is licensed for the treatment of advanced RCC in adults following prior VEGF-targeted therapy.[58] Treatment of patients previously treated with VEGFR pathway inhibitors is outside the proposed product licence for tivozanib. Best supportive care is not a relevant comparator, since if patients are eligible for tivozanib then they would also be eligible for sunitinib and pazopanib. Best supportive care is used in patients in whom targeted therapy is inappropriate.
Abbreviations: IL-2, interleukin-2; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; MTC, mixed treatment comparison (referred to as NMA [network meta-analysis] by the ERG); RCC, renal cell carcinoma; UK, United Kingdom; VEGFR-TKI, vascular endothelial growth factor – tyrosine kinase inhibitor.

3.4 Outcomes

The outcomes specified in the final NICE scope[1] are:

- Overall survival (OS);
- Progression-free survival (PFS);
- Response rates (RR);
- Adverse effects (AEs) of treatment;
- Health-related quality of life (HRQoL).

OS was defined in TIVO-1 as the time between randomisation and death from any cause. The primary analysis was using the intention-to-treat (ITT) population but the CS also presents an adjusted analysis to attempt to control for confounding caused by imbalanced access to subsequent treatments. The imbalance in subsequent therapies was a result of an extension study that gave access to tivozanib for people that progressed on sorafenib, but did not provide subsequent therapy for people who progressed

on sorafenib. A full description of the extension study crossover design can be found in Section 4.2.1, and the impact on the OS results is discussed in Section 4.2.4.1

PFS in the ITT population was the primary endpoint of TIVO-1, defined as the time between date of randomisation and the date of disease progression or death. Local investigators assessed magnetic resonance imagining or computed tomography scans at baseline and every 8 weeks thereafter to identify progressive disease (PD), which was then confirmed within 48 hours by a blinded independent radiology review (IRR) panel. The protocol for assigning PFS, and how this may have affected the clinical effectiveness results, is discussed in more detail in Section 4.2.4.2.

All the outcomes listed above were captured in TIVO-1 and are presented in the CS for tivozanib versus sorafenib. NMAs were conducted for all outcomes except HRQoL. TIVO-1 captured HRQoL using a kidney cancer-specific measure (Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms [FKSI-DRS]), a general cancer measure (the Functional Assessment of Cancer Therapy-General [FACT-G]), and a generic measure of health status (EuroQol five Dimensions questionnaire [EQ-5D]). The FKSI-DRS is likely to give a more sensitive representation of the problems experienced by patients with RCC, whereas the generic measures allow HRQoL to be mapped for the cost-effectiveness analyses (see Section 5.4.7).

Data on response rate were captured using RECIST criteria in TIVO-1 (CS, Table 20, pg. 71), and the CS presents supplementary RECIST response data from the discontinuation study AV-951-07-201 (CS, Table 37) and the biomarker study AV-951-07-202 (CS, Section 4.11.3.2). RECIST is a set of published rules that define when the status of cancer improves, remains stable, or progresses during treatments, and can be used to reduce measurement bias in open-label studies. TIVO-1 response data include complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and overall response rate (ORR; complete response plus partial response).

The CS describes the acronym ORR as 'overall response rate' in some places (CS, Table 10, pg. 52; CS, Table 20, pg. 71; CS Tables 37, 38 and 39), and as 'objective response rate' in others (CS, Table of abbreviations, pg. 10; CS, pg. 58; CS, Table 25, pg. 86; and CS, pg. 103). The ERG understands the ORR, despite the variation in the use of 'overall' or 'objective', to mean the sum of patients demonstrating partial and complete response (CS, Table 10, pg. 52 and the primary reference for TIVO-1[41]). In some cases, including the primary ORR data presented for TIVO-1 (CS, Table 20, pg. 70), response was confirmed by an independent radiology review panel (discussed in more detail in Section 0).

The company presents multiple analyses for treatment-emergent AEs comprising: AEs "of particular interest based on clinical opinion" (diarrhoea, nausea/vomiting, fatigue/asthenia, hypertension and

hand-foot syndrome (HFS) (CS, pg. 94), AEs with a combined incidence of grade 3 and 4 events ≥5%, or with a combined incidence of all grades ≥20%, in any arm of any RCT. The company performed separate NMA for the resulting list of AEs:

- Grade 1 and 2 AEs for naïve patients' population: Alopecia, Anaemia, Asthenia/fatigue, Diarrhoea, HFS, Hypertension, Mucositis/stomatitis, Nausea/vomiting.
- Grade 1 and 2 AEs for overall patients' population: Alopecia, Anaemia, Asthenia/fatigue, Diarrhoea, HFS, Hypertension, Mucositis/stomatitis, Nausea/vomiting, Thrombocytopenia.
- Grade 3 or higher for naïve patients' population: Anaemia, Asthenia/fatigue, Diarrhoea, HFS, Hypertension, Nausea/vomiting, Thrombocytopenia.
- Grade 3 or higher for overall patients' population: Anaemia, Asthenia/fatigue, Diarrhoea, HFS, Hypertension, Mucositis/stomatitis, Nausea/vomiting, Thrombocytopenia.

The ERG's clinical experts agreed that diarrhoea, asthenia/fatigue and hypertension are particularly problematic adverse effects of VEGFR-TKIs for patients and would expect to see them covered in the CS. Clinical experts also considered liver dysfunction to be a rare, but important, class effect of TKIs which is not in the listed AEs covered. Additionally, the use of 'treatment-emergent' AEs may give a less complete overview of relative safety profiles than if 'treatment-related' had been used, the latter generally including events considered causally related to the study drug but falling outside the protocol-defined timeframe for them to be classed 'treatment-emergent'. Protocols for defining and recording AEs in TIVO-1 and across studies in the NMA are discussed in more detail in Section 4.2.4.6.

Outcomes are generally defined clearly either in the CS itself or in the CSRs provided by the company[12, 46], and cover those described in the NICE final scope.[1] Based on advice from clinical experts, the ERG considers that the outcomes presented in the submission are clinically relevant to those in the decision problem.

3.5 Other relevant factors

The final scope issued by NICE[1] did not specify any subgroups to be considered in the CS analyses and there are no known equity or equality issues relating this technology appraisal.

The ERG notes that median length of follow-up in TIVO-1 was not reported in the CS which was requested as part of the clarification process. Follow-up of the TIVO-1 population occurred under the TIVO-1 protocol and the extension study and there were 6 data cuts (see Figure 34); the number of deaths and progression events differ depending on the data cut used. The impact of length of follow-up,

participant flow and crossover on the interpretation of clinical effectiveness evidence from TIVO-1 are discussed in Section 4.2.1.1.

4 CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review

In the company submission (CS), the review of clinical effectiveness is divided into a review of the direct evidence for tivozanib, and a review of indirect evidence submitted from which estimates of clinical effectiveness of tivozanib against comparators not covered by the direct evidence are derived. In the CS, the indirect clinical evidence review originally comprised two sets of network meta-analyses (NMAs), one focusing on studies recruiting a treatment-naïve population (hereafter referred to as the treatment-naïve NMA), and a second mixing evidence for treatment-naïve and prior cytokine-treated patients (hereafter referred to as the mixed pretreated NMA). After reviewing the approach taken by the company, the ERG considered that an alternative approach may generate more robust estimates of effect for tivozanib against the comparators of interest to the decision problem; the ERG's reasoning for suggesting a different approach to the analysis is discussed in greater detail in Section 4.3.

4.1.1 Searches

The company carried out a single search for evidence of clinical effectiveness, cost-effectiveness, quality of life and economic burden of disease. This one search was used to identify direct evidence and indirect evidence to populate the NMAs.

Electronic databases (Medline, EMBASE, Cochrane) were searched from 1980 to July 2016. The search was limited by language to English only. The search strategy contained search terms for the disease area, such as 'renal cell', combined with search terms for study design that was restricted to randomised control trials (RCT). Terms for the interventions of interest were used including both the generic and brand names. No search terms were used to retrieve studies specifically in a first-line population (i.e. treatment naïve) or pretreated population specifically with cytokines, both of which are listed as populations of interest in the National Institute for Health and Care Excellence (NICE) final scope.[1] Specifically, the company included studies of patients who had received prior cytokines and excluded studies of patients had received other targeted therapies (see Table 10), but did not include terms to retrieve the former. Terms relating to the quality of life, economic models and cost-effectiveness included in the search strategy are discussed in Section 5. The ERG notes an 8-month delay between the company's search date (6 July 2016) and the date the CS was submitted to NICE (30 March 2017). The decision to restrict to publications from 1980 onwards is unlikely to have missed relevant evidence, but the search date and exclusion of non-English language records may have led to relevant evidence being overlooked.

The company searched the following clinical trials registries: ClinicalTrials.gov, the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP) and the International

Standard Randomised Controlled Trial Number (ISRCTN) registry. For economic records, the company also searched Heoro.com on 1st July 2016. Compliance with the US Food and Drug Administration (FDA) Amendments Act for clinical trials to publish their results on ClinicalTrials.gov within a year of study completion is known to be poor,[59] so limiting the search to records with published results may have overlooked relevant evidence. The ERG otherwise considered ClinicalTrials.gov search criteria reasonable.

The company searched abstracts of two conferences, the American Society of Clinical Oncology (2015 and 2016) and European Cancer Congress (2015), and excluded any conference abstracts that were more than two years old. No rationale was provided for the two-year restriction and why these conferences alone were chosen; the ERG is aware of other conferences in the field that may have provided relevant evidence, such as European Society for Medical Oncology (ESMO) and European Association of Urology (EAU).

The ERG considers the search strategy carried out by the company for clinical effectiveness studies to be limited in several areas, particularly the search date (July 2016), exclusion of non-English language evidence, the restrictive method used to search ClinicalTrials.gov, and the review of abstracts from only two conferences could mean that relevant evidence has been missed.

4.1.2 Inclusion criteria

The company present a single set of inclusion criteria (Table 7) for the direct and indirect evidence reviews (original treatment naïve NMA and mixed pretreated NMA). The ERG's critique of how the direct evidence relates to the decision problem outlined in the NICE final scope[1] is presented in Section 3, and a critique of applicability of the indirect evidence is presented in Section 4.3.

Table 7. Inclusion criteria used for clinical effectivness literature review (reproduced from CS, Table 10)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Aged ≥ 18 years Any gender Any race Has locally advanced/advanced/metastatic/stage III/stage IV disease No prior TKI or mTOR therapy	No data reported on relevant population
Intervention	Tivozanib monotherapy (or with best supportive care)	No data reported on relevant intervention
Comparators	Axitinib monotherapy (or with best supportive care) Bevacizumab monotherapy (or with best supportive care) Everolimus monotherapy (or with best supportive care) IFN-α monotherapy (or with best supportive care) Interleukin monotherapy (or with best supportive care) Pazopanib monotherapy (or with best supportive care) Sorafenib monotherapy (or with best supportive care)	No data reported on relevant comparator

	Sunitinib monotherapy (or with best supportive care) Temsirolimus monotherapy (or with best supportive care) Any other targeted therapy or immunotherapy Placebo Best supportive care	
Outcomes	Efficacy: •OS •PFS •Time to progression •Overall response rate (complete and partial) •Proportion with stable disease •Time to response •Duration of response Safety: •Incidence and severity of AEs •Withdrawals due to AEs •Deaths •Serious AEs	No data reported on a relevant outcome
Study design	RCT (any blinding) Studies only available as conference abstracts will be included if they report sufficient relevant data to allow inclusion in the analysis Systematic reviews will be used for citation chasing only: •Full text only •Published from 2010 onwards •Including only RCTs in a population with advanced or metastatic RCC receiving a relevant intervention	Other study design
Language restrictions	English full-text publication	Full text publication in other language
Publication dates	1980 onwards (journal articles) Last 2 years of conference abstracts	Published outside relevant dates
Abbreviations: AE, Adverse event; IFN, interferon; mTOR, mammalian target of rapamycin; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor		

The ERG notes the population inclusion criteria presented by the company is broad, covering all adult advanced or metastatic renal cell carcinoma (RCC) patients providing they had not received prior treatment with vascular endothelial growth factor (VEGF) or mammalian target of rapamycin (mTOR) therapies. Although not explicitly stated by the company, the ERG notes that studies in those with other prior therapies (nephrectomy, prior cytokine, or other non-VEGF- or mTOR-targeted therapies) are included. The CS did not present clear criteria relating to all prior types of therapy and how these were applied differentially for the treatment-naive and mixed pretreated NMAs.

The list of eligible comparators encompasses considerably more interventions than those specified by the company as relevant to the decision problem and comparators of interest listed in the final NICE scope[1] (see Section 3.3 for discussion regarding relevant comparators). The company provides no rationale for the chosen comparators, and did not separate comparators by line of therapy, as was done in the NICE final scope.[1] The list of comparators included in the original NMAs led to many studies being included, which may have introduced unnecessary clinical heterogeneity (i.e. baseline prognostic indicators, study duration, rules for crossover etc.). A critique of the studies included in the original CS and the reasoning behind the ERG's request for a more focused NMA are provided in Section 4.3.

The ERG considers the outcomes specified by the company to be appropriate and relevant to those specified in the NICE final scope.[1]

Overall, the ERG considers the company's inclusion criteria for direct and indirect evidence to have several limitations. The broad population and intervention criteria may have introduced unnecessary clinical heterogeneity to the NMAs, a thorough assessment of which was not provided in the CS (Section 4.3). There was a lack of transparency regarding how inclusion criteria were applied for the three avenues of evidence (direct, indirect treatment-naïve, indirect mixed pretreated).

4.1.3 Critique of screening process

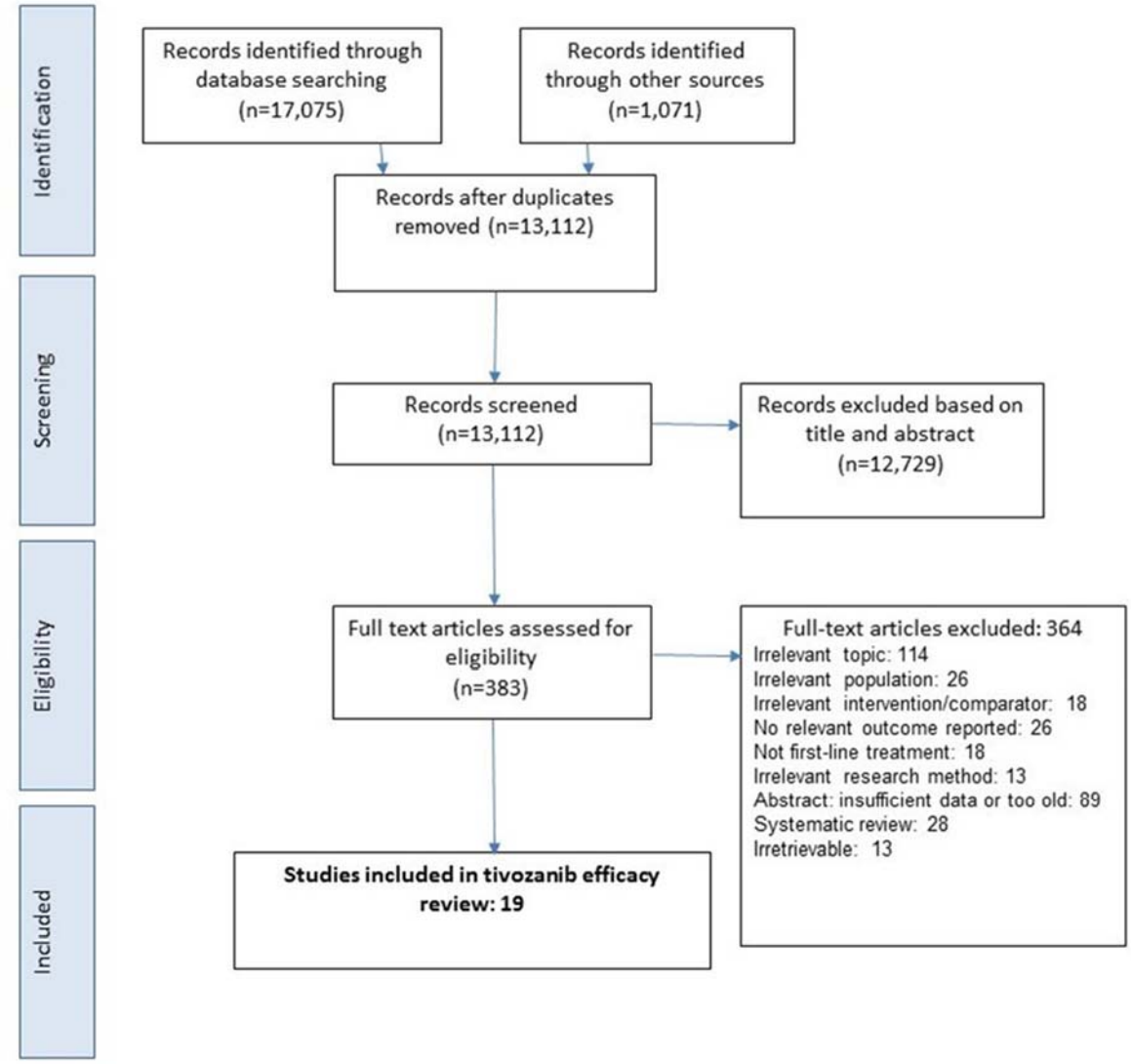
4.1.3.1 Tivozanib literature review

A summary of the screening processes carried out by the company to identify studies investigating tivozanib is provided in Figure 2. A total of 13,112 records were identified from database searches and other sources. Of the retrieved records, 12,729 records were excluded at title and abstract screening. The remaining 383 records were assessed at full text stage for eligibility. According to the company a total of 364 full text articles were excluded resulting in 19 records included at the final stage. The company specified that 13 of these records were attributed to the TIVO-1 study.[60] The additional 6 records were related to a discontinuation tivozanib study[49] discussed further in Section 4.2. The ERG notes a disparity in the screening process numbers proved by the company. The number of full text articles excluded based on reasons provided by the company totals to 345 whereas the company have outlined the total number of excluded full text to be 364. Subsequently the number of included articles in the review totals to 38 as opposed to the 19 proposed by the company. The company provide no additional details regarding these inconsistencies in screening process.

The company outline their reasons for exclusion at the full text screening stage. These include: irrelevant topic; irrelevant population; irrelevant intervention/comparator; no relevant outcome; not first line treatment; irrelevant research method; abstract insufficient data or too old; systematic review; irretrievable. The ERG would agree with most reasons for excluding these full text articles. Although the exclusion due to 'not first-line treatment' is inconsistent with the inclusion criteria outlined by the company for their mixed pretreated NMA (see Table 7). Furthermore, the ERG considers the exclusion of ~71 abstracts (data from CS Appendix 2.4) for being more than 2 years old as this may have overlooked relevant evidence for the comparator drugs.

The ERG considers that the omission of a randomised preference study of tivozanib versus sunitinib (i.e. a relevant comparator) should have been explained by the company; the study was listed in the SmPC evidence requested during clarification (Table 22), and measured mostly short term outcomes, but may have included relevant data and should have, at the least, been listed as an excluded study.

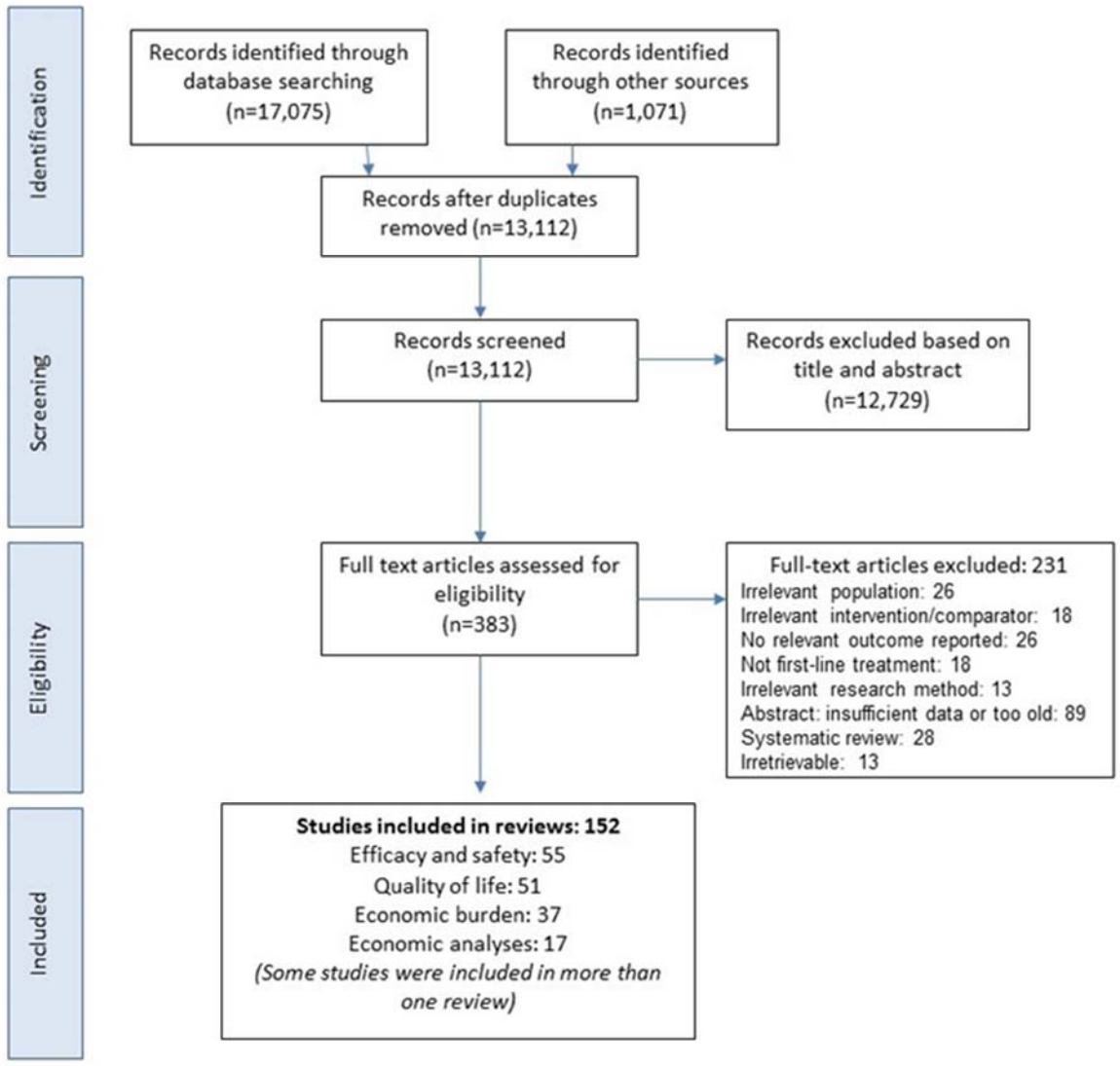
Figure 2. PRISMA diagram for the systematic literature review by the company (reproduced from CS, Figure 1, pg. 51



4.1.3.2 Network meta-analysis literature review

A summary of the screening process carried out by the company to identify studies used to populate the two NMAs in the CS (treatment naïve and mixed pretreated) is provided in Figure 3. A total of 383 records were assessed at full text stage for eligibility, and, of these, 231 articles were excluded. A total of 152 records were included (some in in more than one review): 55 were efficacy or safety studies; 51 quality of life; 37 studies of economic burden; and 17 economic analyses. A total of 24 RCTs were found that reported relevant interventions in patients with advanced/metastatic RCC.

Figure 3. PRISMA diagram for mixed treatment comparison (reproduced from CS, Figure 2, pg. 78)



Of the 24 RCTs identified from the search and screening process, 19 were finally incorporated into the treatment-naïve NMA (17 studies,[7, 9, 61-71] of which 4 were study subgroups[41, 72-74]) and mixed pretreated NMAs (all 19 studies, including the mixed pretreated populations of 5 studies[41, 72-75] and the sole pretreated population for 1 study[76]). Five studies[77-81] were excluded from the NMAs; a summary of these studies with the reason for exclusion in shown in Table 8. The ERG notes the reason for excluding these studies was appropriate: three studies excluded due to invalid outcomes that were not listed in the inclusion criteria[77, 80, 79], one study[78] was excluded due to the lack of relevant comparison for the intervention used in the study, and one study[81] had limited reported data. The ERG is uncertain why four of these studies were included in the CS despite a lack of relevant outcomes[77, 79-81] and other studies excluded for lack of relevant outcomes were not (CS Appendix 2.4). Excluding studies based on outcome reporting when other inclusion criteria are met may be justified if relevant outcomes were not measured; however, the ERG would expect to see a description of studies that measured relevant

outcomes and did not report them as an indication of selective reporting in the evidence base, including relevant records from trial registries without reported results.

Table 8. Studies identified in the search for indirect evidence but excluded from NMA (Text adapted from CS, pg. 80)

Study	Exclusion criteria
Clark 2003	No valid outcome reported: main outcome DFS
Dexeus 1989	Comparators not relevant: chemotherapy vs chemotherapy + immunotherapy
Motzer 2001	No efficacy measures including PFS or OS
Zhao 2013	No valid outcome reported: disease free survival
Zhou 2016	Limited reported data: no HR for PFS and no median PFS

Abbreviation: DFS, disease free survival; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival

A summary of the studies included in the NMAs in the original CS is provided in Table 9. As with the inclusion criteria (4.1.2), the study selection process is not detailed separately for the treatment-naïve and mixed pretreated NMAs; further discussion on the NMA methods and results are detailed in Section 4.3.

Table 9. Summary of RCTs included in the original NMAs (adapted from CS, Tables 25 and 26)

Trial ID	Population	Intervention	Comparator	Methods	Results included in original NMA				
					OS	PFS	ORR	CR	AEs
ARCC[65]	Treatment naïve, IV/recurrent, CC	IFN-α 2a	Temsirolimus	OL Phase 3	✓	✓	✓		✓
ASPEN[61]	Treatment naïve, metastatic, nCC	Sunitinib	Everolimus	OL Phase 2	✓	✓	✓	✓	✓
COMPARZ[9]	Treatment naïve, metastatic, CC	Pazopanib	Sunitinib	OL Phase 3	✓	✓	✓	✓	✓
CROSS-J-RCC[82]	Treatment naïve, metastatic, CC	Sunitinib	Sorafenib	OL, 2-way crossover at progression/AE		✓	✓		
Eisen 2015[62]	Treatment naïve, unresectable/ metastatic, CC	Nintedanib	Sunitinib	OL Phase 2	✓	✓	✓	✓	✓
Escudier 2009[63]	Treatment naïve, III/IV CC	IFN-α 2a	Sorafenib	OL Phase 2, 1-way crossover available at progression		✓		✓	
ESPN[70]	Treatment naïve, metastatic, nCC	Everolimus	Sunitinib	OL Phase 2, 2-way crossover at progression	✓	✓	✓		✓
Gleave 1998[64]	Treatment naïve, metastatic	IFN-γ 1b	Placebo	SB	✓			✓	✓
Hutson 2013[66]	Treatment naïve, metastatic	Axitinib	Sorafenib	OL Phase 3	✓	✓	✓	✓	
Motzer 2009[7]	Treatment naïve, metastatic, CC	Sunitinib	IFN-α	OL Phase 3, 1-way crossover available at progression	✓	✓	✓	✓	
Mulders 2012[75]	Mixed pretreated and treatment naïve, recurrent/metastatic	Cediranib	Placebo	DB Phase 2, 1-way crossover available at progression		✓			✓
Negrier 1998[68]	Treatment naïve, metastatic	Interleukin-2	IFN-α 2a	OL	✓		✓	✓	
PERCY Quattro[69]	Treatment naïve, metastatic	Interleukin-2	IFN-α 2a	OL	✓	✓			✓
RECORD-3[67]	Treatment naïve, metastatic	Everolimus	Sunitinib	OL, 2-way crossover at progression		✓		✓	
Sternberg 2010[74]	Mixed pretreated and treatment naïve, advanced/metastatic	Pazopanib	Placebo	DB Phase 3	✓	✓	✓	✓	
SWITCH[72]	Mixed pretreated and treatment naïve, advanced/metastatic	Sorafenib	Sunitinib	OL Phase 3, 2-way crossover at progression		✓	✓	✓	✓
TARGET[73]	Pretreated, advanced	Sorafenib	Placebo	DB Phase 3, 1-way crossover available at progression	✓	✓		✓	✓
TIVO-1[41]	Mixed pretreated and treatment naïve, recurrent/metastatic CC	Tivozanib	Sorafenib	OL Phase 3, 1-way crossover available at progression	✓	✓	✓	✓	✓
Yang 2003[76]	Pretreated, metastatic	Bevacizumab	Placebo	DB Phase 2		✓	✓	✓	

Abbreviations: AEs, adverse effects; CC, clear cell; CR, complete response; DB, double-blind; IFN, interferon; NMA, network meta-analysis; nCC, non-clear cell; OL, open label; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomised controlled trial; SB, single blind

Overall, the ERG considers the company's screening process to include inaccuracies and lack transparency, and there is no mention in the CS of the process being carried out independently by two reviewers. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram for the direct evidence concerning tivozanib includes numerical errors, and the NMA screening criteria cannot be verified because they were not provided separately for the two populations.

4.1.4 Quality assessment

4.1.4.1 Quality assessment of TIVO-1

The company carried out quality assessment of the TIVO-1 trial[41]; however, the company did not describe whether this was carried out independently by two reviewers and did not give the source of the quality assessment checklist used. The quality assessment evaluated the following domains as 'Yes', 'No' or 'Unclear: randomisation; treatment allocation; baseline characteristics; blinding; drop-out imbalances; outcome reporting and intention to treat analysis.

The company assessed the TIVO-1 trial as low risk of bias with the exception that care providers were not blinded to treatment allocation due to the open label design of the trial. The ERG's quality assessment of TIVO-1 showed some agreement with the company's assessment with regards to randomisation, treatment allocation, imbalances at discontinuation and outcomes reported, which were considered low risk of bias, However, the ERG also noted other domains had an unclear potential for bias, which are discussed below. A summary of the company's assessment of TIVO-1 together with that of the ERG is provided in Appendix 9.3.

Firstly, the ERG identified imbalances between the two treatment groups at the onset of the study. Rates of 'most common metastases sites', 'organs involved' and the Eastern Cooperative Oncology Group (ECOG) and Memorial Sloan Kettering Cancer Center (MSKCC) scores were all disproportionate between the tivozanib and sorafenib groups. Differences in baseline characteristics between the two treatment groups are discussed in Section 4.2.2. Secondly, with regards to outcome assessment, the TIVO-1 study had both an investigator and independent radiology review (IRR) of progression; however, IRR could be bypassed in some situations (see Section 4.2.1.1). As TIVO-1 was an open-label trial, the lack of IRR increases the risk of detection bias, but it was available for most patients and was used as the company's primary analysis. Finally, the company state that an intention to treat (ITT) analysis was used for all clinical efficacy outcomes. However, imbalances in the proportion of patients receiving subsequent therapies, caused in part by the study's one-way crossover design, mean the ITT approach was inappropriate for overall survival (OS). Despite crossover adjustment of OS data being estimated and presented in the CS, the company chose not to use these adjusted results in their

subsequent analyses, further contributing toward biases in the OS data. A full critique of the evidence submitted for tivozanib is provided in Section 4.2.

4.2 Critique of the evidence submitted for tivozanib

One RCT of tivozanib and an associated extension study met the inclusion criteria for the company's clinical effectiveness review of the direct evidence; hereafter referred to as TIVO-1 and the extension study. The main publication of TIVO-1 is Motzer 2013[41], but additional information is derived from the interim[12] and final clinical study reports (CSRs)[46]. Two further studies are presented as supplementary evidence of efficacy and safety: the discontinuation study AV-951-07-201[47, 49] and the biomarker study AV-951-10-202[48, 50]). For completeness, the ERG has summarised the methods and results of the two Phase II studies in Section 4.2.1.2, but does not provide a critique in subsequent sections because neither met the inclusion criteria for the company's review of clinical effectiveness.

4.2.1 Trial conduct

4.2.1.1 TIVO-1 and the extension study

TIVO-1 was a parallel, open-label, randomised Phase III trial in which patients were assigned 1:1 to either tivozanib or sorafenib for the treatment of metastatic or recurrent RCC.[41] Recruitment took place at 76 centres in 15 countries (Bulgaria, Canada, Chile, Czech Republic, France, Hungary, India, Italy, Poland, Romania, Russia, Serbia, the UK, Ukraine and the US). Patients were eligible if they had a clear cell component to their disease, prior nephrectomy, ECOG performance status of 0 or 1,[15] and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.[83] Prior nephrectomy and ECOG score of 0 or 1 are indicators of favourable prognosis (see Section 2.1), which has implications on the applicability of the TIVO-1 population to the full population defined in the NICE final scope (see Section 3.1).

TIVO-1 enrolled 517 patients between February and August 2010.[41] From May 2010 to December 2011, patients who progressed on sorafenib were offered second-line treatment with tivozanib in the extension study (AV-951-09-902)[46], and no provision of second-line therapy was made for patients who progressed on tivozanib. The data cut for progression-free survival (PFS) was in December 2011, the official study end, but patients were followed up for OS and subsequent therapies until June 2013. The overlapping timelines and data cuts of TIVO-1 and the extension study are presented in Appendix 9.1, compiled from the CS and clinical study reports (CSRs)[12, 46]. When TIVO-1 ended in December 2011, patients who had not progressed on tivozanib could continue their treatment by enrolling in the extension study. The few people who had not progressed on sorafenib by December 2011 were offered free treatment with tivozanib in the extension study; continued use of sorafenib was not provided free of charge under the extension protocol (information provided in the clarification responses). The design led to most patients who progressed on sorafenib (and some who did not progress by study end)

subsequently receiving tivozanib, which confounded the results for OS. The confounding was exacerbated due to limited access to medications for people who progressed on tivozanib (shown in Table 13).

The CS includes a participant flow diagram based on the TIVO-1 endpoint on 15 December 2011 (CS, Figure 3, pg. 66), which does not include information about the movement of sorafenib patients into the extension study. Figure 36 (reproduced from CS, Figure 2) shows the basic design of TIVO-1 and the extension protocol. The ERG has compiled information from these sources (CS Figures 2 and 3) with more recent participant flow data presented in the final CSR (e.g. Figure 38) and additional information provided by the company during the clarification process to produce a more complete illustration of the flow of patients in TIVO-1 and the extension protocol (Figure 35). Median follow-up for PFS and OS was longer for tivozanib-treated patients (595 days and 810 days) than sorafenib-treated patients (364 days and 915 days, respectively; information provided during the clarification process).

The ERG noted a number of data inconsistencies between the published paper,[41] CS, interim CSR[12] and final CSR.[46] The ERG asked the company to clarify which data cut (see Figure 34) was used for each outcome included in the CS and whether the analysis included data collected during the extension study, which the company provided. Wherever possible, the ERG has included which data cut was used when discussing results.

Most participants were recruited from centres in Central and Eastern Europe (457/517; 88%) and only four patients were enrolled in the UK (Leicester and Cambridge).[46] The extent to which the population of TIVO-1 is relevant to the NICE final scope,[1] including how recruitment sites affected type of prior and subsequent treatments received, is discussed in Section 3.1.

Tivozanib was given orally as one 1.5mg tablet once a day in four week cycles (3 weeks of treatment and 1 week off).[41] Sorafenib was given as two 200mg tablets twice daily (800mg/day) continuously. Patients took the treatment until disease progression, unacceptable toxicity, death or any other reason for discontinuing the drug. Relative dose intensity was higher in the tivozanib group (93.9%) than the sorafenib group (80.8%; final CSR pg. 154) and different dose reduction rules for tivozanib and sorafenib (sorafenib could be re-escalated but tivozanib could not; final CSR, pg. 54) may have implications on the rates of adverse effects against, cost, and efficacy (discussed in Section 4.2.4 and Section 5).

Mean days of treatment in each group is reported in Table 46 of the final CSR including additional access to as-randomised treatment during the extension study. Converted to months, patients in the tivozanib group spent a mean of 16.0 months on treatment (standard deviation 12.2; range 0.5 to 38.3

months) compared with 12.6 months in the sorafenib group (standard deviation 10.0; range 1 day to 38.0 months).

Participants who enrolled in TIVO-1 were randomised by an Interactive Voice Response/Interactive Web Response (IVR/IWR) system to receive tivozanib or sorafenib. Randomisation was stratified by geographic region, number of prior treatments for metastatic RCC (i.e. 0 or 1), and number of metastatic sites/organs involved (1 or ≥ 2). The study was unblinded, but the measurement of PFS and response included independent review procedures.

PFS was assessed using RECIST criteria[83] based on magnetic resonance imagining or computed tomography at baseline and every 8 weeks. To reduce bias associated with the study's open-label design, investigator-assessed progressive disease (PD) was confirmed within 48 hours by a blinded independent radiology review (IRR) panel, unless investigators considered there to be a significant clinical deterioration, appearance of new lesions, or judged there to be a >50% increase in measurable disease per RECIST. IRR-defined PFS was the primary analysis, and the circumstances by which IRR could be bypassed were reduced in a protocol amendment; the level of agreement between IRR and investigator-assessed PFS is shown in Table 16, but the IRR analysis was the primary analysis and is used to support the NMA (Section 4.3). The CSRs present sensitivity analyses to explore how different methods of PD assignment and confirmation affected the primary endpoint, which are discussed in Section 4.2.4.1.

The secondary endpoints were OS, objective response rate (ORR), safety and tolerability, and health-related quality of life (HRQoL). The appropriateness of the outcomes is discussed in Section 3.4. The CS acknowledges the confounding effect the subsequent therapies on OS and presents a crossover-adjusted analysis, though these data were not included in the NMA. During the clarification process, the ERG requested that the company present results from alternative methods of crossover-adjustment[84] and that the most appropriate be used to inform the NMA. A critique of the statistical approaches used for the OS analyses are provided in Section 4.2.3, and the associated results are described in Section 4.2.4.1.

Protocol amendments are listed in the interim[12] and final[46] CSRs. Within the four sets of protocol amendments described in the interim CSR[12], the ERG considers the following changes to be of note:

- Amendment 1 dated 17 August 2009 (CSR pg. 74–75):

"length of time subjects with documented stable disease or an objective response could continue to receive study drug at the same dose and schedule in this study was changed from "up to 1 year" to "up to 2 years" from the first dose as long as tolerability was acceptable";

- Amendment 3.0 dated 2 June 2011 (interim CSR pg. 76):

"Conditions in which verification [of PD] was not required [by IRR] were modified to remove the requirement for > 50% increase in measureable disease and appearance of new lesions".

In summary, the design of TIVO-1 and the subsequent extension study introduces considerable uncertainty to the estimate of OS due to the substantial imbalance in subsequent therapies between groups. The use of multiple data cuts caused inconsistencies between the results in the published paper, CS and CSRs that have been difficult to disentangle, reducing the ERGs confidence in the study's conduct and the accuracy of data capture through TIVO-1 and the extension study.

4.2.1.2 Non-randomised and non-controlled evidence

The CS and CS appendix 3 include the methods and results of two Phase II studies of tivozanib in RCC as supplementary evidence of efficacy and safety. The results of the Phase II studies do not contribute to the indirect clinical- and cost-effectiveness analyses and are, thus, not included in subsequent sections. AV-951-07-201[47, 49] was identified as a randomised study but is included in the submission under the non-randomised section because patients were preselected on the basis of response for the randomised phase and did not receive continuous therapy as would be the case in normal care. The design of AV-951-07-201 is shown in Appendix Figure 37. The methods and results of both Phase II studies are summarised in Table 10.

Table 10. Summary of non-randomised and non-controlled evidence (adapted from CS Table 36, pg. 100 and summarised from CS appendix 3)

	Discontinuation study[47, 49]	**Biomarker study[48]**
Study number	AV-951-07-201	AV-951-10-202
Objective	To assess activity and safety of tivozanib in RCC	To evaluate biomarkers and their correlation with clinical activity/treatment related toxicity in patients with RCC treated with tivozanib To estimate PFS at 6 months
Population	•Adults •Confirmed measurable recurrent or metastatic RCC or primary RCC not amenable to surgery •Karnofsky performance status ≥70% •Adequate renal, hepatic or haematological function •Treatment naïve, or no more than one prior systemic therapy •No prior VEGF or mTOR targeted therapy	•Adults with unresectable locally recurrent or metastatic RCC •ECOG score 0 or 1 •Prior nephrectomy •Treatment naïve, or no more than one prior systemic therapy •No prior VEGF or mTOR targeted therapy
Location	28 centres in Russia (16), Ukraine (7) and India (5)	21 centres in the US and Canada
Intervention/ comparator	16 weeks open-label tivozanib for patients with RCC (N=272), then one of the following: •12 weeks tivozanib for patients with ≥ 25% tumour shrinkage (N=78) •Discontinuation for patients with ≥ 25% tumour growth (N=50) •Discontinuation for other reasons (N=26)	Tivozanib, single arm (N=105) 21 day screening period followed by 6-month treatment period. Treatment was discontinued earlier for patients who had PD or unacceptable toxicity. Patients without PD or unacceptable toxicity could enrol into an extension study which was ongoing at the time of writing (AV-951-09-901)[85]

	•Randomisation to 12 weeks tivozanib or placebo for patients with < 25% tumour change since baseline (N=118) Patients continuing or switching back to tivozanib after 12 weeks were followed for PFS.	Study terminated following the negative decision from the FDA; primary efficacy analyses of correlations between biomarkers, PFS and objective response were never completed.
Outcomes	•ORR after 16 weeks open-label •% progression-free after the 12-week randomised phase •PFS (randomised subset and overall)	•Correlations between biomarkers, PFS and response •% progression-free after 6 months •ORR •PFS duration estimate
Main results	ORR: 18% during open-label phase. Progression-free after 12 further weeks: 49% tivozanib (N=30), 21% placebo (N=12) Median PFS after treatment with tivozanib or placebo: 10.3 months vs 3.3 months Overall PFS in all treated patients*: 11.7 months	Study terminated early Progression-free at 6 months: 61% ORR: 25% (N=26); 24 people had partial response, 2 had complete response. PFS estimate: 25 weeks
Justification for inclusion	Provides additional evidence for tivozanib in an open label setting and versus placebo	Provides additional evidence for tivozanib in an open label setting
Abbreviations: mTOR, mammalian target of rapamycin; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor. *Patients were censored at the time of random assignment to the placebo group.		

4.2.2 Baseline characteristics

Baseline characteristics of the full mixed pretreated TIVO-1 population and the subpopulation who were treatment-naive are presented in Table 11. The ERG's reasons for focusing on the treatment-naïve subpopulation in TIVO-1 are described in Section 3.1. Patients were between 23 and 83 years of age, with a median age of 59 years. Around three quarters of the population were male. As per the inclusion criteria, all patients had an ECOG performance score of 0 or 1 and their RCC had spread to at least one other organ (though more often to 2 or more). Most people who enrolled in the study were from Central or Eastern Europe; by focusing on the treatment-naïve population, the issue of prior therapies being different to those used in the National Health Service (NHS) is avoided, but OS results remain confounded by disparity between the geographical sites of TIVO-1 and England in the types of subsequent treatment received.

Most baseline characteristics for the treatment-naïve subpopulation were balanced across the two groups and were comparable with those of the total trial population. However, some characteristics indicate the sorafenib group might have slightly better prognosis than the tivozanib group. More people in the sorafenib group than the tivozanib group had an ECOG performance score of 0 in the total trial population (score of 0: 54% sorafenib vs 45% tivozanib), though the difference was less marked in the treatment-naïve subpopulation (52% sorafenib vs 47% tivozanib). Similarly, slightly more people in the sorafenib group had a favourable MSKCC prognostic status, both in the total population and treatment-naïve subpopulation (sorafenib 34% vs tivozanib 27% and 33% vs 27% for total and treatment naïve, respectively). Slightly more people in the tivozanib group than the sorafenib group had involvement of 2 or more metastatic organs in the total population (71% tivozanib vs 66% sorafenib), and this difference was slightly more pronounced in the treatment-naïve subpopulation (71% tivozanib vs 64% sorafenib).

Table 11. Baseline characteristics of the treatment-naïve subpopulation and total randomised population in TIVO-1

		Full population		Treatment-naïve	
		Tivozanib	**Sorafenib**	**Tivozanib**	**Sorafenib**
N (% of randomised)		260 (100)	257 (100)	181 (70)	181 (70)
Median age (range)		59 (23–83)	59 (23–85)	59 (23–83)	59 (23–85)
Male, n (%)		185 (71)	189 (74)	134 (74)	135 (75)
ECOG performance status, n (%)	0	116 (45)	139 (54)	85 (47)	94 (52)
	1	144 (55)	118 (46)	96 (53)	87 (48)
Region ……North America/Western Europe		22 (9)	18 (7)	19 (11)	15 (8)
Central/Eastern Europe		229 (88)	228 (89)	154 (85)	155 (86)
Rest of world		9 (3)	11 (4)	8 (4)	11 (6)
Number of metastatic organs, n (%)	1	76 (29)	88 (34)	53 (29)	65 (36)
	≥2	184 (71)	169 (66)	128 (71)	116 (64)
MSKCC prognostic group, n (%)	Favourable	70 (27)	87 (34)	48 (27)	60 (33)
Intermediate		173 (67)	160 (62)	121 (67)	112 (62)
Poor		17 (7)	10 (4)	12 (7)	9 (5)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Center.
Baseline characteristics for the untreated population from Sternberg 2013 ASCO poster[51]
Selected baseline characteristics for the total population are collated from CS Table 17, page 67, and the clinical study report, Table 12, page 93[46]

As described in Section 3.1, the ERG's clinical experts consider the characteristic of the TIVO-1 population to be comparable to a population with metastatic RCC who would be eligible for treatment with tivozanib in the NHS, despite only four patients being recruited from UK centres. However, the inclusion criteria mean that the TIVO-1 population is restricted to patients with a clear cell component to their RCC, good performance status (ECOG score of 0 or 1) and prior nephrectomy, all of which generally indicate better prognosis than the full population covered by the NICE final scope.[1]

Baseline characteristics of the two Phase II studies are provided in Appendix 9.2.

A comparison of the baseline characteristics of the TIVO-1 population with baseline characteristics of other studies included in the NMA is provided in Section 4.3.

4.2.3 Statistical approach

The target sample size for TIVO-1 was 500 patients (250 randomised to tivozanib and 250 to sorafenib), to observe 310 events of disease progression or death. The sample size was calculated to give 90% power to detect a difference in PFS between tivozanib and sorafenib, based on a p-value of 0.05 and a projected 3-month/44.8% benefit of tivozanib (9.7 months) versus sorafenib (6.7 months). For OS, the calculation was based on assumed survival of 24 months for tivozanib and 18 months for sorafenib, giving approximately 300 events by the final analysis and 70% power to detect a difference between treatments ($p<0.05$).[41]

The primary analyses for the study's efficacy outcomes (OS, PFS, response rates, and HRQoL) were based on the ITT population, defined as all randomised patients. However, during the clarification process, the ERG conveyed that their clinical experts considered only the treatment-naïve population to be relevant to a population who would be eligible for tivozanib in England. Subsequent OS, PFS and adverse effects analyses submitted by the company were restricted to treatment-naïve patients, which became their preferred analysis; analyses of response rates and quality of life still reflect the full population but do not inform the economic model.

In the CS, based on the main publication of TIVO-1[41] and the analyses planned in the protocol, PFS and OS were estimated using a Cox proportional hazards model stratified by number of prior treatments (0 or 1) and number of metastatic sites/organs (1 or ≥2). Information provided during the clarification process showed that the proportional hazards assumption does not hold for PFS (see Appendix 9.4). A range of analyses that do not rely on proportional hazards were subsequently provided by the company for PFS and, for consistency, OS. Results from these new analyses populated the NMA and economic model; methods and results are provided in Section 4.3.3 and 4.3.4, respectively.

The company confirmed that the primary PFS analysis was based on the TIVO-1 IRR data up to December 2011. While some people did progress on tivozanib after this date in the extension study, it was not appropriate to include the data because there were also patients who swapped from sorafenib to tivozanib who had not progressed by December 2011. Patients were censored in the PFS analysis as follows:

- at the December 2011 data cut if they did not have objective tumour progression and were still in the study at that time;
- on the day following their last assessment if there was no objective progression and the patient was known to have received anti-tumour treatment other than the study treatment or had been removed from treatment follow-up for another reason;
- at randomisation if there was no baseline or post-randomisation tumour assessment, unless they were known to have died within 140 days of randomisation.

The CS included a list of planned subgroup analyses for the primary outcome (Table 12).

Table 12. TIVO-1 planned subgroup analyses for PFS (adapted from CS, pgs 58–59)

Subgroup	Categories
Age group	<65, ≥65 years
Race	white, non-white
Gender	male, female
Screening ECOG performance status	0, 1

Time since diagnosis	<1 year, ≥1 year
Geographic region	North America/Western Europe, Central/Eastern Europe, rest of the world
Number of prior treatments for metastatic disease	0, 1
Number of metastatic sites/organs involved	1, ≥2
Systolic blood pressure at baseline	≤140 mmHg, >140 mmHg
Diastolic blood pressure at baseline	≤90 mmHg, >90 mmHg
MSKCC prognostic group	favourable, intermediate, poor

MSKCC risk factors: Karnofsky performance status (KPS) < 80% (equivalent to ECOG status ≥2); lactate dehydrogenase >1.5 times upper limit of normal; serum haemoglobin <lower limit of normal; corrected serum calcium >25.95 mmol/l [10mg/dl; absence of prior nephrectomy. Patients with none of the above were classed as favourable, 1–2 as intermediate, and 3 or more as poor.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan Kettering Cancer Center

OS was defined as the time from randomisation to death from any cause. Median OS in the ITT population was not reached at the protocol-defined data cut of August 2012 so a subsequent data cut took place on 10 July 2013, referred to as the "post-primary efficacy cut" (CS, Table 12). The primary ITT analysis was, by this point, confounded by a subsequent therapy imbalance of 174 (67.7%) in the sorafenib group compared with 79 (30.5%) of the tivozanib group (Table 13). Furthermore, 161 of the 174 sorafenib-treated patients received tivozanib (65.8%), and only 53 tivozanib patients received a second-line targeted agent (20.5%). The imbalance in subsequent therapies was similar in the subset of patients who were treatment naïve (also shown in Table 13).

Table 13. TIVO-1 subsequent therapies received at July 2013 data cut (provided during clarification process)

	Treatment naïve		**Full population**	
	Tivozanib (N=182) [a] N (%)	**Sorafenib (N=181) N (%)**	**Tivozanib (N=259) [a] N (%)**	**Sorafenib (N=257) N (%)**
Received randomised therapy only	128 (70.3)	57 (31.5)	180[b] (69.5)	83 (32.3)
Received subsequent therapy	54 (29.7)	124 (68.5)	79 (30.5)	174 (67.7)
Targeted therapy	37 (20.3)	120 (66.3)	53 (20.5)	169 (65.8)
First targeted therapy used: Tivozanib	0 (0.0)	114 (63.0)	0 (0.0)	161 (62.6)
Other VEGF inhibitor	17 (9.3)	2 (1.1)	24 (9.3)	4 (1.6)
mTOR inhibitor	20 (11.0)	4 (2.2)	29 (11.2)	4 (1.6)
Non-targeted therapy only	17 (9.3)	4 (2.2)	26 (10.0)	5 (1.9)
First non-targeted treatment used: Immunotherapy	NR	NR	13 (5.0)	3 (1.2)
Radiotherapy	NR	NR	5 (1.9)	2 (0.8)
Chemotherapy	NR	NR	1 (0.4)	0 (0.0)
Surgery	NR	NR	2 (0.8)	0 (0.0)
Other	NR	NR	5 (1.9) [b]	0 (0.0)

[a] One patient randomised to tivozanib withdrew consent before receiving treatment and is excluded from this table
[b] 4 patients received tamoxifen and 1 received neovastat. 1 further patient received herbal therapy post-progression but no further details were given so they have not been included in this table.
Abbreviations: mTOR, mammalian target of rapamycin; N, number of patients; VEGF, vascular endothelial growth factor.

The CS presented an analysis to adjust the mixed pretreated population results for crossover using the Inverse Probability of Censoring Weighting (IPCW) method (full details provided in CS pgs 62–65). IPCW is "an observational-based approach whereby data for switchers are censored at the point of switch and remaining observations are weighted with the aim of removing any censoring-related selection bias".[84] During the clarification process, the ERG asked that results be provided from alternative models of crossover adjustment for OS[84] and the company provided results from unstratified and stratified Rank Preserving Structural Failure Time (RPSFT) model for the treatment-naïve population. Of the two RPFST analyses, the company preferred deemed the stratified analyses more appropriate because there were baseline imbalances in TIVO-1 (Section 4.2.2), but still preferred the IPCW approach overall (Box 6). Nonetheless, the company did not use any of the adjusted results to populate the NMA, choosing to use the original unadjusted analysis of the treatment-naïve population (discussed in Section 4.3.3).

Box 6. Company rationale for the Inverse Probability Censoring Weighting (IPCW) method of crossover adjustment (provided during the clarification process)

Although this approach [RPSFT] was considered optimum for the pazopanib submission (which was modelled versus placebo), we believe that the IPCW is more appropriate in this case. This is because the assumption of constant treatment effect breaks down when a one way switch to active comparator, rather than placebo is involved. There is good evidence of differential treatment benefit when switching from one TKI to another following first progression, an effect that can be clearly seen in the SWITCH study, when comparing the second PFS curves for the two arms with the primary PFS curve. This assumption of constant treatment effect is not required in the IPCW approach, which we consequently believe gives a better indication of crossover corrected benefit in this case. In both cases, the risk exists that unknown confounders may bias the results, but the IPCW approach uses a far more robust method to take into account baseline differences, than the stratified RPFST.
Abbreviations: IPCW, inverse probability of censoring weighting; PFS, progression-free survival; RPSFT, rank preserving structural failure time; TKI, tyrosine kinase inhibitor

The ERG disagreed with the company's preference for the IPCW approach because the RPSFT method is thought to be more reliable when a large proportion of patients have crossed over, as was the case in TIVO-1. The pivotal trial[74] included in the CS for pazopanib[86] had a similar subsequent therapy imbalance caused by one-way crossover as TIVO-1 (Sternberg 2010[74] 64% best supportive care, 34% pazopanib; TIVO-1 68% sorafenib, 31% tivozanib), and the RPSFT model was deemed the most appropriate. The choice has since been validated by incorporating each crossover adjustment of Sternberg 2010 into an indirect comparison to compare the results with direct results versus sunitinib from the now published COMPARZ study[9]; the RPSFT adjustment of Sternberg 2010[74] aligned most closely with the head-to-head comparison from COMPARZ.[9]

The CS presents a prespecified subgroup analysis of OS exploring variations in subsequent therapy imbalance by geographical region (CS pg. 76). The subgroup analysis was presented as evidence that OS was confounded by more subsequent therapy in the sorafenib arm (see Section 4.2.4.1).

Response was presented as number of patients in each group (mixed ITT population, not treatment-naïve subgroup) who had complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) and ORR (sum of partial and complete response) during the study.[41] The CS only presents the raw data with no summary effect measure (CS pg. 71, Table 20); however, effect estimates from the CSR[46] were provided during the clarification process as Cochran-Mantel-Haenszel odds ratios (OR) with 95% confidence interval (CI), stratified by number of prior treatments (0 or 1) and number of metastatic sites/organs involved (1 or ≥ 2). Results are presented in Section 4.2.4.3.

For the three HRQoL measures (Functional Assessment of Cancer Therapy-General [FACT-G], FACT Kidney Symptom Index–Disease-Related Symptoms [FKSI-DRS] and EuroQol-5 dimensions [EQ-5D]), least-square means for the mixed ITT population were estimated from assessments over the first year of treatment by repeated-measures mixed-effects models. Results were adjusted for treatment, assessment time, treatment-by-time interaction, baseline score, age, ECOG performance status, geographic region, number of metastatic sites, number of prior treatments, MSKCC prognostic factor status, time from diagnosis to study entry and presence of dose reduction. [redacted] Results are presented in Section 4.2.4.4.

Adverse effects (AE) were captured during TIVO-1 and throughout the extension study up to the last data cut in 2015 (see Figure 34). Crossover and subsequent therapies during TIVO-1 and the extension are unlikely to affect the results because treatment-emergent adverse effects (TEAEs) were recorded, i.e. those occurring during treatment or within 30 days of the last dose. All AE results presented in the CS refer to the mixed ITT population of TIVO-1; the ERG requested that results for the treatment-naïve population be incorporated in the AE NMAs during the clarification process. The CS also includes analyses based on earlier TIVO-1 data cuts in June and October 2012. Rates of different types of AE, number of people in each arm with AEs of a particular grade, and AEs leading to dose reductions, treatment interruption and discontinuation are all reported as number of patients out of the safety population for each group; where analysed, relative risk (RR) with 95 % CI are used. In the published paper and CS, AE reporting is restricted to those occurring in at least 10% of either treatment group. TEAEs are presented in Section 4.2.4.6.

4.2.4 Clinical effectiveness results

4.2.4.1 Overall Survival (OS)

The CS presents results from ITT analyses of OS in the mixed pretreated population from data cuts in August 2012 (protocol-defined), July 2013, and January 2015, as well as the results from the IPCW crossover-adjusted (Table 14); all hazard ratios (HRs) lie in favour of sorafenib and none of the results indicate a statistically significant difference between groups. The HR from the IPCW-adjusted analysis of the full population lies closer to no difference than any of the full population unadjusted analyses, but the estimate is less precise.

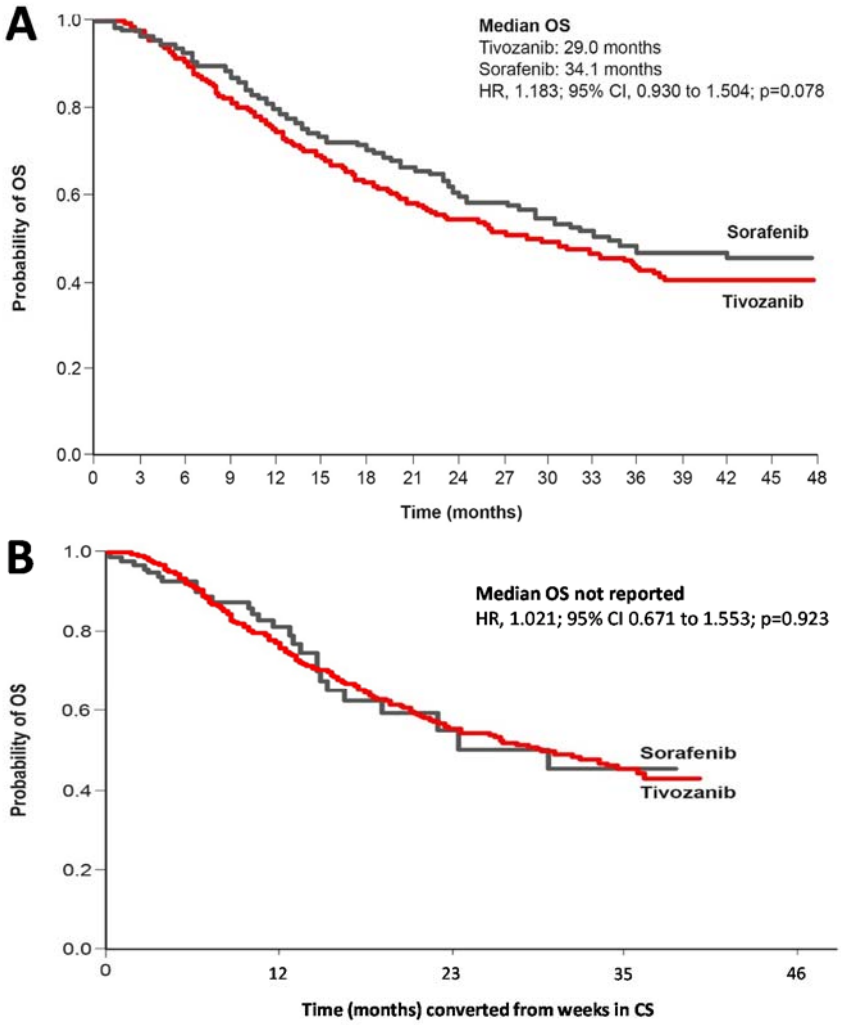
Table 14. OS results for all data cuts and analyses

	Median OS, months		**HR**	**95% CI**	**p-value**	**Source**
	Tivozanib (N=259)	**Sorafenib (N=257)**				
Full population, Aug 2012, unadjusted for crossover	28.8 (118 deaths)	29.3 (101 deaths)	1.245	0.954 to 1.624	0.105	CS, pg. 71
Full population, Jul 2013, unadjusted for crossover	28.2 (133 deaths)	30.8 (121 deaths)	1.147	0.896 to 1.470	0.276	CS, pg. 72 Final CSR pg. 116
Full population, Jan 2015, unadjusted for crossover	29.0	34.1	1.18	0.930 to 1.504	0.078	CS, pg. 72; KM Figure 4A
Full population, IPCW-adjusted*	NR	NR	1.021	0.671 to 1.553	0.923	CS, pg. 73, KM Figure 4B
Treatment-naïve subgroup, unadjusted for crossover, Jul 2013	NR	NR	1.23	0.90 to 1.67	NR	CS appendix 4.3.1; Figure 5A
Treatment-naïve subgroup, RPSFT-adjusted*	KM plot from independent curve fitting – see Figure 5					Clarification responses, Figure 5B and C
Prespecified subgroup analyses by geographical location based on the ITT July 2013 population (% of discontinued patients receiving subsequent therapy is shown in brackets for tivozanib and sorafenib)						
NA & EU (N=186)	32.9 (55.6%)	29.5 (79.5%)	0.846	NR	0.433	CS Table 22, Appendix Table 3
NA & EU5 (N=40)	NA (84.2%)	29.5 (82.4%)	0.497	NR	0.136	CS Table 22, Appendix Table 3
Russia & Ukraine (N=291)	26.3 (28.4%)	32.0 (71.0)	1.383	NR	0.051	CS Table 22, Appendix Table 3

*Unclear which data cut used for the crossover adjustment of the full population, and for the subgroup result for the treatment-naïve population.
NA & EU includes US, Canada, Bulgaria, Czech Republic, France, United Kingdom, Hungary, Italy, Poland and Romania.NA & EU5, includes US, Canada, Italy, France and UK.
Abbreviations: CI, confidence interval; CS, company submission; EU, European Union; HR, hazard ratio; IPCW, inverse probability censoring weighting; ITT, intention-to-treat population; KM, Kaplan-Meier; NA, North America; NR, not reported.

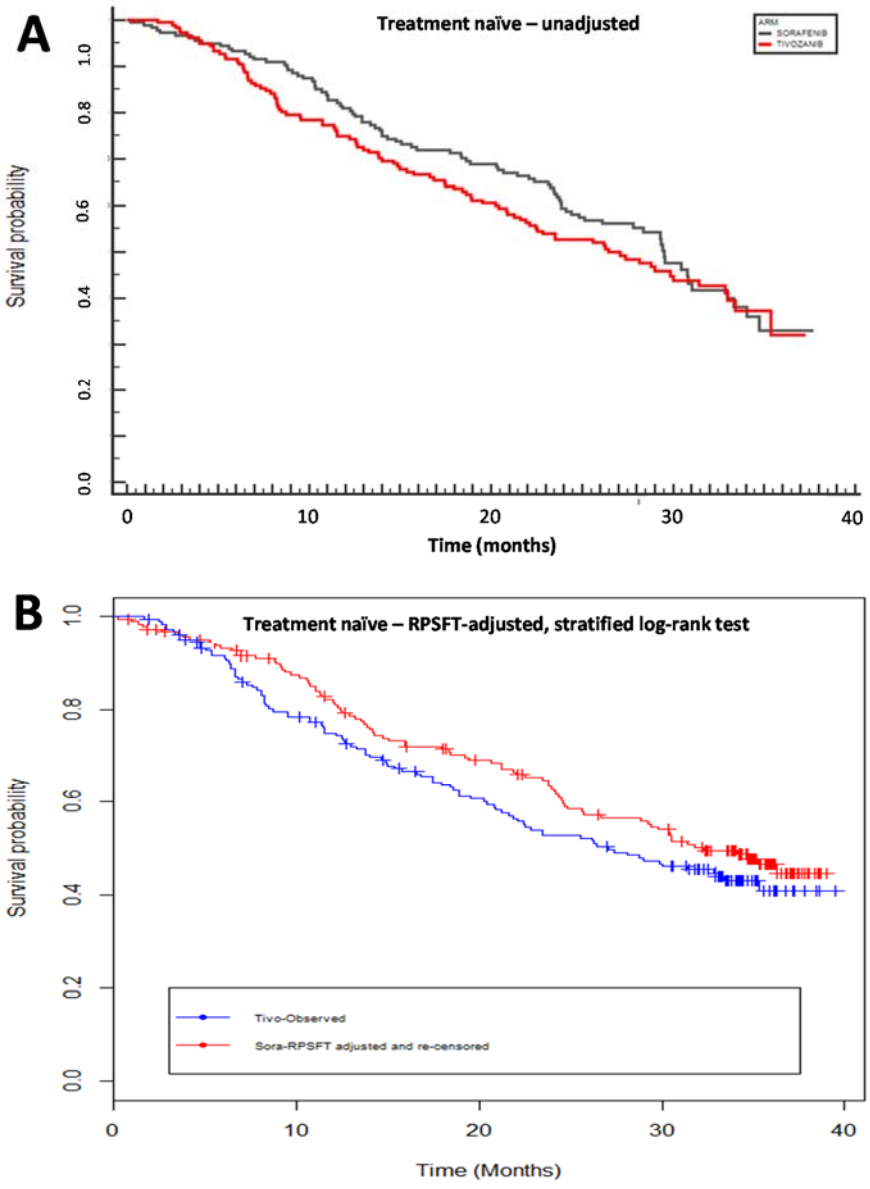
The KM plots in Figure 4 show how the IPCW adjustment brought the tivozanib curve in line with that of sorafenib compared with the unadjusted analysis. No alternative methods of crossover adjustment were presented which limits interpretation of the result; the RPSFT method was only implemented for the treatment-naïve population which was the ERG's primary focus for the critique (see Figure 5).

Figure 4. Kaplan-Meier plots of OS in the full population, final analysis January 2015; **A**, unadjusted and **B**, adjusted for crossover using the IPCW method (bottom; adapted from CS, Figures 8 and 9)



For the treatment-naïve population, which was the focus of the NMA and economic model, the HR unadjusted for crossover lies in favour of sorafenib but is not statistically significant, similar to the unadjusted results for the full population (Figure 5A). IPCW crossover adjustment was not conducted for the treatment-naïve population. The RPSFT method of crossover adjustment favoured by the ERG was conducted (unstratified and stratified by ECOG, MSKCC and number of metastatic sites) and did not have the same effect as the IPCW adjustment (Figure 5B stratified [log-rank]); whereas the IPCW adjustment brought the tivozanib curve closer to the sorafenib arm for the full trial population, the results of the RPSFT adjustment of the treatment-naïve population showed a similar benefit of sorafenib as in the unadjusted analysis.

Figure 5. Kaplan-Meier plots of OS in the treatment-naïve population: **A** unadjusted for crossover, **B**: RPSFT-adjusted, stratified log-rank (clarification responses, Figures 34 and 3, respectively).



The company use the IPCW-adjusted analysis of the full population (Figure 4) and the subgroup analysis by geographical location (Table 14) as evidence that imbalance in subsequent therapies biased OS against tivozanib. While the ERG agrees that second-line therapy for RCC is widely accepted to prolong survival, the bias caused by the subsequent therapy imbalance in TIVO-1 cannot be quantified. RPSFT-adjusted analyses did not support those from the IPCW-adjusted analysis, and the subgroup analyses were reliant on small number of patients. Furthermore, the IPCW and RPSFT adjustments applied to the sorafenib group to control for subsequent tivozanib (constituting 97% of subsequent therapy received in that group) would be expected to bias the results in favour of tivozanib because subsequent therapies in that group were not controlled for (around 30% overall, of which the majority

were targeted therapies; Table 13). In summary, the ERG believes that the estimate of OS in TIVO-1 is unreliable despite efforts to adjust for one-way crossover.

The HR results were not used in the NMA and economic model because methods were brought in line with those used for PFS after proportional hazards was found not to hold; this is discussed in Section 4.3.

4.2.4.2 Progression-free survival (PFS)

The CS presents results from ITT analyses of PFS from the interim data cut used for the main publication (December 2011).[41] All results are presented in Table 15. The ERG considers the results obtained from the original PFS Cox proportional hazards analyses to be inappropriate because proportional hazards do not hold (see Appendix 9.4).

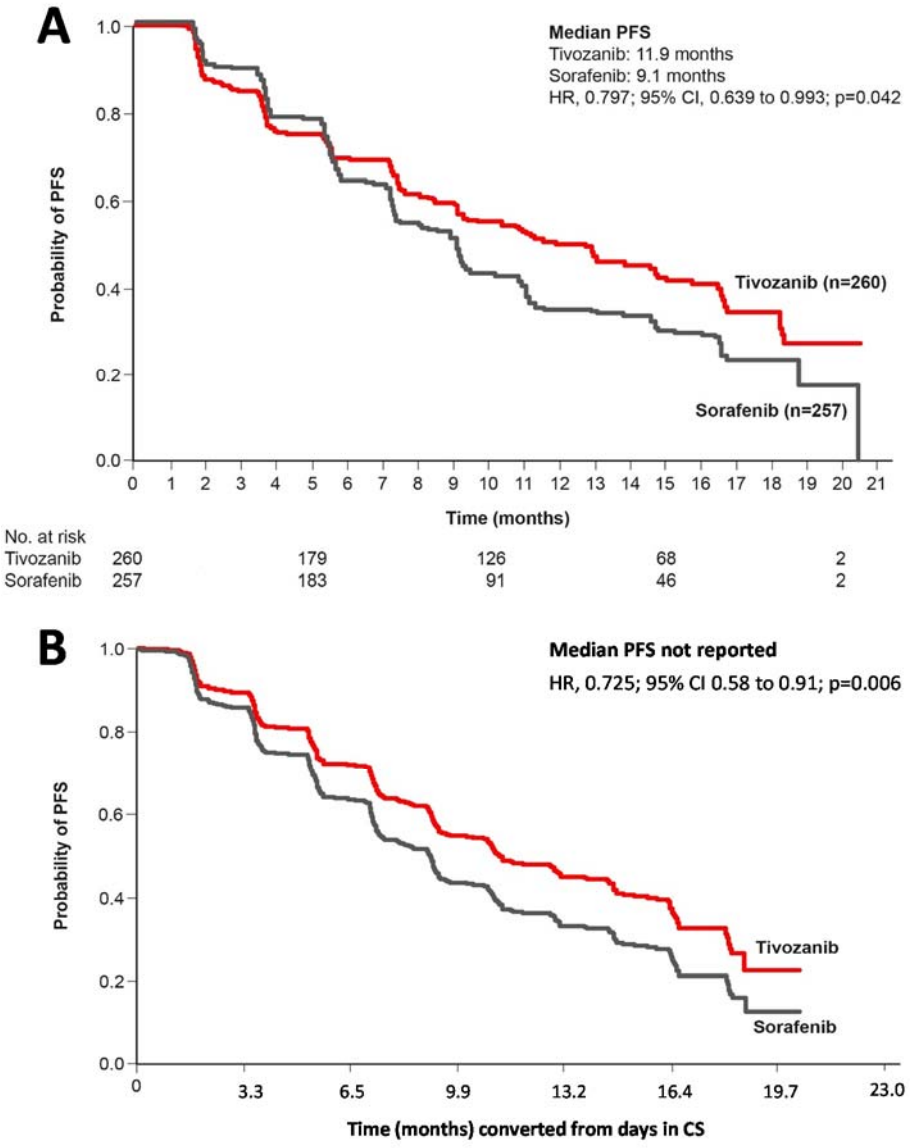
Table 15. PFS results in TIVO-1 for all data cuts and analyses

	Median PFS, months		HR	95% CI	p-value	Source
	Tivozanib (N=260)	Sorafenib (N=257)				
Full population, IRR, Dec 2011	11.9 (153 events)	9.1 (168 events)	0.797	0.639 to 0.993	0.042	CS, pg. 68
Full population, investigator-assessed, Dec 2011	14.7 (144 events)	9.6 (182 events)	0.722	0.580 to 0.899	0.003	CS, pg. 68, interim CSR Table 20
Full population adjusted for baseline imbalance and geographic region – post-hoc	NR	NR	0.725	0.58 to 0.91	0.006	CS, pgs 69–70
Treatment-naïve, IRR, Dec 2011	12.7	9.1	0.756	0.580 to 0.985	0.037	CS appendix, Table 4:C, interim CSR

Abbreviations: CS, company submission; CSR, clinical study report; HR, hazard ratio; IRR, independent radiology review; KM, PFS, progression-free survival

The primary analysis was based on IRR which show a 2.8-month and 3.6-month benefit of tivozanib over sorafenib for the full population and treatment-naïve subgroup, respectively (Table 15); both results are statistically significant. The CS also included a post-hoc analysis adjusted for baseline demographics and geographical region, which also show a statistically significant benefit of tivozanib over sorafenib (Table 15 and Figure 6 B). The post-hoc analysis was based on observed higher rates of unfavourable ECOG and MSKCC in patients from the Ukraine and Russia than the full study population, and poorer prognosis in the tivozanib group than the sorafenib group (see Section 4.2.2). An equivalent adjusted analysis for the treatment-naïve population was not presented.

Figure 6. Kaplan-Meier plots of PFS in the full population: **A**, primary unadjusted analysis; **B**, adjusted for baseline demographics (age, sex, race, baseline ECOG score, number of metastatic sites/organs, MSKCC prognostic group, prior treatments and time since diagnosis) and geographical region (Russia/Ukraine versus all others)



The interim CSR[12] also provides data regarding the agreement between independent and investigator assessed PD, both of which were available for most patients. There was a high level of discordance between IRR and investigator assessments is shown in Table 16. The ERG considers IRR to be more reliable given the study's open-label design. The IRR results formed the company's primary analysis and are used in the NMA (Section 4.3).

Table 16. Discordance between independent radiological review (IRR) and investigator (INV) assessments of progressive disease in the ITT population (adapted from interim CSR[12], Table 25)

Parameter	Tivozanib (N=260)	Sorafenib (N=257)
Disagreement on PFS status, N (%)		
IRR event, INV no event	35 (13.5)	26 (10.1)
IRR no event, INV event	25 (9.6)	39 (15.2)
Disagreement on PD status		
IRR progressed, INV censored	40 (15.4)	30 (11.7)
IRR censored, INV progressed	27 (10.4)	40 (15.6)
Disagreement on PFS date [a]		
Disagreement on progression date	39 (15.0)	61 (23.7)
Disagreement on censoring date	33 (12.7)	18 (7.0)
Overall disagreement (either PD status or date) [a]	139 (53.5)	148 (57.6)
Overall disagreement (either PFS status or date) [a]	132 (50.8)	144 (56.0)

[a] When PFS dates from IRR and INV are different by more than 1 week.
Abbreviations: INV, investigator assessment; IRR, independent radiological review; N, number of patients; PD, progressive disease; PFS, progression-free survival.

Results for PFS show a consistent benefit of tivozanib over sorafenib in the order of 3 months, but the results are unreliable because proportional hazards do not hold. Alternative analyses that do not rely on the proportional hazards assumption were used to incorporate the results in the NMA and economic model, which are discussed in Section 4.3.

4.2.4.3 Response rates

Results for response rates are not available separately for the treatment-naïve subpopulation in TIVO-1. Response rates for the mixed pretreated population based on IRR up to the December 2011 data cut are presented in Table 17. Effect estimates were not presented in the submission but Table 31 from the final CSR[46] indicate higher ORR for tivozanib than sorafenib (OR 1.623, 95% CI 1.101 to 2.391, p = 0.013).

Table 17. Response in TIVO-1 for the mixed ITT population (independent radiology review from CS, Table 20; December 2011 data cut)

	Tivozanib (N=260)	Sorafenib (N=257)
CR	3 (1.2)	2 (0.8)
PR	83 (31.9)	58 (22.6)
SD	134 (51.5)	168 (65.4)
PD	34 (13.1)	19 (7.4)
Not evaluable	6 (2.3)	10 (3.9)
ORR	86 (33.1)	60 (23.3)

Abbreviations: CR, complete response; ITT, intention-to-treat; ORR, objective response rate (sum of partial and complete response); PD, progressive disease; PR, partial response

The final CSR[46] also includes data from a later data cut including patients who remained on their as-randomised treatment after enrolling in the extension study (Table 18). Only response based on investigator assessment was available for the a later analysis including patients who remained on their

as-randomised treatment in the extension study, and the results no longer show a benefit for tivozanib over sorafenib (OR 1.057, 95% CI 0.744 to 1.572, p = 0.681).

Table 18. Response in TIVO-1 including patients who remained on their as-randomised treatment in the extension study (investigator assessment, from CSR Table 32)

	Tivozanib (N=260)	Sorafenib (N=257)
CR	4 (1.5)	2 (0.8)
PR	78 (30.0)	76 (29.6)
SD	135 (51.9)	143 (55.6)
PD	35 (13.5)	26 (10.1)
Not evaluable	7 (2.7)	10 (3.9)
ORR	82 (31.5)	78 (30.4)

Abbreviations: CR, complete response; ITT, intention-to-treat; ORR, objective response rate (sum of partial and complete response); PD, progressive disease; PR, partial response

4.2.4.4 Health-related quality of life (HRQoL)

Results for HRQoL are not available separately for the treatment-naïve subpopulation in TIVO-1. Questionnaires were collected on the first day of each treatment cycle (every 4 weeks) until cycle 24 and at treatment discontinuation or patient withdrawal.[87] However, results presented in the submission from TIVO-1 relate only to the first 12 months of treatment (Table 19). Baseline scores were comparable between groups at the beginning of the study, and both drugs led to similarly stable scores over the first 12 months. None of the results on any of the scales indicated a difference in HRQoL of patients treated with tivozanib compared with sorafenib.

Table 19. TIVO-1 baseline and change from baseline scores health-related quality of life (HRQoL) scores over the first 12 months of treatment (adapted from CS Table 21)

	FACT-G[88] (27 items 0–4; range 0 to 108)			FKSI-DRS[89] (9 items, 0–4; range 0 to 36)			EQ-5D (Index score[90], range 0–1)		
	Tivozanib	Sorafenib	p	Tivozanib	Sorafenib	p	Tivozanib	Sorafenib	p
N	257	248		256	248		256	250	
Baseline									
mean (SD)	77.01 (14.98)	77.27 (15.94)	NR	29.16 (4.77)	29.35 (5.10)	NR	0.73 (0.25)	0.73 (0.26)	NR
Change from baseline									
LS mean (SE)	-2.83 (1.04)	-3.10 (1.02)	0.805	-0.94 (0.33)	-0.93 (0.34)	0.965	-0.05 (0.02)	-0.06 (0.02)	0.391

Reductions from baseline indicate worsening quality of life. Repeated-measures mixed-effects models controlled for: treatment, assessment time, treatment-by-time interaction, baseline score, age, ECOG performance status, geographic region, number of metastatic sites, number of prior treatments, MSKCC prognostic factor status, time from diagnosis to study entry and any dose reduction during the study (CS, pg. 74).
Abbreviations: EQ-5D, EuroQo- 5 Dimensions; FACT-G, Functional Assessment of Cancer Therapy – General; FKSI-DRS, FACT Kidney Symptom Index – Disease-Related Symptoms; LS, least squares; SD, standard deviation; SE, standard error

The company state that the primary data cut was not used because completion rates decreased over time (CS pg. 74). The ERG did not have access to full HRQoL tables from the CSRs but an EQ-5D Table 14.2.25 provided during the clarification process illustrates the rate of decline in available forms over the course of the study (Table 20).

[redacted]

Table 20. EQ-5D completed questionnaires over the course of TIVO-1 (adapted from final CSR, Table 14.2.25)

Cycle	BL	2	4	6	8	10	12	14	16	18	20	22	24	26	End
Tivozanib	257	254	225	194	175	154	140	129	120	114	99	53	20	0	211
Sorafenib	256	248	215	197	167	148	123	97	85	72	65	43	25	3	223
Abbreviations: BL, baseline; End, endpoint analysis EQ-5D, EuroQoL-5 Dimensions;															

The CS includes a paragraph summarising results from *post-hoc* analyses of HRQoL from a manuscript that was unpublished at the time the ERG's report was written.[87] [redacted]

4.2.4.5 Subgroup analyses

The CS includes a forest plot displaying the planned subgroup analyses for PFS in TIVO-1 (Figure 44, Appendix 9.5). Results for prior systemic therapy (0 vs 1) and for geographic region (North America/Western Europe, Central/Eastern Europe, rest of world) are of particular interest for the decision problem. As with the primary results for PFS, the ERG considers results based on the Cox proportional hazards model to be unreliable because the proportional hazards assumption does not hold for PFS in TIVO-1.

The forest plot shows that the benefit of tivozanib versus sorafenib is larger in the subgroup who had received no prior systemic therapies, the subgroup identified as most relevant by the ERG's clinical experts. The difference between the untreated and pretreated subgroups is unlikely to be statistically significant. Nonetheless, where possible based on clinical expert advice, the ERG has focused on data from the treatment-naïve population.

The subgroup analysis for geographic region showed a much larger effect in favour of tivozanib for patients from North America and Western Europe (HR 0.335), but the subgroup is small and the 95% confidence interval (CI) is wide (encompassing the mean estimates for the two other subgroups, Central/Eastern Europe and rest of world).

The CS also includes subgroup analyses for OS: a prespecified subgroup by next-line therapy and region and a *post-hoc* subgroup by next-line therapy only. Results from these subgroup analyses are shown in Table 14. Subgroup results from North America and countries in the European Union (EU), and results from North America and a small subset of Western European countries (Italy, France and the UK) lie in favour of tivozanib, though none of the results is statistically significant. The company use this as evidence to support the hypothesis that the imbalance in subsequent therapies was the driver of the trend towards longer OS in the sorafenib group. The pattern of results is consistent with this assertion, with the largest effect for tivozanib in the subgroup with most balanced subsequent therapy (NA & EU5), and the largest effect for sorafenib in the subgroup with the most imbalanced (Russia & Ukraine). However, the North America and EU subgroup is small (N=40) and the associations do not demonstrate a causal relationship with OS. A *post-hoc* subgroup analysis comparing two-year survival of those who received subsequent therapy and those who were either still on their study treatment or had received no subsequent therapy provides some evidence to support the company's hypothesis that subsequent therapies drove the sorafenib benefit, though the data are immature (Table 21).

Table 21. Two-year survival by next-line therapy (adapted from CS Table 23)

	Tivozanib		**Sorafenib**	
	N	**2-year survival (%), 95% CI**	**N**	**2-year survival (%), 95% CI**
Any next-line anti-cancer therapy	68	50 (38 to 62)	168	64 (56 to 71)
Next-line VEGFR-TKI	18	55 (31 to 78)	158 (156 tivozanib)	63 (56 to 71)
Still on study treatment or no next-line treatment	192	56 (48 to 63)	89	54 (43 to 65)

Abbreviations: CI, confidence interval; N, number of patients; VEGFR-TKI, vascular endothelial growth factor tyrosine kinase inhibitor.

4.2.4.6 Adverse effects

The marketing authorisation for tivozanib had not been granted at the time the ERG's report was written, so no Committee for Medicinal Products for Human Use (CHMP) report was available. A draft summary of product characteristics (SmPC)[54] was provided with the submission appendices. During the clarification process, the company confirmed that safety information in the SmPC is compiled from the 5 tivozanib studies shown in Table 22.

Table 22. Five studies of tivozanib as monotherapy for RCC which provide safety data for the Summary of Product Characteristics (adapted from clarification responses, Table 9)

Study number	**Study Title**	**Number of patients exposed to tivozanib**
AV-951-07-201 Discontinuation study	A Phase 2, Placebo-Controlled, Randomized, Discontinuation Trial of Tivozanib (AV-951) in Patients with Renal Cell Carcinoma	272
AV-951-10-202 Biomarker study	A Phase 2 and Biomarker Study of Tivozanib in Subjects with Advanced Renal Cell Carcinoma	105

AV-951-12-205 (not in submission)	A Phase 2 Randomized, Double-Blind, Crossover, Controlled, Multi-Center, Subject Preference Study of Tivozanib Hydrochloride vs. Sunitinib in the Treatment of Subjects with Metastatic Renal Cell Carcinoma	38 (41 sunitinib)
AV-951-09-301 TIVO-1	A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib (AV-951) to Sorafenib in Subjects with Advanced Renal Cell Carcinoma	259 (257 sorafenib)
AV-951-09-902 Extension study	An Extension Treatment Protocol for Subjects who have Participated in a Phase 3 Study of Tivozanib vs. Sorafenib in Renal Cell Carcinoma (Protocol AV-951- 09-301) – cross-over patients	161*
Total number of patients exposed to tivozanib across the studies		**835**
*Only includes patients who received sorafenib in Study AV-951- 09-301 and then crossed over into the extension study AV-951-09-902 to receive tivozanib. Patients who rolled over from Study AV-951- 09-301 and continued their study treatment (sorafenib or tivozanib) are already counted with Study AV-951-09-301. Abbreviations: RCC, renal cell carcinoma		

Contraindications outlined in the SmPC are summarised in Section 3.2. Briefly, tivozanib is contraindicated for coadministration with St John's Wort, pregnancy, dialysis, and those with histories of arterial thrombotic events, bleeding, QT interval prolongation or gastrointestinal perforation/fistula).[54] Tivozanib is not recommended for patients with severe hepatic impairment and for those with mild to moderate hepatic impairment, the dose should be reduced to alternate days and patients should be monitored closely.[54]

The SmPC lists the following AEs that may require dose reduction, interruption or discontinuation of tivozanib: hypertension, cardiac failure, proteinuria, bleeding, hand-foot syndrome, QT interval prolongation, gastrointestinal perforation and fistula, wound healing complications, and hypothyroidism. The ERG's clinical experts consider the safety considerations listed in the draft SmPC for tivozanib to be broadly comparable with those of other VEGFR-TKIs.

Safety data in the submission are mostly from the TIVO-1 data cut in June 2012 (data cut used for the published paper),[41] with some longer-term follow up from a cut in October 2012, and from the final safety analysis in January 2015 (see Figure 34). Table 23 shows data compiled from the CS and final CSR[46] for TIVO-1 alongside data from the discontinuation[47, 49] and biomarker[48, 50] Phase II studies. In TIVO-1, nearly all patients in both groups experienced at least one treatment-emergent AE of any severity, and slightly fewer patients in the tivozanib group (64.1%) than the sorafenib group (70.4) experienced AEs of Grade 3 or above.[46] No effect estimates are listed for the January 2015 data cut in the final CSR, but are available for the earlier timepoint (June 2012) in the CS (Table 40). At the June 2012 data cut, patients had received tivozanib for 12 months and sorafenib for 9.5 months; these data showed that tivozanib was associated with higher rates of hypertension and dysphonia, and lower rates of diarrhoea, hand-foot syndrome, alopecia, increased AST, increased amylase, increased lipase and hypophosphataemia compared with sorafenib. Fewer patients in the tivozanib group had dose reductions and interruptions due to AEs than the sorafenib group, but more patients in the tivozanib group had fatal AEs than the sorafenib group (10.8% vs 5.8%).

Table 23. Common adverse events observed in TIVO-1 full population and the two Phase II studies

	TIVO-1		Discontinuation	Biomarker
	Tivozanib (N=259)	Sorafenib (N=257)	Tivozanib (N=272)	Tivozanib (N=105)
At least one treatment-emergent AE	91.9	96.9	89.0	100
Grade 3+	64.1	70.4	49.6	74.3
Most common treatment-emergent AE, all grades (≥10% in either group)				
Hypertension	44.8	35.4	46.0	63.8
Fatigue	20.5	16.0	16.9	58.1
Diarrhoea	24.3	33.1	14.3	49.5
Nausea	13.1	7.4	4.4	49.5
Dysphonia	21.2	4.7	22.8	48.6
Decreased appetite	10.8	9.3	0.4	32.4
Asthenia	17.0	17.1	22.4	7.6
Dyspnoea	12.0	8.6	18.8	21.9
Hand-foot syndrome	13.9	54.1	NR	NR
Stomatitis	11.6	8.9	NR	NR
Weight decreased	18.9	21.0	NR	NR
Back pain	14.7	8.2	NR	NR
Alopecia	2.3	21.4	NR	NR
Discontinuation due to AE	14.7	13.2	9.2	10.5
Dose reduction due to AE	11.6	37.7	8.0	10.5
Dose interruption due to AE	22.4	37.0	4.0	13.3
Deaths due to AE	10.8	5.8	5.5	1.2
Total deaths	133 (51.4)	121 (47.1)		

TIVO-1 data are from the final analysis (20 January 2015) unless otherwise specified; data from CS pg. 108 and final CSR Table 48 and Table 49. Total deaths for TIVO-1 are from the July 2013 data cut.
Abbreviations: AE, adverse effects; CS, company submission

Rates of Grade 3 and Grade 4 adverse events were reported only for TIVO-1 from the June 2012 data cut, shown in Table 24. Compared with sorafenib, tivozanib was associated with higher rates of Grade 3 hypertension, and lower rates of Grade 3 diarrhoea, hand-foot syndrome, increased lipase and hypophosphatemia. There were no statistically significant differences in rates of Grade 4 AEs as events were rare.

Table 24. Grade 3 and 4 treatment-emergent AEs in TIVO-1 full population (adapted from CS Tables 41 and 42)

	Grade 3			Grade 4		
AE	Tivozanib (%)	Sorafenib (%)	RR (95% CI)	Tivozanib (%)	Sorafenib (%)	RR (95% CI)
Hypertension	25	18	1.46 (1.04–2.04)	2	<1	3.97 (0.45–35.3)
Fatigue	5	4	1.54 (0.68–3.50)	0	0	NE
Diarrhoea	2	7	0.35 (0.14–0.87)	0	0	NE
Nausea	<1	<1	0.99 (0.06–15.8)	0	0	NE
Dysphonia	0	0	NE	0	0	NE

Decreased appetite	<1	1	0.50 (0.05–5.44)	0	0	NE
Asthenia	4	3	1.42 (0.55–3.67)	<1	0	NE
Dyspnoea	2	2	0.79 (0.22–2.92)	0	0	NE
HFS	2	17	0.12 (0.05–0.29)	0	0	NE
Stomatitis	<1	1	0.50 (0.05–5.44)	0	0	NE
Weight decreased	3	4	0.77 (0.29–2.04)	0	0	NE
Back pain	3	2	1.59 (0.53–4.79)	0	0	NE
Alopecia	0	0	NE	0	0	NE
Clinical chemistry						
Increased ALT	1	3	0.28 (0.06–1.35)	0	1	NE
Increased AST	2	3	0.62 (0.21–1.87)	0	1	NE
Increased amylase	4	6	0.60 (0.27–1.34)	1	1	1.49 (0.25–8.83)
Increased lipase	9	20	0.44 (0.28–0.69)	2	4	0.54 (0.20–1.44)
Hypophosphatemia	4	26	0.16 (0.09–0.30)	0	0	NE
Proteinuria	3	3	1.13 (0.42–3.08)	0	0	NE
Haematology						
Low haemoglobin	2	3	0.71 (0.23–2.20)	2	<1	3.97 (0.45–35.3)
Neutropenia	2	1	1.65 (0.40–6.85)	<1	1	0.50 (0.01–5.44)
Thrombocytopenia	0	0	NE	<1	0	NE

TIVO-1 data are from the final analysis (20 January 2015) unless otherwise specified; data from CS pg 108 and final CSR Table 48 and Table 49.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CS, company submission; CSR, clinical study report; HFS, hand foot syndrome; NE, not estimated; RR, risk ratio

Number of deaths by the latest safety follow-up in January 2015 were not reported; at the July 2013 data cut there were 133 deaths in the tivozanib group and 121 in the sorafenib group (final CSR, Table 26). The description of deaths in the CS is based on the published dataset from June 2012. At that stage, 13 deaths in the tivozanib group and 12 in the sorafenib group were not due to progression. The tivozanib deaths were due to myocardial infarction (n=2), cardiac failure (n=2), hypertension (n=1), dyspnoea (n=1), cerebrovascular accident (n=1), aortic aneurysm rupture (n=1), arteriosclerosis of the coronary artery (n=1), cardiac arrest (n=1), apnoea (n=1), pulmonary embolism (n=1) and unspecified (n=1). The sorafenib deaths were due to cerebrovascular accident (n=3), cardiac failure (n=1), arteriosclerosis of the coronary artery (n=1), coronary artery insufficiency (n=1), haemorrhage (n=1), pleural effusion (n=1), jaundice (n=1), acute respiratory distress syndrome (n=1) and pulmonary embolism (n=1), and pulmonary embolism and acute cardiac failure (n=1).

4.2.5 Summary of the evidence submitted for tivozanib

The company's literature search and review was based on a single search and eligibility criteria which caused a lack of transparency in the selection process. Nonetheless, the ERG agrees that TIVO-1 and the extension study form the RCT evidence for tivozanib. TIVO-1 was a parallel, open-label, Phase III RCT which randomised 517 patients with metastatic or recurrent RCC to tivozanib or sorafenib[41] Results of two Phase II studies were submitted as supplementary non-randomised data, but a randomised preference study of tivozanib versus sunitinib (i.e. a relevant comparator) was omitted,

despite being listed as contributing to the safety data on which the SmPC is based. The Phase II biomarker and discontinuation studies serve only as supplementary non-randomised data. The ERG considers that the omission of a randomised preference study of tivozanib versus sunitinib (i.e. a relevant comparator) should have been explained by the company; the study was listed in the SmPC evidence requested during clarification (Table 22), and measured mostly short term outcomes, but may have included relevant data and should have, at the least, been listed as an excluded study.

The way TIVO-1 and the extension study were designed introduces considerable uncertainty to the estimate of OS due to the substantial imbalance in subsequent therapies between groups. The use of multiple data cuts caused inconsistencies between the results in the published paper, CS and CSRs[12, 46] that have been difficult to disentangle, reducing the ERGs confidence in the study's conduct and the accuracy of data capture through TIVO-1 and the extension study.

The ERG's clinical experts consider the characteristic of the TIVO-1 population[41] to be comparable to a population with metastatic RCC who would be eligible for treatment with tivozanib in the NHS, despite only four patients being recruited from UK centres. However, the inclusion criteria mean that the TIVO-1 population is restricted to patients with a clear cell component to their RCC, good performance status (ECOG score of 0 or 1) and prior nephrectomy, all of which generally indicate better prognosis than the full population covered by the NICE final scope.[1]

Outcomes measured in TIVO-1 were in line with those listed in the decision problem. The definitions of OS, PFS and response are in line with other studies in the field. The risk of investigator bias due to the open-label design was reduced by the primary analyses for PFS and response being based on independent review procedures.

OS was confounded by imbalance between groups in the number of people getting subsequent therapy after progression on the first treatment; this was caused by the one-way crossover design and was compounded by lower access to targeted therapies in the countries where most people were recruited than would be expected in the UK. The unadjusted estimates of OS are difficult to interpret due to probable confounding due to imbalanced subsequent therapies, and methods used to remove confounding gave inconsistent results with varying levels of uncertainty. At best, tivozanib may have similar OS to sorafenib, but the evidence submitted does not rule out the possibility that it is worse. Unadjusted analyses show longer OS in the sorafenib group in the full population (primary cut in Aug 2012, HR 1.25, 95% CI: 0.95 to 1.62; and final cut in January 2015, HR 1.18, 95% CI: 0.93 to 1.50) and in the treatment-naïve population (HR 1.23, 95% CI: 0.90 to 1.67; unknown data cut). The RPSFT-adjusted analysis of the treatment-naïve population also favoured sorafenib (Figure 5); but IPCW-adjusted analysis showed similar survival between tivozanib and sorafenib (Figure 4). Subgroup analysis of regions where subsequent therapies were balanced favoured tivozanib but were based on

small numbers of patients. The ERG would expect the crossover adjusted results to be more favourable for tivozanib, given that nearly all subsequent therapy was adjusted for in the sorafenib arm and the 30% received in the tivozanib arm was not adjusted for.

Tivozanib led to around a 3-month benefit in PFS based on IRR compared with sorafenib, and the benefit was robust to the population used (full or treatment-naive). However, proportional hazards do not hold for the outcome so the Cox proportional hazards model was inappropriate; the ERG places more emphasis on analyses that were run for the NMA which are presented in Section 4.3.

The tivozanib benefit observed for ORR at the December 2011 data cut (OR 1.623, 95% CI: 1.101 to 2.391, p=0.013) did not persist at a later analysis including patients who had continued their randomised therapy in the extension study (OR 1.057, 95% CI: 0.744 to 1.572, p = 0.681); all results for response were only available for the full population. HRQoL data are for the first 12 months of treatment; both drugs led to similarly stable scores over the first 12 months and none of the results indicated a difference between treatments.

Tivozanib was associated with higher rates of hypertension and dysphonia, and lower rates of diarrhoea, hand-foot syndrome, alopecia, increased AST, increased amylase, increased lipase and hypophosphataemia of any grade compared with sorafenib (June 2012). Fewer patients in the tivozanib group had dose reductions and interruptions due to TEAEs than the sorafenib group, though this may be explained by the rules for dose reduction in each group and that the different dosing schedules affected interruption rates. More patients in the tivozanib group had fatal TEAEs than the sorafenib group (10.8% vs 5.8%). Compared with sorafenib, tivozanib was associated with higher rates of Grade 3 hypertension, and lower rates of Grade 3 diarrhoea, hand-foot syndrome, increased lipase and hypophosphatemia (June 2012); there were no statistically significant differences in rates of Grade 4 TEAEs as events were rare. The ERG would agree that tivozanib appears to be associated with generally lower rates of TEAEs than sorafenib except for hypertension, though the open-label design does introduce the possibility of bias in the way they were recorded.

4.3 Critique of the network meta-analysis (NMA)

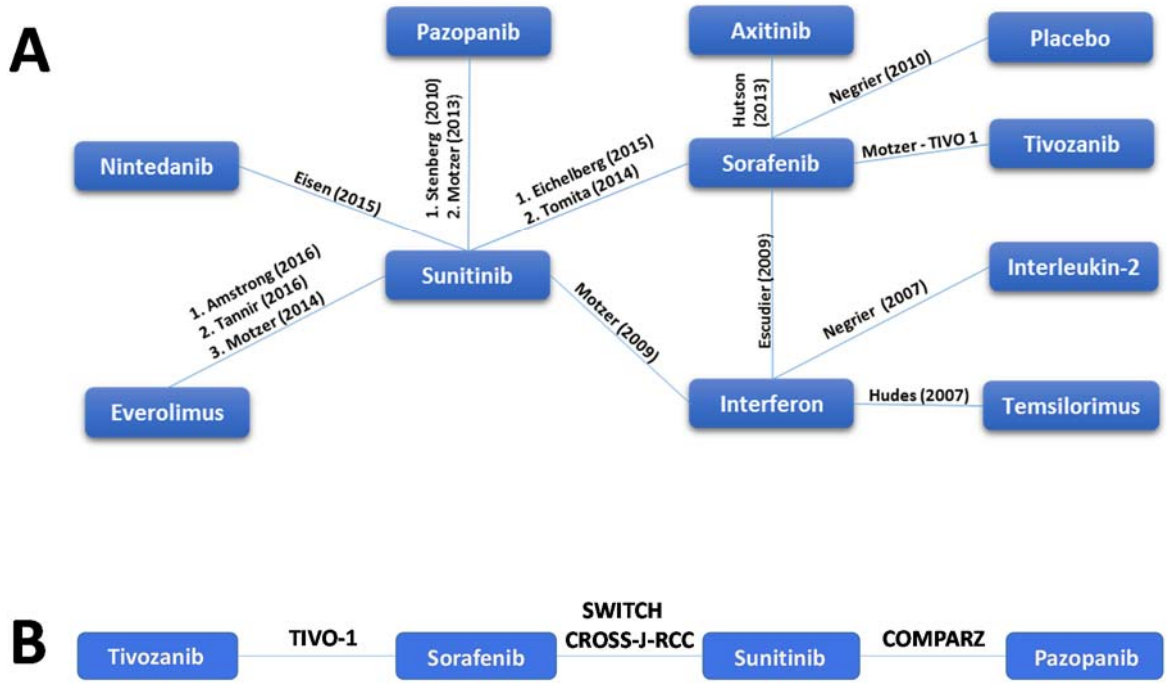
The company conducted NMAs to provide estimates of tivozanib against the comparators listed in the final scope issued by NICE.[1] The literature search for the original NMAs identified 24 RCTs (see Section 4.1.3.2), of which 19 were included in at least one of the original NMAs (Table 9). The NMA in the original CS was split into evidence purely from treatment-naïve patients (N=17[7, 9, 41, 61-74]including four study subgroups[41, 72-74]), and mixed evidence for treatment-naïve and pretreated patients (N=19[7, 9, 41, 61-76]). For reasons already discussed (Section 3.1), the ERG focuses only the evidence for treatment-naïve patients, and did not consider cytokines a relevant comparator (Section 3.3). The ERG noted that multiple comparators had been included in the original NMAs that were not required to link tivozanib

with the comparators of interest (Section 3.3 and Section 4.1.2). The ERG was concerned that studies had not been fully assessed for clinical heterogeneity (i.e. baseline prognostic indicators, study duration, rules for crossover etc.), and that TIVO-1 OS results unadjusted for crossover had been used in the NMA.

During the clarification process, the ERG presented two alternative methods of analysis that it considered would reduce the uncertainty in the original NMA and better control for the possible confounding of OS in TIVO-1. The first proposed option was to limit the treatment-naïve NMA to studies required to link tivozanib with pazopanib and sunitinib using OS results from a range of different methods for crossover adjustment, with the company identifying their preferred analysis from the ERG's suggestions and presenting the others as scenario analyses. The second option presented by the ERG was to conduct a matched adjusted indirect comparison (MAIC) to adjust the population who received tivozanib in TIVO to match the characteristics of the population in COMPARZ, a head-to-head study comparing sunitinib and pazopanib. The MAIC would avoid the TIVO-1 confounding because it would not rely on the within-study comparison. Shortfalls of the MAIC method is that randomisation is broken and, as it would have been an "unanchored" analysis, there would be no way to ensure that all appropriate prognostic indicators and treatment-effect modifiers were adjusted for.

The company chose to provide results based on the simplified NMA (first option) which became the company's preferred structure for the NMA. Four studies linked tivozanib with sunitinib and pazopanib: TIVO-1,[41] COMPARZ[9] (pazopanib versus sunitinib), CROSS-J-RCC[82] and SWITCH[72] (both sunitinib versus sorafenib). Sternberg 2010,[74] a study comparing pazopanib to placebo, did not form a necessary link because the only other study of pazopanib, sunitinib, tivozanib or sorafenib that linked to placebo was conducted in a pretreated population (TARGET[73]; sorafenib versus placebo). The NMA diagram for PFS from the original submission is shown together with the network preferred by the ERG in Figure 7. It should be noted that the original diagram included an error, and Sternberg 2010[74] should link pazopanib with placebo.

Figure 7. Treatment-naïve NMA diagrams for PFS; **A**, original from the CS (reproduced from Figure 13; note that Sternberg 2010 should connect pazopanib with placebo and not sunitinib); **B**, simplified network



4.3.1 Trial conduct

TIVO-1,[41] COMPARZ,[9] CROSS-J-RCC[82] and SWITCH[72] are all multicentre, Phase III, open-label randomised controlled trials (RCTs). CROSS-J-RCC[82] and SWITCH,[72] the two studies comparing sunitinib with sorafenib, were both designed to assess drug sequencing, so all randomised participants were offered the alternative drug at disease progression. The conduct of TIVO-1 is described in detail in Section 4.2.1.1, including the one-way crossover allowed in the extension protocol. Details of the conduct of the 19 studies identified for the company's original NMA are included in the CS appendices and are not reproduced in this report.

The one-way crossover design of TIVO-1 confounded the estimates of OS because more patients in the sorafenib group received subsequent therapy (68.5%) than the tivozanib group (29.7%; Table 13). Most subsequent therapy in both groups was with targeted agents. OS results from crossover-adjusted analyses were made available by the company for TIVO-1 (IPCW for the full population in the CS, and RPSFT for the treatment-naïve population) but neither was used to populate the NMA because crossover-adjustments were not available for CROSS-J-RCC[82] and SWITCH[72] which also included treatment-switching protocols. Information about crossover and subsequent therapy from the CS, clarification responses and the ERG's own consideration of the included studies is presented in Table 25.

Table 25. Study design and access to 2nd line therapies on- and off-protocol

	COMPARZ	CROSS-J-RCC	SWITCH	TIVO-1 naïve
Study design	Phase III open-label RCT	Phase III open-label crossover RCT	Phase III open label crossover RCT	Phase III open-label RCT
1st line treatments compared	Pazopanib versus sunitinib	Sunitinib versus sorafenib	Sunitinib versus sorafenib	Tivozanib versus sorafenib
Outcomes	PFS (including IRR), OS, ORR, AEs, HRQoL, resource utilisation	PFS (1st line, 2nd line and total), OS, AEs	PFS (1st line and total), time to progression, OS, AEs	PFS (including IRR), OS, ORR, AEs, HRQoL
Follow-up period	40 months	36 months	Not reported; mean follow-up from end of treatment 10.3 months	24 months, longer for those entering the extension
Protocol regarding treatment switching	Physician's choice at PD in both groups	Access to sorafenib after PD or unacceptable AE on sunitinib, and vice versa	Access to sorafenib after PD on sunitinib, and vice versa	Access to tivozanib at PD or end of study for sorafenib group. Physician's choice for tivozanib
Total who received any 2nd line therapy	NR	NR	Sunitinib: 55.0% Sorafenib: 64.1	Tivozanib: 29.7% Sorafenib: 68.5%
Received protocol-defined 2nd line therapy	Pazopanib: 0% Sunitinib: 0%	Sunitinib: 52.7% Sorafenib: 74.6	Sunitinib: 42% Sorafenib: 57%	Tivozanib: n/a Sorafenib: 63.0%
Received off-protocol 2nd line therapy	NR	NR	Sunitinib: 13.0% Sorafenib: 7.1%	Tivozanib: 29.7% Sorafenib: 5.5%
Crossover-adjusted results available	N/A	No	No	Yes

Abbreviations: AE, adverse effects; HRQoL, health- related quality of life; IRR, independent radiology review; N, number of patients; NR, not reported; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RCT, randomised controlled trial

SWITCH's two-way crossover protocol meant that the number receiving second-line therapy was more balanced across the groups (55% sunitinib, 64% sorafenib), and most of those received the protocol-defined alternative VEGFR-TKI (Table 25). In CROSS-J-RCC,[82] more people in the sorafenib group (74.6%) than the sunitinib group (52.7%) switched to the protocol-defined alternative VEGFR-TKI meaning the imbalance is less distinct in number and type than was observed in TIVO-1; the number of people receiving subsequent therapy off-protocol in CROSS-J-RCC[82] was not reported. COMPARZ[9] did not include protocol-defined 2nd line therapy; subsequent therapies are not discussed, but may be more likely to be balanced because both groups received usual care after progression.

No adjustments were made to OS results from COMPARZ,[9] CROSS-J-RCC[82] or SWITCH.[72] The implications of treatment-switching and subsequent therapy for the OS NMA is discussed in Sections 4.3.3 and 4.3.4.

TIVO-1 was an international study but 88% of participants were recruited from Russia and Ukraine. COMPARZ[9] had fairly well balanced recruitment across Europe, North America and Asia, CROSS-J-

RCC[82] was conducted solely in Asia (Japan), and SWITCH[72] solely in Europe (Germany, Austria and Switzerland).

Inclusion criteria were broadly similar across trials, shown in Table 26; all studies required patients to be at least 18 years of age, have metastatic disease, ECOG of 0 or 1 or Karnofsky score of ≥70, and no significant cardiovascular disease. Of note, only SWITCH[72] included any histology rather than just clear cell, only CROSS-J-RCC[82] and SWITCH[72] included patients with favourable or intermediate MSKCC risk status, and only TIVO-1 specified at enrolment that patients had undergone nephrectomy.

COMPARZ[9] and SWITCH[72] defined their population inclusion criteria as 'advanced or metastatic' RCC, CROSS-J-RCC[82] as metastatic, and TIVO-1[41] as 'metastatic or recurrent'. While this may have led to variation in the baseline prognosis of the populations, this does not appear to have been the case, as shown in Section 4.3.2 (Table 27).

Table 26. Study inclusion and exclusion criteria

	COMPARZ[9]	CROSS-J-RCC[82]	SWITCH[72]	TIVO-1 naïve[41]
Inclusion criteria				
Clear cell component	✓	✓		✓
Metastatic RCC	✓	✓	✓	✓
ECOG 0 or 1		✓	✓	✓
Karnofsky ≥ 70	✓			
MSKCC favourable or intermediate		✓	✓	
Measurable disease (RECIST)	✓	✓	✓	✓
≥ 18 years	✓	✓ [a]	✓ [a]	✓
Naïve to systemic therapy	✓	✓	✓	✓ [b]
Prior nephrectomy				✓
Adequate organ function*	✓		✓	✓
Exclusion criteria				
Significant cardiovascular disease	✓	✓	✓	✓
Uncontrolled hypertension	✓			✓
Brain metastases	✓		✓ [c]	✓ [c]
Prior VEGFR-TKI or mTORi	✓	✓	✓	✓
Clinically serious infections			✓	

[a] CROSS-J-RCC age criteria were 20–80, SWITCH 18–85
[b] TIVO-1 inclusion criteria allowed 1 prior systemic therapy but only those who had received none were included in the NMA
[c] TIVO-1 included brain metastases if they had been stable for at least 3 months following prior treatment, SWITCH excluded if symptomatic.
*included hematologic, renal, hepatic function in TIVO-1 and SWITCH, undefined in COMPARZ
Abbreviations: ECOG, Eastern Cooperative Oncology Group; mTORi, mammalian target of rapamycin inhibitor; RCC, renal cell carcinoma; RECIST, response evaluation criteria in solid tumors; VEGFR-TKI, vascular endothelial growth factor tyrosine kinase inhibitor

SWITCH[72] stratified randomisation by MSKCC score, CROSS-J-RCC[82] by MSKCC, nephrectomy and enrolling institution, COMPARZ[9] by Karnofsky performance score, nephrectomy and level of lactate dehydrogenase, and TIVO-1[41] by geographic region and number of metastatic sites/organs.

Stratification by number of prior therapies in TIVO-1 was not relevant as the NMA includes only the patients who had received none.

Relative dose intensity (RDI) was much higher in the tivozanib group (94%) than the sorafenib group (81%) in TIVO-1,(final CSR pg. 154)[46] and higher than the assumed dose intensities for pazopanib and sunitinib in the pazopanib single technology appraisal (STA)[25] (86% for both). Dose intensity is not reported in COMPARZ,[9](results of which were not available for inclusion in the pazopanib STA) SWITCH[72] or CROSS-J-RCC,[82] so it is not possible to assess whether the estimates provided by the NMA reflect differences in dose intensity between treatments.

The primary outcome in all studies was PFS, measured from randomisation to disease progression or death from any cause, whichever was sooner. Those who had not progressed were censored in all studies. TIVO-1,[41] COMPARZ[9] and SWITCH[72] required confirmation of progression by RECIST criteria using computerised tomography (CT) or magnetic resonance imaging (MRI), and no details were available for CROSS-J-RCC.[82] TIVO-1[41] and COMPARZ[9] included IRR, which is not described in CROSS-J-RCC[82] and SWITCH.[72] In CROSS-J-RCC[82] and SWITCH,[72] where patients switched to the alternative treatment at progression, PFS was available for the first randomised treatment and for the two treatment together for patients who received both; the former was used for the PFS NMA.

All four studies measured OS as a secondary endpoint, defined as the time from randomisation to death from any cause. Response was reported in all studies except CROSS-J-RCC,[82] but SWITCH[72] did not confirm response with IRR. The original NMA for complete response was not updated to the simplified network due to time constraints. Only TIVO-1[41] and COMPARZ[9] reported HRQoL which precluded indirect comparison as there was no link between tivozanib, pazopanib and sunitinib. All studies reported AEs using Common Terminology Criteria for Adverse Events (CTCAE).

The TIVO-1 protocol allowed follow-up for 24 months from enrolment, though the subset of participants who enrolled in the extension study were followed up for longer; median and mean follow-up for OS and PFS is described in Section 4.2.1.1. At the data cut-off for SWITCH,[72] there was a mean follow-up from end of last treatment of 10.3 months. CROSS-J-RCC followed-up participants for 36 months[91] and COMPARZ[9] for 40 months.

4.3.2 Baseline characteristics

Baseline characteristics for all 19 studies originally included in the NMAs were provided in the CS appendices. The ERG has not reproduced them in this report because the original NMA results were replaced by those from the simplified NMAs requested by the ERG (i.e. based on the four trials linking tivozanib to pazopanib and sunitinib: COMPARZ,[9] CROSS-J-RCC,[82] SWITCH[72] and TIVO-1[41]; the baseline characteristics of participants in these four trials are presented in Table 27.

TIVO-1[41] limited the population to patients meeting a set of prognostic indicators based on Phase II results (prior nephrectomy, clear cell variant, ECOG score of 0 or 1), some of which overlapped with the other studies. While there was some variation in inclusion and exclusion criteria across the studies (see Table 26), the studies were broadly similar regarding key disease-related criteria (e.g. histology, performance status, nephrectomy, number and site of metastases). Median age ranged from 59 to 67. Participants were more often male in line with prevalence in the population, though a higher proportion were male in CROSS-J-RCC[82] (84%) than the other studies (~75%). Most participants in all studies had intermediate MSKCC status, with few or none in the poor category. Most participants had two or more metastatic sites in all studies, of which lung was the most common; TIVO-1[41] had a higher proportion with lymph node metastases than the other studies (see Table 27).

Though TIVO-1[41] was the only study to specify that patients had prior nephrectomy, most patients in the other studies had also undergone nephrectomy (range 82% to 92%). Similarly, CROSS-J-RCC[82] and SWITCH[72] included only patients with favourable or intermediate MSKCC risk status, but COMPARZ[9] and TIVO-1[41] included only a small proportion with poor status (1.9% and 3.3%, respectively). However, regarding MSKCC risk status, the population distributions across categories show that more people in SWITCH[72] had favourable risk status than the other three studies.

The eligibility criteria for COMPARZ,[9] CROSS-J-RCC[82] and SWITCH[72] stated that only patients who were naïve to systemic treatment were eligible, but a small proportion of the SWITCH[72] population had received prior treatment with cytokines (3%). TIVO-1[41] included patients who had received one prior systemic therapy for metastatic RCC but disaggregated data for the 70% in each group who were naïve to systemic therapies are used for the NMA.

Table 27. Baseline characteristics of studies included in the simplified treatment-naïve network meta-analysis

Study	**COMPARZ[9] (NCT00720941)**		**CROSS-J-RCC[82] (NCT01481870)**		**SWITCH[72] (NCT00732914)**		**TIVO-1 treatment naïve[41] (NCT01030783)**	
Stage of RCC	Advanced or metastatic		Metastatic		Advanced or metastatic		Recurrent or metastatic	
Type of RCC	CC		CC		All histologies; CC: 87%		CC	
Prior systemic therapies	0		NR		Cytokines 3%[a]		0	
Treatment groups	**Pazopanib**	**Sunitinib**	**Sorafenib**	**Sunitinib**	**Sorafenib**	**Sunitinib**	**Tivozanib**	**Sorafenib**
N randomised	557	553	63	57	182	183	181	181
Median age, yrs (range)	61 (18–88)	62 (23–86)	66 (44–79)	67 (41–78)	64 (39–84)	65 (40–83)	59 (23–83)	59 (23–85)
Male (%)	71	75	84	84	76	74	74	75
Ethnicity (white, %)	NR		NR		NR		96	97
MSKCC (%) Favourable	27	27	22	21	39	45	27	33
Intermediate	58	59	78	79	59	51	67	62
Poor	12	9	0	0	0.5	0.5	7	5
Performance status (%)	KPS 70–80: 25 90–100: 75	KPS 70–80: 24 90–100: 76	NR	NR	ECOG 0: 66 ECOG 1: 31 ECOG 2: 0	ECOG 0: 60 ECOG 1: 38 ECOG 2: 0.6	ECOG 0: 47 ECOG 1: 53 ECOG 2: 0	ECOG 0: 52 ECOG 1: 48 ECOG 2: 0
Number of metastatic sites (%)	1 organ: 21 2 organs: 37 ≥3 organs: 42	1 organ: 20 2 organs 37 ≥3 organs: 44	1 site: 3 2 sites: 11 ≥3 sites: 86	1 site: 12 2 sites: 16 ≥3 sites: 72	1 site: 21 2 sites: 38 ≥3 sites: 40	1 site: 29 2 sites: 34 ≥3 sites: 36	1 organ: 29 ≥2 organs: 71	1 organ: 36 ≥2 organs: 64
Common metastases (%) Lung	76	77	75	70	79	72	82	79
Lymph	40	45	24	33	48	40	70	65
Bone	20	15	33	23	12	17	23	20
Liver	15	20	10	7	20	24	26	19
Prior nephrectomy (%)	82	84	89	88	92	92	100	100

For Performance status and MSKCC, percentages that do not total 100 are due to missing data; additional CROSS-J-RCC baseline characteristics were taken from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4382117/; and Tomita 2017 poster[82] *mean values where median was not reported.

[a] Despite inclusion criteria of no prior systemic therapy, 3 people in the sorafenib group and 8 in the sunitinib group had received prior cytokines, 14 and 15 respectively had received 'other' cancer therapies that were not systemic, and 16 and 23 had had radiotherapy; [b] No person had received prior VEGFR-TKI (exclusion criterion for TIVO-1); [c] ethnicity and common metastases for TIVO-1 are for the full population

Abbreviations: CC, clear cell variant of renal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; KPS, Karnofsky Performance Scale; MSKCC, Memorial Sloane Kettering Cancer Center Risk Score; NR, not reported; RCC, renal cell carcinoma; RCT, randomised control trial; TKI, tyrosine kinase inhibitor; VEGF-R, vascular endothelial growth factor receptor.

4.3.3 Statistical approach

The CS included a set of NMAs based on HR for the survival outcomes, OS and PFS, and OR for response and adverse effects. The ERG questioned the use of HR at the clarification stage and requested that proportional hazards be tested by the company, which revealed the assumption does not hold in TIVO-1.[41] A new NMA and economic model were subsequently provided for the simplified NMA, firstly based on fitting the survival data to a Weibull parametric curve[92] and then using the fractional polynomial (FP) approach.[93] The company did not present model selection or curve fitting statistics for the parametric curve NMA to justify the use of the Weibull distribution, but stated that a preferred NMA based on log-normal curves (the best fitting distribution for the TIVO-1 data) could not be submitted in time for submission to the ERG. Subsequently, the company submitted OS and PFS NMAs based on the FP approach as their preferred analysis, which hereafter forms the basis of the ERG's critique.

The final FP-based NMA and economic model were only made available to the ERG just over two weeks before the report was due to be submitted to NICE. A one-week extension was granted by NICE to allow the ERG to validate the model and perform exploratory analyses (see Section 5.4.5). The company's rationale for choosing the FP approach is shown in Box 7.

Box 7. Company rationale for the chosen NMA of survival data with fractional polynomials (reproduced from additional analyses provided by the company)

The fractional polynomial method uses parametric survival functions which includes survival distributions such as Weibull or Gompertz together with more flexible fractional polynomials. Use of fractional polynomials allows for change of hazards over time and offers more freedom in distribution selection. With first or second order fractional polynomials the hazard functions of the interventions compared in a trial are modeled and the difference in the parameters of these fractional polynomials within a trial are considered the multidimensional treatment effect and synthesised (and indirectly compared) across studies. Therefore, with this approach the treatment effects are represented with multiple parameters rather than a single parameter or outcome [Jansen, 2011]. This method is described in detail in a paper by Jansen 2011 and was used in the recent ACD consultation - cabozantinib for previously treated advanced RCC [ID931]. It has also been successfully used to compare first-line treatments for RCC, reported in an abstract [Mihajlovic, 2015]. The deviance information criterion (DIC) is used to compare the goodness-of-fit of different fixed and random effects models with first and second order fractional polynomials with different powers. The model with the lowest DIC, is the model providing the 'best' fit to the data and is used in the base case. The lowest DIC in this analysis was the second-order fractional polynomial.
Abbreviations: NMA, network meta-analysis; RCC, renal cell carcinoma.

A shortcoming of conducting NMA by modelling trial-observed KM data with survival distributions, with or without FPs, is that the curves for each treatment must be derived from the same distribution; thus, the curve providing the best fit on average across treatments may underestimate some treatments

and overestimates others. Thus, a range of first and second order powers should be tested to identify the best fit.[93] The ERG note that the company had limited time to conduct these alternative analyses because they were part of the clarification process rather than the original CS. The company presented goodness-of-fit statistics for four first order FPs (-2, -1, -0.5, 0) and one second order FP (P1 = -2, P2 = -1) from a fixed effect model, shown in Table 28 (OS) and Table 29 (PFS). The ERG ran further permutations of powers in its exploratory analyses (Section 5.4.5) to validate the company's preferred choice of the second order FP (P1 = -2, P2 = -1). While ideally results from a random effects model should also be presented, the ERG does not consider this to be a significant limitation because the network was linear and only the direct comparison of sorafenib and sunitinib was based on data from more than one study.[72, 82]

Table 28. Goodness-of-fit estimates for fixed effects fractional polynomial models for different powers P1 and P2: overall survival (reproduced from the company's additional analyses)

Power 1	Power 2	Dbar	Dhat	pD	DIC
-2	-	851.253	838.089	13.165	864.418
-1	-	876.164	862.514	13.65	889.814
-0.5	-	907.434	893.538	13.895	921.329
0	-	943.204	929.288	13.916	957.12
-2	**-1**	**835.061**	**815.808**	**19.253**	**854.314**

Abbreviations: Dbar, residual deviance; Dhat, deviance at the posterior mean; pD, effective number of parameters; DIC, Deviance Information Criterion

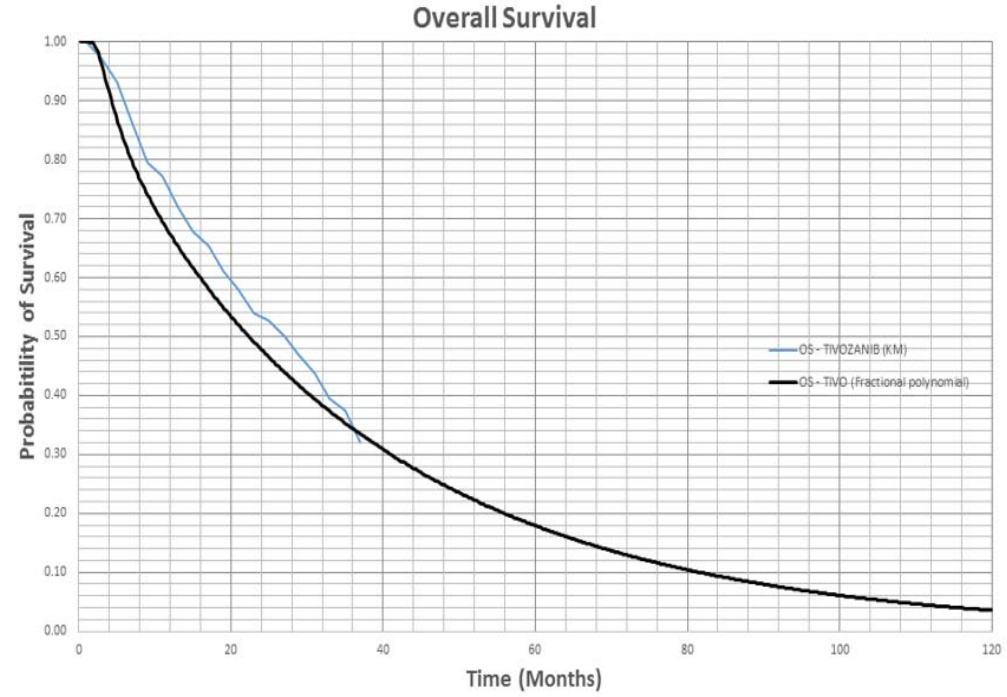
Table 29. Goodness-of-fit estimates for fixed effects fractional polynomial models for different powers P1 and P2: progression-free survival (reproduced from the company's additional analyses)

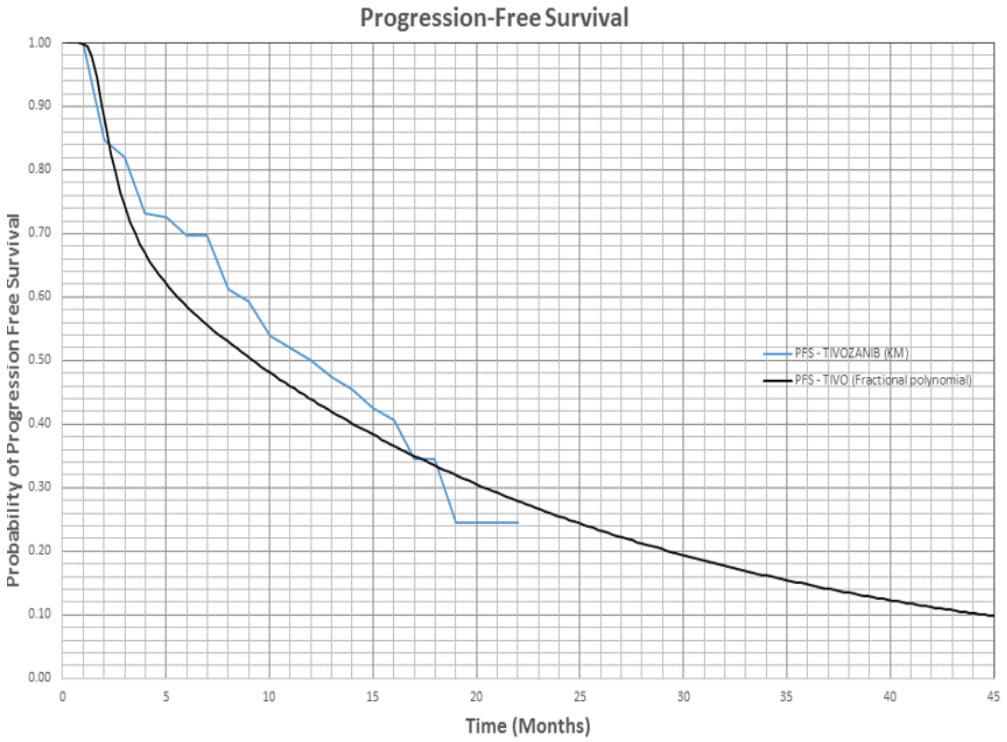
Power 1	Power 2	Dbar	Dhat	pD	DIC
-2	-	960.183	946.642	13.541	973.724
-1	-	1012.51	998.625	13.883	1026.39
-0.5	-	1089.43	1075.55	13.883	1103.31
0	-	1164.6	1150.77	13.827	1178.43
-2	**-1**	**919.32**	**905.807**	**13.513**	**932.832**

Abbreviations: Dbar, residual deviance; Dhat, deviance at the posterior mean; pD, effective number of parameters; DIC, Deviance Information criterion.

The company presented graphs showing the FP model fit for the baseline KM curves observed in TIVO-1 for OS and PFS, but did not present equivalent fits for the baseline KM data from other trials contributing to the network. Figure 8 shows the fit of the baseline tivozanib KM data to the FP curve generated by the chosen second order NMA; the company did not present graphs to illustrate how well the FP approach estimated the underlying KM data before conducting the NMA.

Figure 8. Fit of the FP curves generated by the NMA to the observed Kaplan-Meier data for tivozanib in TIVO-1 (reproduced from the company's additional analyses)





Inputs for the FP-based NMAs came from the digitised KM curves for PFS and OS in each treatment group in the four studies constituting the simplified network (COMPARZ, CROSS-J-RCC, SWITCH and TIVO-1). For each treatment, patient level data for time of event or censoring (and number of patients at that time), number of deaths, and number of patients censored in the time interval were recreated according to the method in Guyot 2012.[94] NMAs were conducted in WinBUGS according to

a Bayesian framework, and the company provided code for the Ouwens Weibull approach[92] and the Jansen FP approach.[93] A number of details provided for the Weibull analysis were not provided for the FP-based NMA (e.g. how model parameters were estimated, number of iterations for the burn-in and number to estimate the posterior medians and credible intervals, and how convergence was checked [e.g. with the Gelman-Rubin statistic[95]]).

NMAs for the binary outcomes, response and AEs, were based on OR using the binomial likelihood and logit link. Continuity corrections were applied where the models were unstable due to zero cells as recommended by NICE Decision Support Unit (DSU).[96] WinBUGS code was provided for the original CR analysis but not for the original or updated AE analyses; data inputs for CR and AEs were checked but the NMAs were not replicated by the ERG due to time constraints.

For response, despite several available outcomes being available for TIVO-1, NMA results were only provided for CR; 13 of the original 19 RCTs identified reported ORR (CS, Table 25, pg. 86), including all of the studies in the simplified network.[9, 41, 72, 82] The ERG is aware of the amount of work required to rerun the analyses for OS and PFS and did not consider the response rate analyses a priority, so results from the simplified NMA were not requested for CR or for ORR. Only the original CR analysis is available for critique but the ERG has compiled raw data for the full set of response outcomes for the four studies of interest (see Section 4.3.4.3).

NMAs for AEs in the CS were based on various combinations of the 19 studies originally included in the NMA, depending on what was reported in different studies, for both treatment-naïve and mixed pretreated populations. As with the other outcomes, the company provided results from the simplified NMA based on COMPARZ,[9] CROSS-J-RCC,[82] SWITCH[72] and TIVO-1[41] for key AEs identified by the ERG's clinical experts: diarrhoea, fatigue/asthenia, hypertension, increased ALT and increased AST. All studies measured AEs as treatment-emergent, i.e. from beginning the study drug up to 30 days after discontinuing. As such, the issue of treatment-switching does not affect the results. Results were reported as OR and 95% credible interval (CrI) provided from the simplified NMAs. The company chose to use results from the original NMA to populate the economic model (Section 5).

Table 30 shows how the final analyses differ from those presented in the original CS.

Table 30. Methods of indirect comparison in the original submission and revised analyses (adapted from the company's additional analyses document)

Outcome	Approach in original submission	Revised approach as per clarification questions (base case)

OS	NMA based on HRs for two populations: Mixed pretreated (14 studies, 12 treatments) Treatment naïve (13 studies, 11 treatments) TIVO-1 crossover data not incorporated	Simplified structure NMA, treatment-naïve only using fractional polynomials 4 studies: COMPARZ, CROSS-J-RCC, SWITCH, TIVO-1 4 treatments: pazopanib, sorafenib, sunitinib, tivozanib TIVO-1 crossover data not incorporated
PFS	NMA based on HRs for two populations: Mixed pretreated (16 studies, 11 treatments) Treatment naïve (15 studies, 11 treatments)	Simplified structure NMA, treatment-naïve only using fractional polynomials 4 studies: COMPARZ, CROSS-J-RCC, SWITCH, TIVO-1 4 treatments: pazopanib, sorafenib, sunitinib, tivozanib
Response	NMA based on ORs for the mixed pretreated population (15 studies, 11 treatments)	Not updated during the timeframe
AEs	20 NMAs based on ORs for individual AEs for the treatment naïve and mixed pretreated. Different combinations of the 19 studies identified by the company in the CS.	Simplified structure NMA, treatment-naïve only for Grade 3+ AEs identified by the ERG's clinical experts (diarrhoea, fatigue, hypertension and liver disorder*) 4 studies: COMPARZ, CROSS-J-RCC, SWITCH, TIVO-1 4 treatments: pazopanib, sorafenib, sunitinib, tivozanib
HRQoL	None presented	Narrative 2 studies: COMPARZ and TIVO-1 4 treatments: pazopanib, sorafenib, sunitinib, tivozanib
*Diarrhoea, fatigue, hypertension and liver function were highlighted by the ERG's clinical expert as being of importance with regards to VEGFR-TKIs as a class. Abbreviations: AEs, adverse effects; CS, company submission; HRQoL, health-related quality of life; HRs, hazard ratios; NMA, network meta-analysis; ORs, odds ratios; OS, overall survival; PFS, progression-free survival; VEGFR-TKI, vascular endothelial growth factor tyrosine kinase inhibitors.		

During the clarification process, the ERG asked for the crossover-adjusted OS data to be included instead of the unadjusted results that were confounded by substantial imbalance in access to subsequent therapies (Table 13). Details of the crossover-adjustments in the original submission and those provided in the clarification process are described in Section 4.2.3 and results are provided in Section 4.2.4.1. (Table 14, Figure 4 and Figure 5). The company did not include the crossover-adjusted results in either the original or the simplified NMA because crossover-adjusted data were not available for CROSS-J-RCC[82]and SWITCH.[72] Considering on- and off-protocol subsequent therapies (Section 4.3.1), the imbalance was most pronounced in TIVO-1, and more balanced in CROSS-J-RCC[82] and SWITCH[72], so the company's rationale may not be valid. The KM plot of the ERG's preferred method of crossover adjustment (RPSFT) was visually similar to the KM plot of the unadjusted data (see Figure 5), which would not be expected if the company's assertion is true that OS results are substantially confounded by one-way crossover. Nonetheless, the ERG considers that incorporating the RPSFT-adjusted TIVO-1 results into the primary OS NMA or as a scenario analysis would have provided a useful comparison for the preferred NMA based on the unadjusted data.

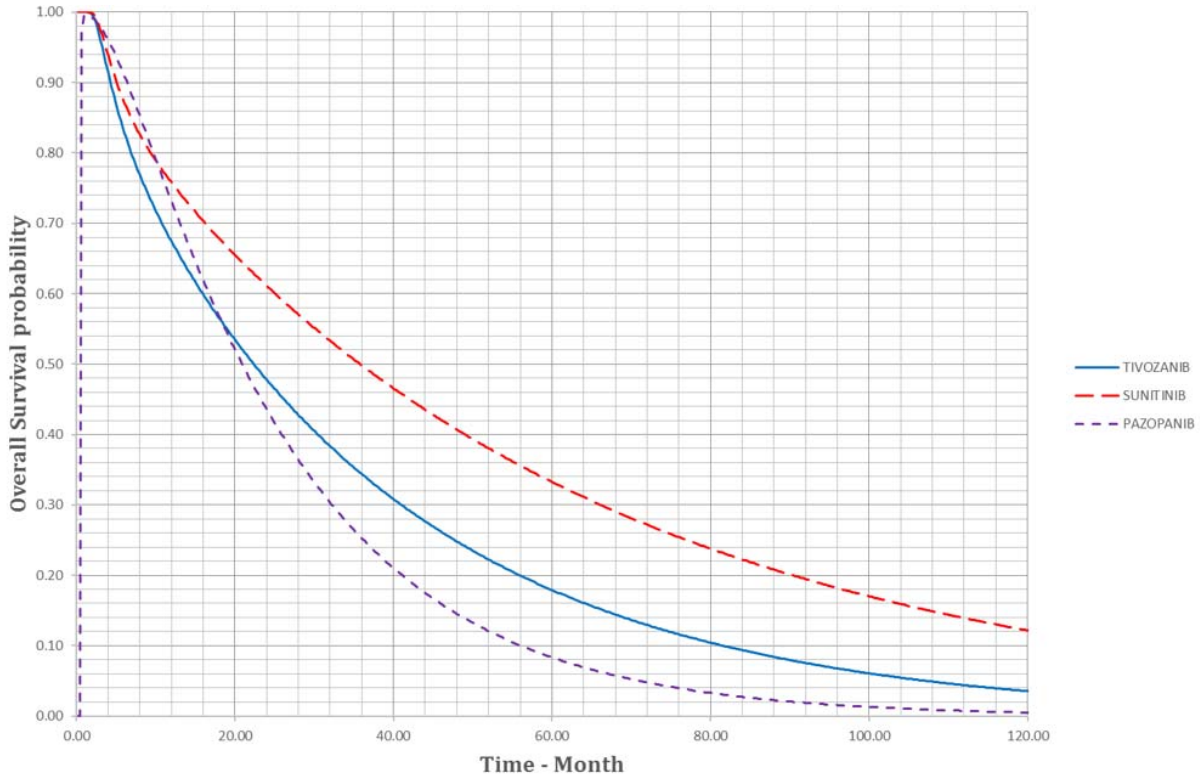
The company did not provide a synthesis of HRQoL data in the original CS, quantitative or otherwise, stating that there was insufficient evidence to support a reliable NMA (CS, Table 1, pg. 13–16 and CS page 85). For the primary simplified NMA, as stated in 4.3.1, the two studies (CROSS-J-RCC[82] and SWITCH[72]) providing a link between TIVO-1[41] and COMPARZ[9] did not report HRQoL or response rates so no NMA could be conducted. The ERG presents a narrative summary of results from TIVO-1 and COMPARZ in Section 4.3.4.4.

4.3.4 Clinical effectiveness results

4.3.4.1 Overall survival (OS)

Figure 9 shows OS results from the FP-based NMA submitted by the company. Median survival estimates obtained from the economic model extrapolation were 22.2 months for tivozanib, 35.2 months for sunitinib and 20.8 months for pazopanib (see Section 5.4.5).

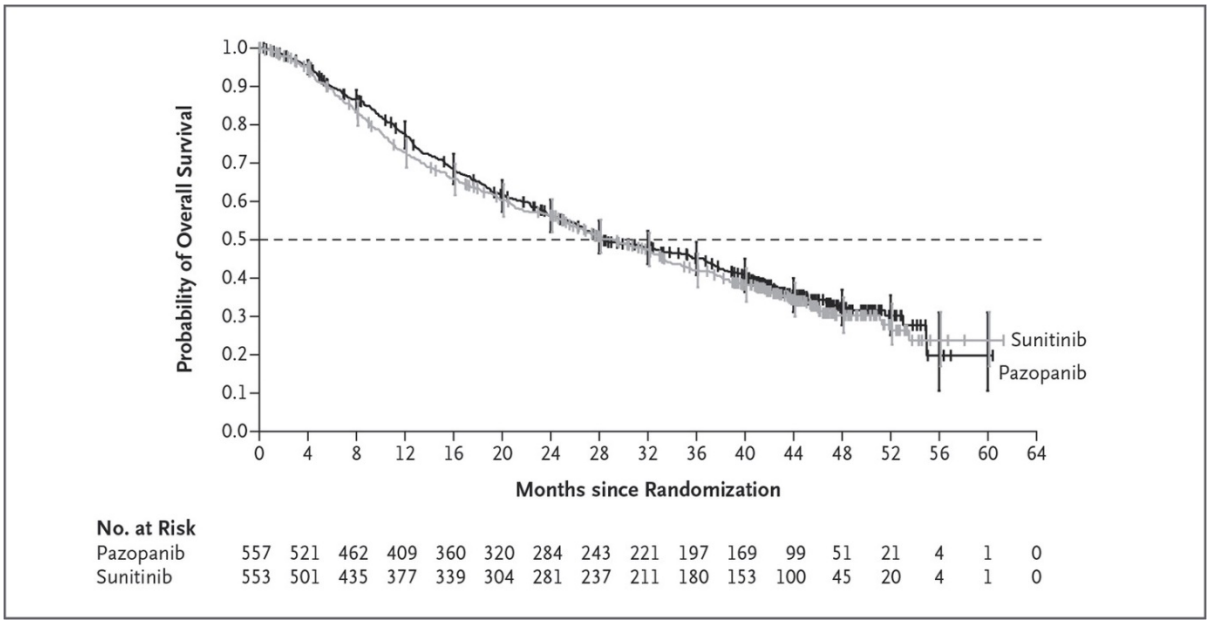
Figure 9. OS curves from the company's preferred second order fractional polinomial for tivozanib (solid blue), sunitinib (dashed red) and pazopanib (dashed purple); from the company's additional analyses



The ERG has limited confidence in these results for several reasons. First, the pazopanib curve begins at 0 (i.e. no survival at the beginning of treatment), suggesting an error in the analysis or the formula used to implement the results in the model. Second, the benefit shown for sunitinib over pazopanib contradicts the results observed in the head-to-head COMPARZ[9] trial, the only evidence from which the relative effect of the two treatments is derived in the NMA. The COMPARZ[9] study showed similar

OS for pazopanib and sunitinib, with an HR of 0.91 (95% CI: 0.76 to 1.08) in favour of pazopanib and around 20% still alive after 5 years; a KM plot of the most up-to-date data is shown in Figure 10 (reprinted with permission from Massachusetts Medical Society). Third, the extrapolation suggests that over 10% of patients taking sunitinib would still be alive after 10 years, which the ERG's clinical expert considered highly unlikely.

Figure 10. Kaplan-Meier plot for overall survival in the COMPARZ[9] study (From New England Journal of Medicine, Motzer, R. J., et al., Overall Survival in Renal-Cell Carcinoma with Pazopanib versus Sunitinib, 370 (18) [letter to the editor]. Copyright (2014) Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society)



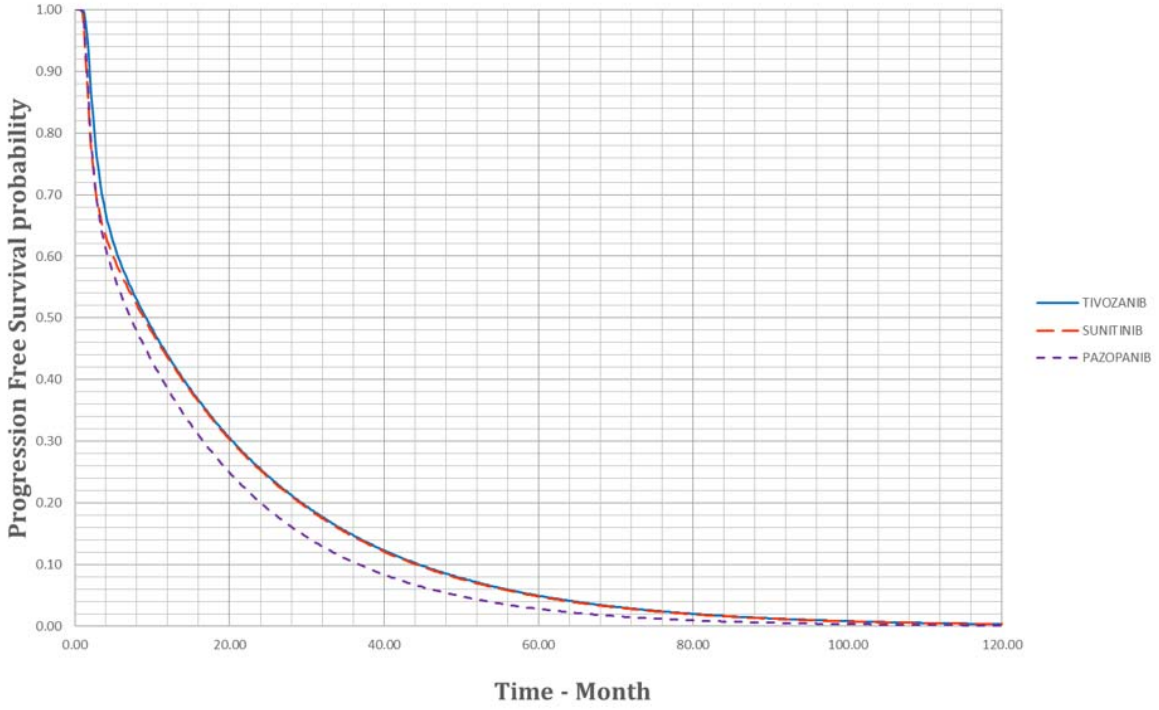
All four trials in the NMA report OS results as HR with accompanying CIs and none show a statistically significant difference between groups. However, median OS was shorter for sunitinib than sorafenib in the two trials informing the direct comparison, which may be confounded by higher rates of crossover from sorafenib to sunitinib than the opposite direction in both trials (see Table 25). Given that there is also likely to be confounding in the direct comparison between tivozanib and sorafenib (Section 4.2.1), and that none of the results are adjusted for crossover, all NMA results for OS should be interpreted with caution.

The ERG performed various checks to identify the source of the inconsistencies observed in the company's FP-based NMA, and subsequently performed additional analyses to provide more reliable results. However, trial results cannot be adjusted for crossover without individual patient data, so the ERG's preferred analysis of OS is likely to be equally confounded by crossover. Full details of the additional work undertaken by the ERG are shown in Section 4.4.

4.3.4.2 Progression-free survival (PFS)

Figure 11 shows the survival curves generated from the FP-based NMA for PFS. Median PFS estimates obtained from the economic model extrapolation were 9.1 months for tivozanib, 8.9 months for sunitinib and 7.2 months for pazopanib (see Section 5.4.5). The curves generated for tivozanib and sunitinib are very similar, with pazopanib showing slightly less favourable results. The benefit of sunitinib over pazopanib is in keeping with the head-to-head results observed in COMPARZ [9] which showed a HR of 1.05 in favour of sunitinib (95% CI: 0.90 to 1.22), and it is clinically plausible that all patients have progressed by 10 years.

Figure 11. PFS curves from the company's preferred second order fractional polinomial NMA for tivozanib (solid blue), sunitinib (dashed red) and pazopanib (dashed purple); from the company's additional analyses



However, as with OS, shape and scale parameters from the ERG's replication of the NMA did not match the company's results, so the ERG conducted a range of exploratory analyses to find and correct the source of the discrepancies; this work is described in Section 4.4.

4.3.4.3 Response rates

TIVO-1[41] measured CR, PR, SD, PD and ORR, but an NMA was only presented for CR, despite 13/19 of the RCTs identified as relevant reporting ORR (CS, Table 25, pg. 86). The ERG considered new analyses for OS and PFS as the priority during the time-limited clarification stage, so did not ask the company to run additional NMAs for response rate. As such, the only NMA results are for CR in the mixed pretreated population (CS Table 30), which are not consistent with the analyses on which the rest of the critique is based. Median ORs from the original analyses for tivozanib versus sunitinib

(median OR 1.126, 95% CrI: 0.116 to 13.02), and tivozanib versus pazopanib (median OR 2.855, 95% CrI: 0.134 to 81.02) both show a trend in favour of tivozanib, but the differences were not statistically significant and the CrIs were wide because CR events were rare (CS, Table 30).

The ERG has compiled response data from three of the four studies contributing to the simplified NMA for other outcomes (Table 31); CROSS-J-RCC[82] did not report response rates. Neither the company nor the ERG provided a formal analysis of these data and there are inherent difficulties in comparing single arm data across studies, so the data are presented for information only. TIVO-1 and COMPARZ[9] response outcomes were based on IRR which was not done in SWITCH.[72].

Table 31. Response rates observed in TIVO-1, SWITCH and COMPARZ

	Tivozanib	Sorafenib		Sunitinib		Pazopanib
	TIVO-1 full (N=257)	TIVO-1 full (N=260)	SWITCH (N=177)	SWITCH (N=176)	COMPARZ (N=553)	COMPARZ (N=557)
% CR	1.2	0.8	2.8	3.4	0.5	0.2
% PR	31.9	22.6	28.2	25.6	24.2	30.5
% SD	51.5	65.4	38.4	34.7	43.8	38.8
% PD	13.1	7.4	NR	NR	19.0	17.4
% Not evaluable	2.3	3.9	NR	NR	12.5	13.1
% ORR	33.1	23.3	31.1	29.0	24.8	30.7

Rates in TIVO-1 and COMPARZ are from independent radiology review, SWITCH data were only available based on investigator assessment; TIVO-1 data from CS, Table 20; December 2011 data cut; COMPARZ data from supplementary appendix for Motzer 2013[9]; SWITCH data are from Eichelberg 2015[72] for first line therapy. CROSS-J-RCC did not report response rates.
Abbreviations: CR, complete response; ITT, intention-to-treat; ORR, objective response rate (sum of partial and complete response); PD, progressive disease; PR, partial response

4.3.4.4 Health-related Quality of Life (HRQoL)

An NMA was not possible using the studies of interest; data on quality of life were not available in CROSS-J-RCC[82] or SWITCH,[72] and different scales were used in COMPARZ[9] than TIVO-1.[41]

TIVO-1 used the FACT-G (range 0–108)[88], FKSI-DRS (range 0–36)[89] and the index score of the EQ-5D (range 0–1).[90] Full results are shown in Section 4.2.4.4 but briefly, baseline scores for the full mixed pretreated population (treatment-naïve results not available) were comparable between groups at the beginning of TIVO-1 and remained similar over the first 12 months of treatment; the primary 24-month data cut was not used due to poor completion rates, but none of the results on any of the scales indicated a difference in HRQoL of patients treated with tivozanib compared with sorafenib. [redacted].

The COMPARZ{Motzer, 2013 #3148} study used the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F; range 0–52), the 19-item FACT Kidney Symptom Index (FKSI-19; range 0–76), the Cancer Therapy Satisfaction Questionnaire (CTSQ; range 0–100) and the Supplementary Quality of Life Questionnaire (SQLQ; range varies by symptom). Authors of the study note that HRQoL scores were better in the pazopanib group than the sunitinib group during the first 6 months of treatment for both primary HRQoL end points (fatigue and treatment side effects)[9]and that other significant differences generally favoured pazopanib over sunitinib, though effect magnitude varied.

The lack of a common comparator or measure between TIVO-1[41] and COMPARZ[9] prevents useful comparisons of tivozanib with pazopanib and sunitinib.

4.3.4.5 Adverse effects

The analyses presented in the CS were based on combinations of the 19 studies originally included in the NMA, for both treatment-naïve and mixed pretreated populations. As with the other outcomes, the ERG considered that NMAs based on only the necessary studies to compare tivozanib with sunitinib and pazopanib would provide more reliable results for the treatment-naïve population. After clarification, the company provided NMA based on COMPARZ,[9] CROSS-J-RCC,[82] SWITCH[72] and TIVO-1[41] for key AEs identified by the ERG's clinical experts: diarrhoea, fatigue/asthenia, hypertension, increased ALT and increased AST. All studies measured AEs as treatment-emergent, i.e. from beginning the study drug up to 30 days after discontinuing. As such, the issue of treatment-switching does not affect the results. ORs and CrIs provided from the simplified NMAs are shown in Table 32. Only the results shown in bold show a statistically significant difference between treatments.

Table 32. NMA results for selected Grade 3 and 4 adverse events (adapted from the company's clarification responses)

	Median odds ratio (95% credible interval)		
	Tivozanib vs sorafenib	**Tivozanib vs sunitinib**	**Tivozanib vs pazopanib**
Diarrhoea	0.329 (0.086 to 1.007)	**0.113 (0.025 to 0.430)**	**0.097 (0.020 to 0.399)**
Fatigue/asthenia	1.746 (0.590 to 5.662)	0.685 (0.173 to 2.849)	1.220 (0.294 to 2.294)
Hypertension	**1.760 (1.048 to 2.985)**	1.422 (0.639 to 3.182)	1.421 (0.598 to 3.391)
ALT increased	0.231 (0.000 to 7.128)	0.150 (0.000 to 3.698)	0.058 (0.000 to 1.873)
AST increased	0.134 (0.000 to 3.215)	0.660 (0.000 to 1.064)	**0.030 (0.000 to 0.753)**

Statistically significant differences shown in bold. OR < 1 favours tivozanib, OR > 1 favours the comparator treatment.
Abbreviations: NMA, network meta-analysis; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Rates of adverse events observed in each of the studies, i.e. the inputs for the simplified NMA are reproduced in Section 5, but the company chose to use the original NMA to populate the economic model which has substantial limitations (Section 5). Pairwise estimates for tivozanib versus sunitinib and pazopanib from the original NMA in the treatment-naïve population are reproduced in Table 33.

Table 33. Pairwise estimates for selected TEAEs from the original treatment-naive NMA (adapted from CS, Table 32)

		Tivozanib vs sunitinib		Tivozanib vs pazopanib	
		Median odds ratio	95% credible interval	Median odds ratio	95% credible interval
Grade 1 and 2	Alopecia	0.614	0.147 to 2.14	0.325	0.074 to 1.202
	Anaemia	2.328	0.001 to 4147	6.420	0.003 to 1134
	Asthenia/Fatigue	0.920	0.473 to 1.793	0.910	0.453 to 1.834
	Diarrhoea	0.708	0.368 to 1.351	0.558	0.281 to 1.102
	HFS	**0.221**	**0.101 to 0.478**	0.455	0.199 to 1.023
	Hypertension	**2.356**	**1.146 to 4.921**	1.847	0.859 to 4.028
	Mucositis/Stomatitis	0.408	0.149 to 1.123	1.328	0.470 to 3.763
	Nausea/Vomiting	0.521	0.222 to 1.245	0.490	0.204 to 1.203
Grade 3 and over	Anaemia	0.029	0 to 43.36	0.112	0 to 158.5
	Asthenia/Fatigue	0.953	0.245 to 4.014	1.699	0.417 to 7.42
	Diarrhoea	0.545	0.097 to 3.144	0.461	0.078 to 2.779
	HFS	**0.186**	**0.033 to 0.835**	0.407	0.069 to 1.935
	Hypertension	1.200	0.474 to 3.109	1.191	0.447 to 3.255
	Nausea/Vomiting	0.559	0.007 to 330.1	0.694	0.009 to 409.9
	Neutropenia	//	//	0.068	0 to 89.41
	Thrombocytopenia	0.237	0.001 to 160.5	1.653	0.009 to 1134

Statistically significant differences shown in bold. OR < 1 favours tivozanib, OR > 1 favours the comparator treatment.
Abbreviations: NMA, network meta-analysis; HFS, hand-foot syndrome; TEAE, treatment-emergent adverse effects

The original NMAs show higher rates of Grade 1 or 2 hypertension for tivozanib compared with sunitinib but not compared with pazopanib, and lower rates of Grade 1 or 2 and Grade 3+ HFS with tivozanib compared with sunitinib but not compared with pazopanib. Lower rates of Grade 3+ diarrhoea with tivozanib compared with sunitinib and pazopanib seen in the simplified NMA results (Table 32) were not apparent in the original analyses.

There is some evidence that tivozanib is associated with lower rates of diarrhoea and HFS than sunitinib and pazopanib, and higher rates of hypertension, though this depends on the severity of AE and NMA on which conclusions are based. Pairwise estimates for most TEAEs from the simplified and original NMAs do not indicate statistically different odds. Overall, results of the NMAs do not provide robust evidence to support the company's assertion that tivozanib has a favourable safety profile compared with pazopanib and sunitinib, which was primarily based on single-arm comparisons between studies and not the results of the NMA (CS, pgs 113–115).

4.3.5 Summary of the network meta-analysis (NMA)

The company conducted NMAs to support the clinical effectiveness review of tivozanib versus the comparators listed in the final scope issued by NICE.[1] The ERG considers the company's search strategy for indirect evidence to be limited in several respects, meaning relevant studies may have been

missed; registry searches were limited to records with published results, conference abstract searches were limited to ASCO 2015 and 2016 and ECCO 2015, searches were conducted in July 2016 and not updated, and non-English language publications were excluded.

With regards to inclusion criteria for the clinical effectiveness review, the ERG had concerns that the broad intervention criteria (axitinib, bevacizumab, everolimus, interferon-a, interleukin, pazopanib, sorafenib, sunitinib, temsirolimus, any other targeted therapy or immunotherapy, best supportive care and placebo) was not explained. There was a long list of included studies (N=24), of which 17[7, 9, 41, 61-74] (including 4 study subgroups[41, 72-74]) contributed to a set of treatment-naïve NMAs and 19[7, 9, 41, 61-76] to a set of mixed pretreated NMAs. The ERG considered that clinical heterogeneity (i.e. baseline prognostic indicators, study duration, potential crossover, differences in subsequent treatments, etc.) was not considered adequately to justify NMA. A lack of transparency regarding differential sifting processes for the treatment naïve and mixed pretreated NMAs prevented the ERG from validating the process (Section 4.1.3.2). For reasons already discussed (Section 3.1), the ERG focuses only the evidence for treatment-naïve patients, and did not consider cytokines a relevant comparator (Section 3.3).

The ERG noted that the method of analysis chosen for the survival analyses (OS and PFS) was likely to be inappropriate because proportional hazards did not appear to hold in TIVO-1. Additionally, the ERG considered that insufficient analyses were presented to explore the effect of subsequent therapy confounding of OS in TIVO-1, despite claiming that sorafenib survival relative to tivozanib was overestimated in TIVO-1. The company presented the IPCW approach (full population) to adjust survival of the 63% of patients in the sorafenib arm who switched to tivozanib as per the one-way crossover design, but did not show results of an NMA using the adjusted results.

During the clarification stage of the STA, the ERG recommended two alternative routes of analysis to provide more reliable results than those originally submitted by the company. The first proposed option was to conduct a treatment-naïve NMA limited to only the studies required to link tivozanib with pazopanib and sunitinib. As part of this option, the ERG suggested that alternative methods for the OS and PFS NMAs be used if proportional hazards did not to hold. The ERG also proposed that a range of crossover-adjustments for OS in TIVO-1 be explored[41] and that the adjusted results from the company's preferred approach be used to populate the NMA (recommended by the NICE DSU[84] and followed in the submission for pazopanib[86]). The second option presented by the ERG was to conduct an MAIC to adjust the population who received tivozanib in TIVO-1[41] to match the characteristics of the population in COMPARZ,[9] a head-to-head study comparing sunitinib and pazopanib. An MAIC would avoid the TIVO-1[41] confounding by not relying on the within-study comparison with sorafenib. Shortfalls of the MAIC method are that randomisation is broken and, as it would have been an "unanchored" analysis,

there would be no way to identify if all appropriate prognostic indicators and treatment-effect modifiers hadn't been adjusted for.

The company chose to use a simplified NMA structure, and alternative NMA methods for OS and PFS and crossover adjustment as their preferred route of analysis. The simplified NMA was based on four studies linking tivozanib with sunitinib and pazopanib: TIVO-1,[41] COMPARZ[9] (pazopanib versus sunitinib), CROSS-J-RCC[82] and SWITCH[72] (both sunitinib versus sorafenib). Proportional hazards tests for TIVO-1 showed that the assumption does not hold so the company based the OS and PFS NMAs on curves fitted to the baseline KM data observed for each treatment in each study; first using parametric curves (Weibull distribution) and later using the FP approach.

The company conducted an RPSFT approach to adjust results for the treatment naïve population in TIVO-1 but again did not provide an NMA using the adjusted results, stating that crossover-adjusted data were not available for other studies in the network. Looking at the other studies in the NMA, the ERG notes that more first-line sorafenib patients received subsequent therapy (75%[82] and 64%[72]) than first-line sunitinib patients (53%[82] and 55%[72]), which may have biased results in favour of sorafenib in both two-way sunitinib-sorafenib studies; the imbalances were less pronounced than in TIVO-1, meaning the unadjusted OS results from TIVO-1 may still underestimate tivozanib in the NMA.

The ERG notes that the unadjusted OS results for the treatment-naïve population may underestimate tivozanib compared with sorafenib because 66.3% of the sorafenib group received subsequent targeted therapy (63% receiving tivozanib) compared with 20.3% of the tivozanib group. Thus, it may follow that the crossover adjusted analyses overestimate tivozanib, because only 3.3% of sorafenib patients in the treatment-naïve population received subsequent targeted therapy other than tivozanib (Table 13) and the tivozanib group was not adjusted. The company's assertion that tivozanib OS survival is underestimated is supported only by the KM plot for the IPCW adjusted analysis of the full population (Figure 4), but not by the RPSFT results which show similar results to the unadjusted results (Figure 5).

The ERG considered inclusion criteria and baseline characteristics of the four trials in the simplified NMA similar (Table 27), and the ERG's clinical experts considered them to be broadly representative of patients who might be eligible for tivozanib in England. All studies required patients to be at least 18 years of age, have metastatic disease, ECOG of 0 or 1 or Karnofsky score of ≥70, and no significant cardiovascular disease. Median age ranged from 59 to 67 and participants were more often male in line with prevalence in the population. Most or all patients had clear cell RCC (87 to 100%), prior nephrectomy (82 to 100%), intermediate MSKCC status (with few or none in the poor category), and two or more metastatic sites (of which lung was the most common). TIVO-1[41] had a higher proportion with lymph node metastases than the other studies. Relative dose intensity (RDI) of tivozanib in TIVO-

1[41] (94%) was higher than the sorafenib group (81%), and higher than was observed in the first-line TKI trials supporting the NICE submission for pazopanib (86% for pazopanib and sunitinib)[25]; RDI was not available for COMPARZ, CROSS-J-RCC or SWITCH so it was not possible to quantify any possible effect on efficacy and safety estimates from the NMAs. Possible implications on cost are explored in the ERG's economic scenario analyses (Section 5).

The company's preferred curves for OS (second order FP, P1=-2, P2=-1) included an implausible curve for pazopanib which began at 0 survival. Additionally, the ERG noted that the difference between pazopanib and sunitinib contradicted results from the head-to-head COMPARZ[9] trial, the only evidence from which the relative effect of the two treatments is derived in the NMA. The extrapolation also suggests that over 10% of patients taking sunitinib would still be alive after 10 years, which the ERG's clinical expert considered highly unlikely. The ERG performed various checks to identify the source of the inconsistencies, and considered that further second order FP-based NMAs should be explored.[93] Full details of additional work undertaken by the ERG, including alternative clinical effectiveness estimates, can be found in Section 5.4.5.

For PFS, the company's results from the preferred second order FP-based NMA (P1=-2, P2=-1) showed similar efficacy for tivozanib and sunitinib, and slightly lower PFS for pazopanib. The second order FP results were more in keeping with the head-to-head results observed in COMPARZ and with those from the earlier Weibull analysis provided by the company (median PFS: tivozanib, 17 months; sunitinib, 16 months; pazopanib, 14 months; Figure 12). However, as with OS, errors were noted during the ERG's validation checks, so a range of exploratory analyses were performed; as with OS, this work is described in Section 5.4.5.

NMAs based on ORs were presented by the company for response rates (CR only) and were not updated to the preferred simplified structure due to time constraints during the clarification process; response outcomes were not included in the model so did not affect the ERG's base case. The mixed pretreated NMA is not consistent with the analyses on which the rest of the critique is based; median ORs for tivozanib versus sunitinib (median OR 1.126, 95% CrI: 0.116 to 13.02) and tivozanib versus pazopanib (median OR 2.855, 95% CrI: 0.134 to 81.02) both favour tivozanib, but the differences were not statistically significant and the CrIs were wide because CR events were rare (CS, Table 30). The ERG compiled response data from the three studies reporting response outcomes, but formal analysis was not undertaken due to time constraints and there are inherent difficulties in comparing single arm data across studies.

The lack of a common comparator or measure between two studies reporting HRQoL outcomes (TIVO-1[41] and COMPARZ[9]) prevented meaningful comparisons of tivozanib with pazopanib and sunitinib.

The company presented NMAs for multiple individual TEAEs in the original submission and subsequent results from the simplified NMA were provided for important TEAEs identified by the ERG's clinical experts (diarrhoea, fatigue/asthenia, hypertension, liver dysfunction). The original NMAs show higher rates of Grade 1 or 2 hypertension for tivozanib compared with sunitinib but not compared with pazopanib, and lower rates of Grade 1 or 2 and Grade 3+ HFS with tivozanib compared with sunitinib but not compared with pazopanib. Lower rates of Grade 3+ diarrhoea with tivozanib compared with sunitinib and pazopanib seen in the simplified NMA results were not apparent in the original analyses. Overall, results of neither NMAs provide robust evidence to support the company's assertion that tivozanib has a favourable safety profile compared with pazopanib and sunitinib, which was primarily based on single-arm comparisons between studies and not the results of the NMA (CS, pgs 113–115).

4.4 Additional work on clinical effectiveness undertaken by the ERG

The ERG noted several issues with the FP-based NMA submitted by the company for OS and PFS that may have led to unreliable estimates of tivozanib compared with sunitinib and pazopanib (Section 4.3). As such, the ERG considered that various checks should be performed and additional analyses explored reduce the uncertainty of the clinical effectiveness results for OS and PFS. Details of the work conducted and results from the ERG's preferred FP-based NMA, which inform the ERG's base case, are presented in Section 5.4.5.

4.5 Conclusions of the clinical effectiveness section

- Marketing authorisation (MA) for tivozanib has not yet been granted by the EMA. The proposed MA is for the treatment of adult patients with advanced RCC who are VEGFR and mTOR pathway inhibitor-naïve and are either untreated or who have failed prior therapy with interferon-alpha (IFN-α) or interleukin-2 (IL-2)

- The clinical evidence submitted for tivozanib is based primarily on TIVO-1, a parallel, open-label, randomised Phase III trial which randomised 517 patients with metastatic or recurrent RCC to tivozanib or sorafenib[41] The study was generally well conducted but was unblinded and the one-way crossover design makes OS difficult to interpret.

- The ERG considers efficacy and safety evidence for the 70% of patients in TIVO-1 who were treatment-naïve to be relevant to the decision problem outlined in the NICE final scope.[1]

- For the treatment-naïve population in TIVO-1, OS unadjusted for crossover favoured sorafenib (HR 1.23, 95% CI: 0.90 to 1.67) and PFS based on IRR favoured tivozanib by around 3 months (HR 0.76, 95% CI: 0.58 to 0.99; though proportional hazards do not hold). ORR, only available

for the full population, favoured tivozanib at the main data cut (OR 1.623, 95% CI: 1.101 to 2.391, p=0.013), but not when the analysis included patients who remained on their as-randomised treatment in the extension study (OR 1.057, 95% CI: 0.744 to 1.572, p = 0.681). Tivozanib was associated with lower rates of diarrhoea, hand-foot syndrome, alopecia, increased AST, increased amylase, increased lipase and hypophosphataemia of any grade, and lower rates of Grade 3 diarrhoea, hand-foot syndrome, increased lipase and hypophosphatemia compared with sorafenib. Tivozanib was associated with higher rates of hypertension and dysphonia of any grade and more patients in the tivozanib group had fatal TEAEs than the sorafenib group (10.8% vs 5.8%).

- Sorafenib, the comparator used in TIVO-1, is not recommended by NICE for the first-line treatment of metastatic RCC, so NMAs were conducted to provide evidence for tivozanib against all relevant comparators for the treatment-naïve population. Cytokines were listed as a comparator in the NICE final scope but the ERG and its clinical experts do not consider them a relevant comparator. The analyses in the CS were superseded by a different network structure (4 studies instead of 19), and the survival outcomes were reanalysed with NMA using fractional polynomials (FP) after proportional hazards was found not to hold in TIVO-1.

- The company's preferred NMAs, submitted as part of the clarification process, used the FP approach for OS and PFS, and were all based on 4 studies linking tivozanib with sunitinib and pazopanib: TIVO-1,[41] COMPARZ[9] (pazopanib versus sunitinib), CROSS-J-RCC[82] and SWITCH[72] (both sunitinib versus sorafenib).

- Populations of the four studies in the NMA were comparable and were considered to reflect broadly a population who might be eligible for treatment with tivozanib in the UK; median age ranged from 59 to 67 and participants were more often male in line with prevalence in the population. Most or all patients had clear cell RCC (87% to 100%), prior nephrectomy (82% to 100%), intermediate MSKCC status (with very few or none in the poor category), and two or more metastatic sites (of which lung was the most common).

- In the NMA, ECOG performance status [15] and percentage with prior nephrectomy may suggest more favourable prognosis than the full population outlined in the NICE final scope.[1]

- The ERG considered OS results from the company's FP-based NMA improbable; pazopanib appears much less effective than sunitinib which contradicts the underlying head-to-head evidence from COMPARZ[9] The ERG explored alternative FP-based NMAs for OS and present its preferred analysis in Section 5.4.5

- The company's FP-based NMA suggests PFS with tivozanib may be similar to sunitinib, and that both may have a slight benefit over pazopanib. The company's results are consistent with head-to-head results from COMPARZ[9] The ERG explored alternative FP-based NMAs for PFS and present its preferred analysis in Section 5.4.5

- The company were unable to provide results from treatment-naïve NMAs for response or HRQoL; NMA results for CR were only available for the full population, and HRQoL data were only reported in two trials with no common comparator.

- NMA results show lower rates of Grade 3+ diarrhoea with tivozanib compared with sunitinib and pazopanib, but most results were not statistically significant. The ERG does not consider that results from the NMAs provide robust or consistent evidence to support the company's assertion that tivozanib has a favourable safety profile compared with pazopanib and sunitinib; the ERG considers it invalid to base safety conclusions on single-arm comparisons between studies (CS, pgs 113–115).

4.5.1 Clinical issues

- The ERG considers the company's search strategy to be limited in several respects, meaning relevant studies may have been missed; registry searches were limited to records with published results, conference abstract searches were limited to ASCO 2015 and 2016 and ECCO 2015, searches were conducted in July 2016. The CS includes no detail of duplicate sifting and quality assessment, and separate eligibility and sifting processes for the treatment-naïve and pretreated evidence were not described.

- Results of two Phase II studies were submitted as supplementary non-randomised data, but a randomised preference study of tivozanib versus sunitinib (i.e. a relevant comparator) was omitted, despite being listed as contributing to the safety data on which the SmPC is based.

- The design of TIVO-1 and the concurrent extension study made participant flow difficult to disentangle. There were multiple data cuts across the two studies and several data inconsistencies were noted.

- The CS did not provide evidence relevant to a pretreated population because the 30% who were pretreated in TIVO-1 had received different treatments (primarily cytokines) than would be given in England.

- TIVO-1 results for OS are expected to be confounded by imbalance in subsequent targeted therapies, primarily due to one-way crossover from sorafenib to tivozanib: 66.3% of the

sorafenib group received subsequent therapies (63% received tivozanib) and 20.3% of the tivozanib group. The two trials providing the direct comparison of sorafenib and sunitinib are likely to be confounded by higher rates of crossover from sorafenib to sunitinib than the opposite direction in both trials (see Table 25).

- NMA results for OS should be interpreted with caution because the unadjusted results from direct comparisons are likely to be confounded by treatment crossover. An adjusted analysis was available for TIVO-1 but not the other studies in the NMA, so the company chose to include unadjusted data. TIVO-1 unadjusted results may underestimate, and adjusted results may overestimate, the effectiveness of tivozanib because the analyses did not adjust for subsequent targeted therapy received in the tivozanib group (20.3%).

- The company's preferred NMAs for OS and PFS were based on FP curves modelling the KM data observed for each treatment in each study (after proportional hazards was found not to hold in TIVO-1). The ERG's validation of the OS and PFS FP-based NMAs uncovered flaws in the results and the way they were implemented in the model; the company's curves for OS were implausible given the underlying data and estimated survival at 10 years.

- The ERG performed various checks to identify the source of the inconsistencies observed in the company's FP-based NMA, and subsequently performed additional analyses to provide more reliable results. Trial results cannot be adjusted for crossover without individual patient data, so the ERG's preferred analysis of OS is likely to be equally confounded by crossover.

- An MAIC matching the TIVO-1 tivozanib group to the COMPARZ trial, suggested to the company as an option at the clarification stage, may provide more reliable results because it would not rely on the within-study comparison with sorafenib (hence removing the suspected confounding due to one-way crossover on OS, and possible biases from baseline imbalances in ECOG performance status).

- NMA results for response do not reflect the treatment-naïve population due to time constraints during the clarification process and HRQoL data did not support NMA.

5 COST EFFECTIVENESS

5.1 Introduction

This section provides a structured description and critique of the systematic literature review and *de novo* economic evaluation submitted by the company for tivozanib for treating advanced renal cell carcinoma (RCC) in adult patients who have not been previously treated with targeted therapy (VEGFR inhibitor or mammalian target of rapamycin (mTORs) inhibitor) but who may have previously received cytokines. The company provided a written submission of the economic evidence along with an electronic version of the Microsoft© Excel based economic model. Table 34 summarises the location of the key economic information within the company's submission (CS).

Table 34. Summary of key information within the company's submission

Information	Section (CS)
Details of the systematic review of the economic literature	5.1
Model structure	5.2.2
Technology	5.2.3
Clinical parameters and variables	5.3
Measurement and valuation of health effects and adverse events	5.4
Resource identification, valuation and measurement	5.5
Results	5.7, additional analyses document
Sensitivity analysis	5.8
Validation	5.10
Strengths and weaknesses of economic evaluation	5.11
Abbreviations used in table: MS, manufacturer's submission.	

5.2 Summary of the company's key results

The company's revised base case results for tivozanib versus sunitinib and pazopanib are presented in Table 35, full incremental results are given in Table 36 and the results of the probabilistic sensitivity analysis (PSA) are presented in Table 37.

Table 35. Pairwise analysis cost-effectiveness results - revised base case (Company's additional analysis results document, Table 4 and 5)

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Tivozanib	£70,476	1.757	-	-	-
Sunitinib	£105,566	2.425	-£35,091	-0.668	£52,533 (SW Quadrant)
Pazopanib	£58,537	1.432	£11,938	0.325	£36,757
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; IFN: Interferon; QALY, Quality-adjusted life year; SW, south-west.					

Table 36. Fully incremental cost-effectiveness results of revised base case - Second order FP-based NMA (P1= -2, P2= -1) (Company's additional analysis results document, Table 6)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Pazopanib	£58,537	2.076	1.432	£11,938	-	-	-
Tivozanib	£70,476	2.543	1.757	£35,091	0.467	0.325	£52,533
Sunitinib	£105,566	3.586	2.425	£11,938	1.043	0.668	£47,361
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

Table 37. Mean probabilistic ICERs (Company's scenario analysis document, Table 25 and Table 26)

Therapy	Tivozanib versus sunitinib	Tivozanib versus pazopanib
Deterministic ICER	£52,533 (SW Quadrant)	£36,757
Mean probabilistic ICER	£55,039 (SW Quadrant)	£32,336
Abbreviations in table: ICER, incremental cost-effectiveness ratio; SW, south-west		

5.3 ERG comment on company's review of cost-effectiveness evidence

The company carried out a single search to identify studies assessing clinical and cost-effectiveness of treatments for patients with metastatic RCC. The search also aimed to identify studies reporting the quality of life of patients in this population and the economic burden associated with metastatic RCC.

The company provides an overview of the search in Section 4.1 of the CS, with the search terms and results presented in Appendix 2. The company searched the following online databases: Pubmed, Embase and the Cochrane Library. The search was carried out on 21 July 2016 and was restricted to studies published from 1995 onwards. The search terms for cost-effectiveness studies, quality of life studies and resource use studies combined population terms (renal cell carcinoma) with terms related to study type. The inclusion and exclusion criteria applied by the company to identify cost-effectiveness studies are summarised in Table 38.

Table 38. Inclusion and exclusion criteria applied in search for cost-effectiveness studies (CS, pg 122, Table 47)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Aged ≥ 18 years Any gender Any race Has locally advanced/advanced/metastatic/stage III/stage IV disease	No data reported on relevant population
Intervention	Any intervention included in the efficacy review	No data reported on relevant intervention
Comparators	Any of the included interventions Placebo Best supportive care	No data reported on relevant comparator
Outcomes	Cost per life-year saved Cost per QALY gained Costs saved	No data reported on a relevant outcome
Study design	Cost-benefit analyses Cost-effectiveness analyses	Other study design

	Cost-utility analyses Systematic reviews will be used for citation chasing only Studies only available as conference abstracts will be included if they report sufficient relevant data to inform model development or parameterisation	
Language restrictions	English only	Full text publication in other language
Publication dates	1995 onwards (journal articles) Last 2 years of conference abstracts	Published outside relevant dates
Abbreviations in table: QALY, quality-adjusted life-year.		

The company did not provide information on the number of economic evaluation, quality of life, and resource use studies identified, or the number of studies in these categories that were reviewed in full for inclusion. A total of 15 cost-effectiveness studies were identified by the search, with four studies[97-100] considered to be of relevance to the UK. Across the four studies the following interventions were assessed; pazopanib, sorafenib, temsorilimus, sunitinib, bevacizumab, Interferon-alpha (IFN-α) and best supportive care (BSC).[97-100] The studies were quality assessed in line with the guidelines presented in the publication by Drummond and Jefferson.[101]

The ERG considers the inclusion and exclusion criteria applied by the company to be appropriate and the search terms to be in line with guidelines published by the Health Information Research Unit at McMaster's University.[102] Due to time constraints, the ERG was unable to replicate the company's search and appraisal of identified abstracts for all databases.

The ERG asked the company to provide a justification for restricting studies included to those published after 1995 at clarification stage. The company stated the following, "*The systematic literature search for cost-effectiveness studies was limited to those published from 1995 onwards to allow the review to focus on economic analyses that best reflected current clinical practice and costs. Older studies were considered unlikely to have involved the newer targeted therapies that are now standard of care in this population and costs and resource use data used to parameterise the models were considered unhelpful for the current clinical context. The economic analyses identified by this later search date were built on and modified older models, and included evaluations of previous manufacturers' submissions to NICE, which were used to inform the development of the model used in this submission.*" The justification provided by the company is reasonable, and applying this is unlikely to have an impact on the results of the review.

The ERG considers that is likely that all cost-effectiveness studies relevant to the decision problem have been identified in the search.

5.4 Overview and critique of company's economic evaluation

The company developed a *de novo* economic model in Microsoft Excel® to assess the cost-effectiveness of tivozanib compared with sunitinib, pazopanib and IFN-α for patients with recurrent or metastatic RCC who are treatment naïve.

The company's base case analysis relies on the fractional polynomial (FP) method based on a network meta-analysis (NMA) of relevant trials to estimate the relative treatment effectiveness between tivozanib, sunitinib and pazopanib respectively, due to the absence of direct head-to-head trials. The FP-based NMA is an appropriate method to employ when proportional hazards (PHs) does not hold for trials within the network, which the company found was the case for the TIVO-1 trial. However, the ERG found several issues with the implementation of the FP-based NMA in the economic model and these are discussed further in Section 5.4.5.

Two reporting errors were found in the original CS relating to the progression-free survival (PFS) estimates used for the extrapolation. In the CS, the company state that median PFS was based on independent radiology review (IRR), however the model incorporated PFS data based on investigator review. Furthermore, data used for PFS and overall survival (OS) were based on the overall intention-to-treat (ITT) population rather than the treatment naïve population. The ERG raised these issues during the clarification stage and were rectified by the company in their response to clarification questions.

The remaining sections of this report give a more detailed description and critique of these issues, as well as additional specific issues relating to each of the key aspects of the economic analysis, starting with a quality assessment in Section 5.4.1 based on the NICE reference case and Philips checklists.

5.4.1 NICE reference case checklist

Table 39 and Table 40 summarise the ERG's quality assessment of the company's economic evaluation. Table 39 summarises the ERG's appraisal of the company's economic evaluation against the requirements set out in the NICE reference case checklist for the base case analysis, with reference to the NICE final scope outlined in Section 3.[1] Table 40 summarises the ERG's appraisal of the quality of the company's *de novo* economic model using the Philips checklist.[103]

Table 39. NICE reference checklist

Attribute	Reference case	Does the *de novo* economic evaluation match the reference case?
Decision problem	The final scope developed by NICE	No, the company did not include the secondary treatment comparisons specified in the final NICE scope[1] since it is positioning tivozanib as a first-line VEGFR-TKI treatment.
Comparator(s)	Alternative therapies routinely used in the NHS	Yes, the company included pazopanib, sunitinib and IFN-α in the original base case. However, in the revised base case analysis removed IFN-α from the analysis as the company state that cytokines are no longer routinely administered in UK clinical practice for first-line treatment of RCC and this was verified with the ERG's clinical expert who agreed with the company's justification.

Perspective costs	NHS and Personal Social Services	Yes.
Perspective benefits	All health effects on individuals	Yes.
Form of economic evaluation	Cost-utility analysis	Yes.
Time horizon	Sufficient to capture differences in costs and outcomes	Yes.
Synthesis of evidence on outcomes	Systematic review	Yes.
Outcome measure	Quality adjusted life years	Yes.
Health states for QALY	Described using a standardised and validated instrument	Yes, utility data were based on EQ-5D data collected in the TIVO-1 trial.[41]
Benefit valuation	Time-trade off or standard gamble	Yes, time trade-off.
Source of preference data for valuation of changes in HRQoL	Representative sample of the public	Yes.
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes.
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	Yes.
Sensitivity analysis	Probabilistic sensitivity analysis	Yes.
Abbreviations used in the table: CS, company submission; EQ-5D, EuroQoL-5 Dimensions; ERG, Evidence Review Group; HRQoL, health-related quality of life; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; QALY, quality-adjusted life year; VEGFR-TKI, Vascular endothelial growth factor receptor tyrosine kinase inhibitor.		

Table 40. Philip's checklist[103]

Dimension of quality	Comments
Structure	
S1: Statement of decision problem/objective	Clearly stated.
S2: Statement of scope/perspective	Clearly stated (UK NHS and PSS) and consistent with the scope.[1]
S3: Rationale for structure	The structure and modelling approach is consistent with previously used models in technology assessments of first-line treatments of RCC.
S4: Structural assumptions	The ERG considers the company's structural assumptions to be appropriate and in line with published oncology models.
S5: Strategies/ comparators	Tivozanib was compared to pazopanib and sunitinib in the company's (revised base case) FP model.
S6: Model type	A partitioned survival (area under the curve model) was used which the ERG considers to be appropriate.

S7: Time horizon	A time horizon of 10 years is used, with less than 2% of patients being alive at that time point based on the extrapolation of OS KM data from the TIVO-1 trial.
S8: Disease states/pathways	The model included three health states: alive pre-progression, alive post-progression and death.
S9: Cycle length	The cycle length is appropriate to adequately capture differences in costs and effects between treatments. No half-cycle correction was applied due to the short length of cycles.
Data	
D1: Data identification	A single systematic review was carried out to identify studies assessing clinical and cost-effectiveness studies assessing first-line treatments of metastatic RCC, in addition to studies evaluating the quality of life of RCC patients.
D2: Pre-model data analysis	The company carried out an NMA based on a network consisting of four trials[9, 41, 72, 82] utilising the FP method. This method was chosen by the company as an alternative to the hazard ratio based analysis originally used in the CS which required proportional hazards to hold which was not the case in the TIVO-1, and therefore the ERG did not consider to be appropriate.
D2a: Baseline data	The baseline characteristics were based on the characteristics of the treatment-naïve patients in the TIVO-1 trial,[41] and are reflective of treatment-naïve patients encountered in UK clinical practice according to the ERG's clinical experts.
D2b: Treatment effects	Relative treatment effects were derived from a fixed effects FP model based on a network meta-analysis of relevant trials, which is an appropriate method when proportional hazards does not hold for trials included in the network (which was the case for the TIVO-1 trial). A selection of first order and one second order FP-based NMAs were assessed using goodness of fit statistics. The company selected the second order FP-based NMA (P1= -2, P2= -1) as the basis of the NMA to extrapolate PFS and OS outcomes as this has the lowest Deviance Information Criterion (DIC) statistic out of all the models assessed. The company explored the use of the next best fitting FP model, which was the first order FP (P=-2) in a sensitivity analysis. However, the ERG discovered that the FP parameters were implemented incorrectly in the model, producing implausible extrapolations for OS. Furthermore, the ERG could not replicate the FP parameters produced by the company.
D2c: Costs	The ERG's clinical experts disagreed with the exclusion of blood tests in the resource use assumptions made by the company for disease management. The ERG disagreed with the approach taken by the company to estimate the costs of subsequent treatments in the model, specifically the assumption that 40% of patients receive best supportive care while 60% receive axitinib. There are currently various second-line treatments available in the NHS for metastatic RCC, and per clinical expert opinion sought by the ERG and reported in the cabozantinib STA[29] only a small proportion of treatments (10%) would not receive active treatments after progression on first-line therapy. In addition, the company assumed lifetime costs for second line therapy which does reflect clinical reality. The ERG carried out a scenario analysis for subsequent therapies in the model in line with current UK clinical practice.
D2d: Quality of life weights (utilities)	The health state utility values used in the model are based on values estimated for the ITT population of the TIVO-1 trial. The ERG's clinical experts stated that patients with prior cytokine treatment may have a lower quality of life compared to treatment-naïve patients and therefore the HSUVs may be underestimating the quality of life of patients in the model since 30% of patients in the TIVO-1 trial received prior cytokine treatment.[41] The company applied utility decrements for patients experiencing adverse events identified from the pazopanib STA CS,[25] which the company incorrectly states are based on the VEG105192 trial.[74] The utility decrements reported in the pazopanib STA were in fact based on a vignette study carried out on a sample of the UK general population and not from patients with RCC.[25]The ERG disagrees with using these values in the model, since they are not based on data collected from patients experiencing the condition as stipulated in the NICE reference case.[104]
D3: Data incorporation	The company did not provide sufficient details on how treatment effectiveness data was incorporated in the revised base case FP model.

Assessment of uncertainty	
D4a: Methodological	The company explored a range of first order FP-based NMAs, but only one second order FP-based NMA to select the best fitting curve for the extrapolation of PFS and OS for all treatments. The ERG considers that the company should have explored further second order FP-based NMAs as the nature of second order FP-based NMA means that it has greater flexibility and will therefore produce better fitting curves compared to first-order FPs.
D4b: Structural	Exploration of structural uncertainty through sensitivity analysis was limited.
D4c: Heterogeneity	No subgroup analyses were carried out.
D4d: Parameter	Parametric uncertainty was explored through deterministic sensitivity analyses and a probabilistic sensitivity analysis around the base case. However, the ERG had insufficient time to fully validate the sensitivity analyses carried out by the company.
Consistency	
C1: Internal consistency	The ERG identified a fundamental flaw in the survival calculation the company used to generate the PFS and OS curves based on the parameters generated by the selected FP-based NMA. The company's calculation estimated a hazard for the whole period up to a model cycle, rather than the cumulative hazard within a model cycle which would produce are under the curve estimates. The ERG was unable to replicate the company's FP parameter estimates that were used in the model by running the WinBUGs code supplied by the company. Therefore, the ERG implemented its own estimates in the model, which produced significantly different curves which better reflected the underlying data but still produced implausibly long tails. There was also an error in adjusting monthly disease management costs to weekly costs in the model, which the ERG corrected.
C2: External consistency	The extrapolated clinical outcomes in the company's model lacked face validity, since the extrapolations of PFS and OS curves show the curves of sunitinib to be superior to those of pazopanib, while in the COMPARZ trial[9] which is the source of the data underlying this comparison in the network shows the reverse to be true.
Abbreviations in table: CS, company's submission; ERG, evidence review group; FP, fractional polynomial; HSUV, health-state utility value; ITT, intention to treat; KM, Kaplan Meier; NHS, National Health System; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PSS, Personal Social Services; RCC, renal cell carcinoma; STA, single technology appraisal.	

5.4.2 Population

The population considered by the company for this single technology appraisal (STA) is based on the proposed marketing authorisation which includes adult patients with advanced renal cell carcinoma (RCC), who have not been previously treated with targeted therapy (VEGFR inhibitor or mammalian target of rapamycin (mTORs) inhibitor) but who may have previously received cytokines. This population can be split into those who have untreated RCC (also referred to as, "treatment naïve") and those who have pretreated disease with cytokines, which is reflective of the NICE final scope.[1] However, the company have produced their base case analysis on the treatment naïve population, as they assert throughout the CS that this population is reflective of what would be seen in UK clinical practice, since cytokines have been replaced by VEGFR-TKIs as the standard of care for advanced RCC at first line of treatment (CS, page 13). In addition, tivozanib is being positioned as a first line VEGFR-TKI treatment by the company. The ERG's clinical experts also confirmed this view, stating that in the UK patients are rarely, if not at all, treated with cytokines instead of VEGFR-TKIs. The ERG considers

that in the UK as VEGFR-TKIs are the first line treatment option for patients with advanced RCC, this positions tivozanib as a first line option for it to comply with its marketing authorisation for use in VEGFR-TKI-naïve patients

As mentioned in Section 3.1, the ERG considers the baseline characteristics of the modelled treatment naïve population to be reflective of patients with recurrent or metastatic RCC in the UK. However, because of the inclusion criteria used in TIVO-1, the baseline characteristics of the population in the economic model primarily refer to those treatment naïve patients with clear cell RCC, good performance status (ECOG score of 0 or 1) and prior nephrectomy, and hence may have a better prognosis than the full population covered by the NICE final scope.[1]

5.4.3 Interventions and comparators

5.4.3.1 Comparison with NICE final scope

The intervention and comparators considered in the economic analysis were tivozanib (intervention) and sunitinib, pazopanib and IFN-α (comparators). These are in line with the NICE final scope for untreated RCC.[1] The NICE final scope also included previously treated RCC for which the comparators of interest were axitinib, nivolumab, everolimus, cabozantinib and BSC.

The NICE final scope reflects the proposed indication for tivozanib, which the company describes as, "… the treatment of adult patients with advanced RCC who are VEGFR and mTOR pathway inhibitor-naïve and are either untreated or who have failed prior therapy with IFN-α or IL-2" (Section 2.2 of the CS, page 29).

As mentioned in the previous section, the company's rationale for the deviation from the NICE final scope was that in the UK, VEGFR-TKIs have replaced cytokines to become the standard of care for first line treatment of patients with recurrent or metastatic RCC. Clinical experts involved with TA333 advised the committee that use of cytokines was rapidly decreasing, with the majority of patients starting treatment on sunitinib or pazopanib.[26]

The company also state that tivozanib will not be used in patients with advanced RCC previously treated with VEGFR-TKIs and mammalian target of rapamycin (mTOR) and as such the comparators listed in the NICE final scope for previously treated RCC are not relevant. As mentioned previously, the ERG considers that the company has positioned tivozanib as a first line VEGFR-TKI treatment, but that because of the limited used of cytokines in the UK, this could be considered the untreated population. As such, the ERG considers sunitinib and pazopanib the most relevant comparators.

Please refer to Section 3 for more detail on the comparison of the CS to the NICE final scope.

5.4.3.2 Treatment regimens

Table 41 presents the modelled treatment regimens implemented in the economic model.

Table 41. Treatment regimens assumed in the economic model

Treatment	Dose regimen
Tivozanib	1,340µg daily taken orally for 3 weeks followed by 1 week rest
Sunitinib	50mg daily taken orally for 4 weeks followed by 2 weeks rest
Pazopanib	800mg daily taken orally administered continuously
IFN-α	3 MU 3x weekly for 1 week; 6 MU 3x weekly for second week; 9 MU 3x weekly thereafter
Abbreviations in table: IFN-α, Interferon alpha; MU, milliunit;µg, microgram; mg, milligram	

Time on treatment was modelled using parametric survival distributions for PFS, as specified by the marketing authorisations for the treatments modelled (Table 67, page 150 of the CS) and published papers for sunitinib and pazopanib. [9, 105] PFS is discussed in more detail in Section 5.4.5.

The company assumed the relative dose intensity (RDI) for all treatments was 100%. During clarification stage the ERG requested the company to provide a scenario using RDIs for each treatment reported in the published literature, which the company declined to provide as they were unable to obtain RDI data for sunitinib and pazopanib from the trials included in the network. However, they did state the RDI for tivozanib from the TIVO-1 trial was 94%. The ERG reviewed the ERG reports associated with the TA215 (pazopanib) and TA169 (sunitinib) and found that RDI reported for both treatments was 86%. This issue is explored further in Section 5.4.8.

For all treatments, discontinuation from treatment was primarily due to progressive disease. However, from the two published papers of trials for sunitinib and pazopanib and mentioned in the CS (page 112), discontinuation rates were between 19-20% for sunitinib and 14-24% for pazopanib. The treatment discontinuation rate for tivozanib from the TIVO-1 trial was 4%.[9, 105]

The ERG considers that the modelled treatment durations and the use of 100% RDI for sunitinib and pazopanib are potentially overestimating comparator treatment costs. The impact of RDI on the ICER is explored in Section 5.4.8.

Subsequent therapy

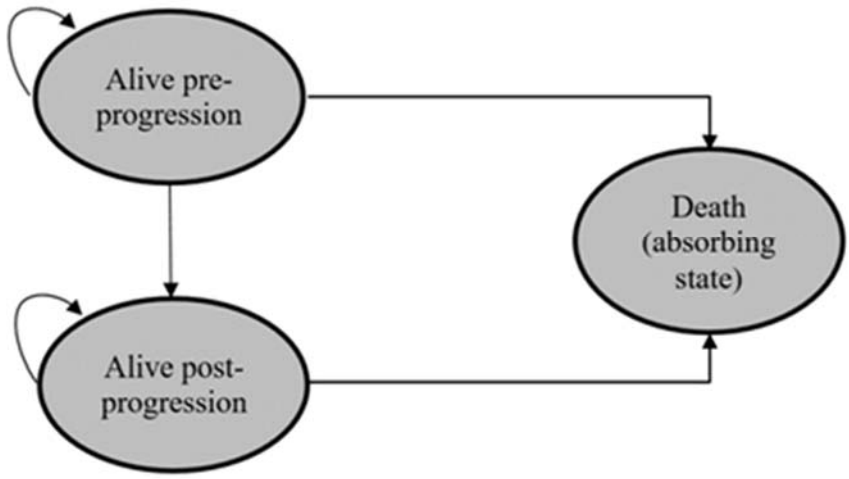
Axitinib was assumed to be given as a subsequent treatment once a patient experienced disease progression. The modelled treatment regimen for axitinib was 5mg orally twice per day, which is in line with the AXIS trial and what is recommended for UK practice.[106]

The company assumed that once a patient progressed and started 2nd line treatment with axitinib, they would continue treatment until death (Table 67 of the CS). The ERG considers this assumption is not reflective of current clinical practice and this is explored further in Section 5.4.8.

5.4.4 Modelling approach and model structure

The company developed a *de novo* economic model in Microsoft Excel® to assess the cost-effectiveness of tivozanib compared with sunitinib, pazopanib and IFN-α for patients with recurrent or metastatic RCC who are treatment naïve. A partitioned survival model (presented in Figure 12) was implemented, comprising of three health states: alive pre-progression, alive post-progression, and dead. The company stated that the approach adopted was similar to that used for NICE TA215 for pazopanib for the same indication.[25]

Figure 12. Model structure (CS, page 127, Figure 20)



All patients enter the model in the alive pre-progression health state and are assumed to be on active treatment (either tivozanib, sunitinib, pazopanib or IFN-α). A patient can remain in the alive pre-progression state until they experience disease progression (thus transitioning into the alive post-progression health state) or die (in which case the patient transitions into the death health state). When a patient transitions into the alive post-progression health state, primary treatment is terminated and second line treatment is initiated immediately. A patient remains in this health state until death.

A cycle length of one week was implemented in the model with the justification that the length was sufficiently long enough to capture differences in costs and effects between treatments. The proportion of patients occupying a health state during any given cycle is based on parametric survival curves for each clinical outcome. A description of how the survival curves were estimated and implemented in the model is provided in detail in Section 5.4.5.

The company used a life time horizon of 10 years for the model based on the parametric extrapolation of OS in the TIVO-1 study which estimated that greater than 98% of patients would be dead after 10 years.

5.4.4.1 ERG critique

The ERG considers the company's model to have an appropriate structure, capturing all relevant health states and clinically plausible transitions between health states that are largely similar to other published oncology models. The one-week cycle length used in the model is suitable to capture changes in the health state of patients, allowing for robust estimates of costs and benefits to be calculated for each treatment. The 10-year time horizon of the model was verified with the ERG's clinical expert who agreed that patients in this stage of their disease would not live longer than 10 years. No errors were found in the Excel calculations used in the model. A critique of the methods used to estimate proportions of patients within each health state is given in Section 5.4.5.

5.4.5 Treatment effectiveness

5.4.5.1 Overview of method selection

From the time of the initial CS, there have been several iterations of relative treatment effectiveness for tivozanib, sunitinib and pazopanib estimated by the company. The CS presented relative treatment effectiveness estimated using hazard ratios for the treatment naïve population applied to baseline PFS and OS extrapolated curves for tivozanib. The tivozanib curves were estimated using Kaplan-Meier (KM) data for the overall ITT population from the TIVO-1 trial and extrapolated using a Weibull distribution. Treatment naïve hazard ratios were obtained using a NMA of relevant studies (see Section 4.3 for more detail). The ERG found that there were several issues with the data being used in the model compared to what was reported by the company, most notably that the tivozanib KM data for PFS and OS related to the overall ITT population, despite the company's focus for the analysis on the treatment naïve population. This was raised during the clarification stage and the company subsequently amended the KM data to reflect the treatment naïve population in the first economic model submitted with the clarification response.

Another issue the ERG found with the analysis was that the company did not provide any assessment for assuming the proportional hazards (PHs) assumption holds for the trials included in the network or for the TIVO-1 trial. At clarification stage the ERG requested the company to provide a thorough assessment of PHs. The company provided log cumulative, log(survival function/ (1-survival function)) and log(inverse standard normal distribution function(1-survival function)) plots for the TIVO-1 trial data for PFS and OS. Based on visual inspection of the plots, the company determined that the PH assumption was violated for PFS and only held for OS after 2-3 months. During the clarification stage, the ERG suggested two methods that can be employed if there is a violation of the PH assumption,

which included a parametric NMA and the FP-based NMA.[92, 93] The company decided that the most appropriate method to estimate treatment effectiveness given the violation of the PHs assumption was to conduct an NMA based on parametric curves as described by Ouwens *et al.* 2010.[92]

The parametric NMA was based on a simplified network, as requested by the ERG (see Section 4.3 for more detail) and used the Weibull distribution. No model selection or curve fitting statistics for the parametric NMA were presented in the clarification response to justify the use of the Weibull distribution using a fixed effects (FE) model. However, the company acknowledged that the Weibull distribution did not provide a good fit to the tivozanib KM data for PFS and OS and requested additional time to implement the lognormal for the parametric NMA. The justification for wanting to implement the lognormal distribution was based on a curve fitting exercise for PFS and OS based on KM data from the TIVO-1 trial. Akaike information criterion (AIC) statistics for tivozanib and sorafenib were presented and revealed the best fitting curve for PFS and OS for the tivozanib arm was the lognormal distribution. The best fitting curve for PFS for sorafenib was the lognormal distribution and for OS, the Weibull distribution was estimated to have the best fit.

The ERG notes that it is methodologically inappropriate for the company to use the curve fitting exercise for the TIVO-1 trial data to determine the most appropriate curve to use for the parametric NMA, as the parametric NMA relies on data for pazopanib and sunitinib which would influence what the best fitting distribution produced would be for the "family" of related curves. Though this becomes a moot point as two weeks before the submission of the ERG report was due, the company informed NICE that they were unable to provide the lognormal analysis in the timeframe provided and instead wished to submit an updated base case analysis that implemented the FP-based NMA to estimate relative treatment effectiveness.[93] The remainder of this section focuses on the implementation of the FP-based NMA for PFS and OS outcomes in the economic model. Section 5.4.8.1 presents the base case ICERs from the CS, ICERs generated using the parametric NMA and the revised base case ICERs using the FP-based NMA to provide some insight on the impact of the different treatment effectiveness methods explored by the company. Please refer to the Appendix 9.4 and 9.6 for details of all the aforementioned plots and curve fit statistics.

5.4.5.2 Economic modelling of fractional polynomial estimates

As mentioned in Section 5.4.4, treatment effectiveness was implemented in the model using a partitioned survival model for PFS and OS outcomes. As described in Section 4.3, the FP-based NMA was selected by the company and was based on a simplified network consisting of four trials related to tivozanib, sunitinib and pazopanib. Published KM data for PFS and OS for the treatment naïve population were digitized for all treatments. A fixed effects model was implemented and first and second order FP-based NMAs with different powers were assessed using the Deviance Information Criterion (DIC) to compare goodness of fit across the models (Table 28 and Table 29 in Section 4.3).

Four first order FP-based NMAs (-2, -1, -0.5 and 0) and one second order FP-based NMA (P1 = -2 and P2 = -1) were considered. For the extrapolation of both PFS and OS, the second order FP-based NMA had the lowest DIC and was implemented in the economic model. The first order FP (P1 = -2) was the next best fitting model for the extrapolation of PFS and OS and was implemented in the model as a scenario analysis.

Parameter (β_n) estimates from the FP-based NMA were produced and were used in the following survival calculation, based on the hazard function, to produce the treatment specific PFS and OS estimates for each cycle of the model:

$$S_{kt} = e(-e(\beta_{0k} + \beta_{1k} * t^{p1} + \beta_{2k} * t^{p2}) * t) \quad \text{(equation 1)}$$

where k = treatment, t = time and p = power

Figure 13 and Figure 14 presents the extrapolated PFS and OS survival curves based on the second order FP-based NMA for tivozanib, sunitinib and pazopanib

Figure 13. Extrapolated progression-free survival curves (second order fractional polynomial)

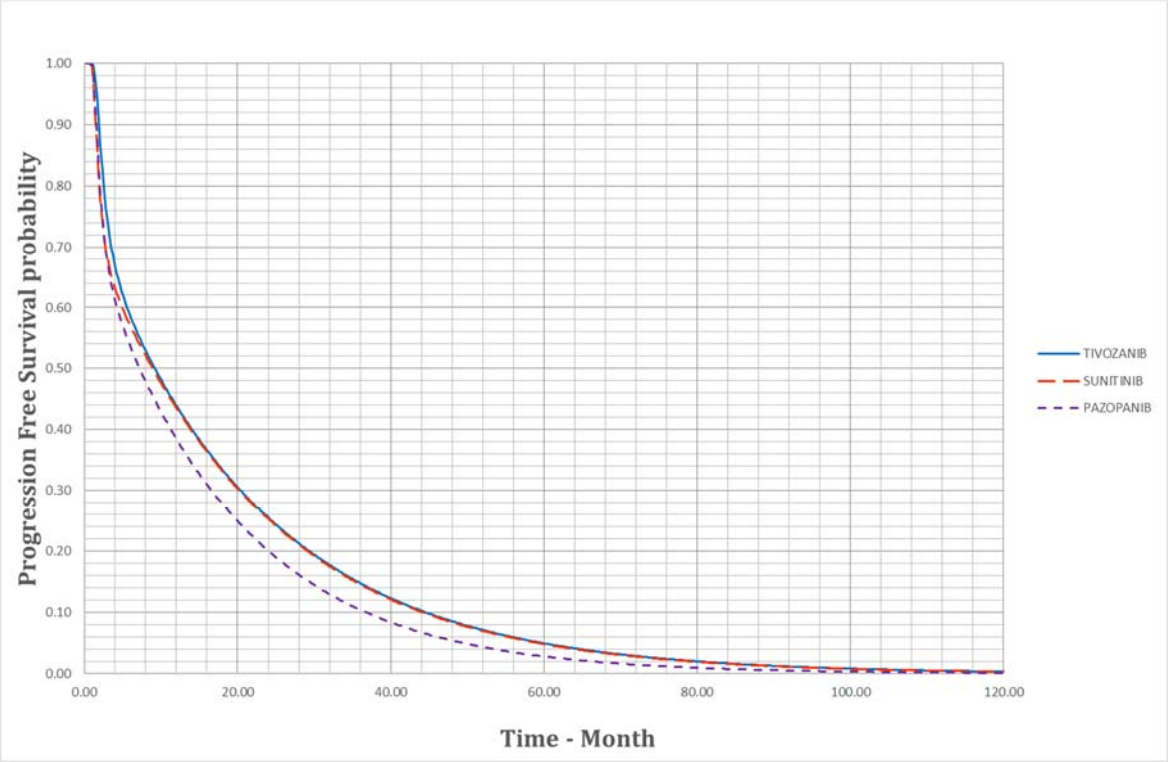


Figure 14. Extrapolated overall survival curves (second order fractional polynomial)

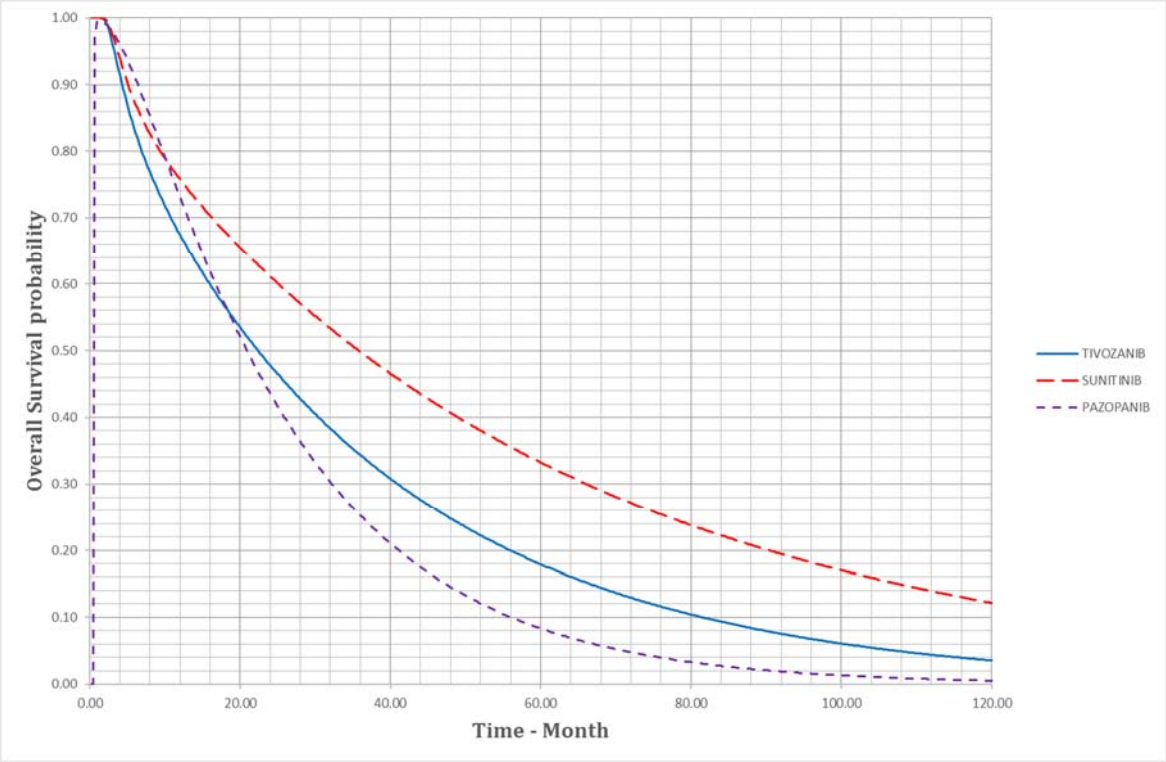


Table 42 presents median survival by treatment based on the extrapolation.

Table 42. Median survival estimates obtained from economic model

Treatment	Median PFS (months)	Median OS (months)
Tivozanib	9.1	22.2
Sunitinib	8.9	35.2
Pazopanib	7.2	20.8
Abbreviations in table: PFS, progression-free survival; OS, overall survival.		

Based on the extrapolated second order FP curve, the proportion of patients in each of the three health states for each treatment were estimated as follows (CS, page 130):

- Pre-progression state = estimated PFS.
- Post progression state = estimated OS – estimated PFS.
- Death = 1 – estimated OS.

5.4.5.3 ERG critique

As mentioned previously, three economic models have been submitted by the company to the ERG. During the clarification stage, the ERG highlighted several issues with the tivozanib KM data for PFS and OS obtained from the TIVO-1 trial. The first issue was that in the CS, the company state that PFS data used in the model was based on IRR, however the ERG found that the estimates related to

investigator review. In the clarification response, the company stated that it was, "*an inadvertent error - the model should be based on IRR in line with primary outcome analysis of the study*". The second error related to median OS estimates in the economic model, which did not match what was reported in the original company submission. In their clarification response, the company state that, "*the wrong curve was inadvertently used"*. Lastly, all KM data reported in the CS and used in the economic model related to the overall ITT population rather than the treatment naïve population, which was the focus of the base case analysis.

The company submitted a second economic model (model 2) based on the parametric NMA and stated that the KM for PFS and OS have been amended to reflect the treatment naïve population for both outcomes and IRR data is now used for PFS. However, this model was superseded by the FP based economic model (model 3). The ERG cross checked the KM data used in model 3 and model 2 and found that the data were not the same and no reference was made in the document submitted with the revised analysis by the company to suggest the reason for the discrepancy. Furthermore, when interrogating the data used in the FP-based NMA, the ERG found that the numbers at risk used related to the KM data presented in model 2 and that data in model 3 were not implemented in the revised analysis. Table 43 presents the median estimates of PFS and OS for tivozanib from the KM data used in each of the three models. Treatment naïve KM data is not presented in the clinical study report (CSR) or the published paper for the TIVO-1 trial and therefore could not be validated. The ERG has limited confidence in the data integrity of the economic model due to the inconsistencies between the models, errors acknowledged by the company related to data used, and the lack of explanation from the company as to the sources and analysis of the data provided.

Table 43. Kaplan-Meier data presented in economic models

Data source	Data characteristics	Median PFS (months)	Median OS (months)
Reported in submission	IRR, overall ITT population	11.9	28.8
Model 1 (Original CS)	Investigator review, overall ITT population	14.7	36.0
Model 2 (parametric NMA)	IRR, treatment naïve population	14.5	26.0
Model 3 (FP)	IRR, treatment naïve population	12.0	27.0
Abbreviations in table: PFS, progression-free survival; OS, overall survival; CS, company submission; NMA, network meta-analysis; FP, fractional polynomial; IRR, independent radiology review; ITT, intention to treat.			

The ERG discovered several issues with implementation of the parameter estimates generated by the FP-based NMA. Calculation of OS for pazopanib is subject to error in the economic model as the OS estimates start from 0 (all patients dead) rather than 1 (all patients alive). It is only after cycle 5 that OS reaches 1 before declining over time as would be expected, as can be seen in Figure 14. The ERG validated the formulae used in the model for pazopanib and discovered the calculation of OS for all treatments was incorrect as the formula essentially multiples the hazard function at each time point by

time (see equation 1) and assumes that the hazard would be constant up to that time point. For example, if the time point is 6 months, the calculation estimates the 6-month hazard and multiples it by 6 months, essentially calculating a within period hazard. However, this is incorrect as the estimates generated do not reflect the total area under the survival curve for the hazard function. The ERG corrected the calculation by multiplying the hazard function by the cycle length used in the model to estimate the approximate cumulative hazard within a cycle. This amendment is outlined in equation 2:

$$H_{kt} = e(\beta_{0k} + \beta_{1k} * t^{p1} + \beta_{2k} * t^{p2}) * \text{cycle length} \quad \text{(equation 2)}$$

where k = treatment, t = time and p = power

It should be noted that equation 2 is adapted if P1=P2=P, then the model becomes a 'repeated powers' model (equation 3) and if P=0, $t^0 = \log[t]$ (equation 4)[93]

$$H_{kt} = e(\beta_{0k} + \beta_{1k} * t^{p1} + \beta_{2k} * t^{p2} * \log[t]) * \text{cycle length} \quad \text{(equation 3)}$$

$$H_{kt} = e(\beta_{0k} + \beta_{1k} * t^{p1} + \beta_{2k} * \log[t]) * \text{cycle length} \quad \text{(equation 4)}$$

Using this function, the overall cumulative hazard is generated and implemented in the survival function to generate the area under the curve. Figure 15 illustrates the difference between the company estimation and the ERG estimation, based on the 6-month time point example described previously.

Figure 15. Illustration and comparision of company and ERG survival calculation

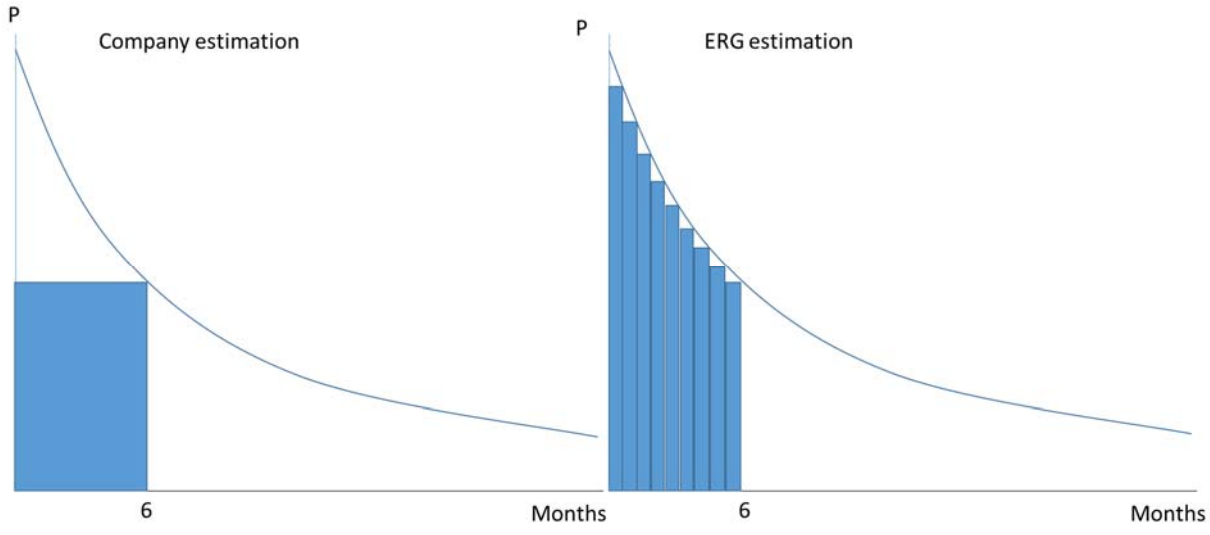


Figure 16 and Figure 17 presents the PFS and OS curves for all treatment based on the ERG's calculation and shows the issues seen with OS for pazopanib are now rectified.

Figure 16. Corrected second order FP-based NMA (P1=-2, P2= -1) progression-free survival curves for all treatments

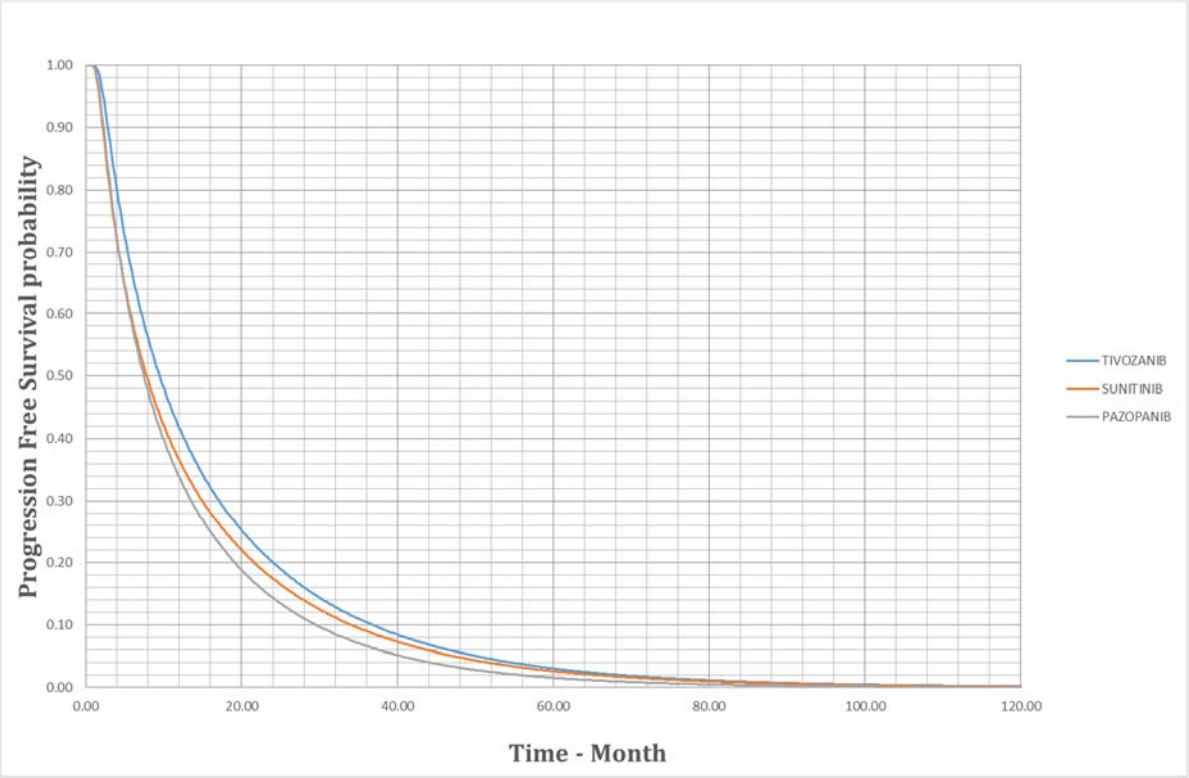
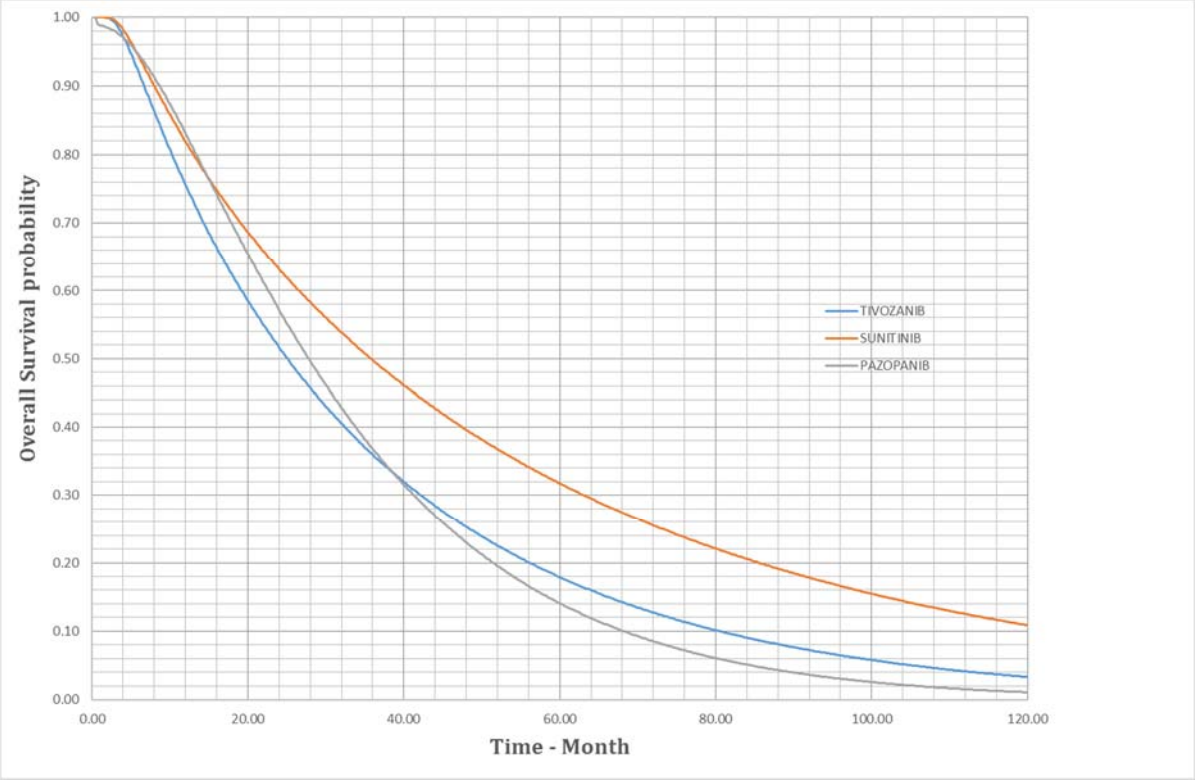


Figure 17. Corrected second order FP-based NMA (P1=-2, P2= -1) overall survival curves for all treatments



Upon visual inspection of the company's corrected second order FP PFS and OS curves (Figure 16 and Figure 17, respectively), the ERG finds that the second order FP-based NMA for OS produces long tails for sunitinib and tivozanib that are clinically implausible. The ERG's clinical expert stated that survival can be expected to reach 0 (all patients dead) after 8 or 9 years. The corrected economic model predicts that 3% of tivozanib patients and 10% of sunitinib patients would be alive after 10 years. In addition, the difference in OS between sunitinib and pazopanib is not reflective of the what was seen in the COMPARZ trial, which showed that the KM curve for pazopanib was superior to the KM curve for sunitinib.[9] The latter issue is discussed further in Section 4.3. Given these issues, the ERG considers that the extrapolation produced by the company for the second order FP-based NMA curves does not pass face validity and is clinically implausible. In addition, the parameter estimates produced by the company with the ERG corrected calculation produce PFS estimates that are greater than OS estimates for the first five cycles of the model.

As a validation exercise of the company's results, the ERG reran the FP-based NMA using the data provided by the company. The ERG was unable to replicate the results produced by the company for second order FP-based NMA (P1= -2, P2 = -1), which was used as the base case, and the for first order FP (P1 = -2), which was used in a scenario analysis. The ERG was unable to identify the reasons for the differences in its estimates generated compared to the company's estimates. However, given that the company's curves do not pass clinical or face validity, the ERG has limited confidence that the parameter estimates produced by the company are correct and as such the parameter estimates obtained by the ERG was implemented in the model to produce alternative PFS and OS curves and presented in Figure 18 and Figure 19. Table 44 presents a comparison of median PFS and OS produced by the company's second order FP-based NMA (P1= -2, P2 = -1) estimates and the ERG's estimates.

Figure 18. ERG second order FP-based NMA (P1= -2, P2= -1) PFS curves

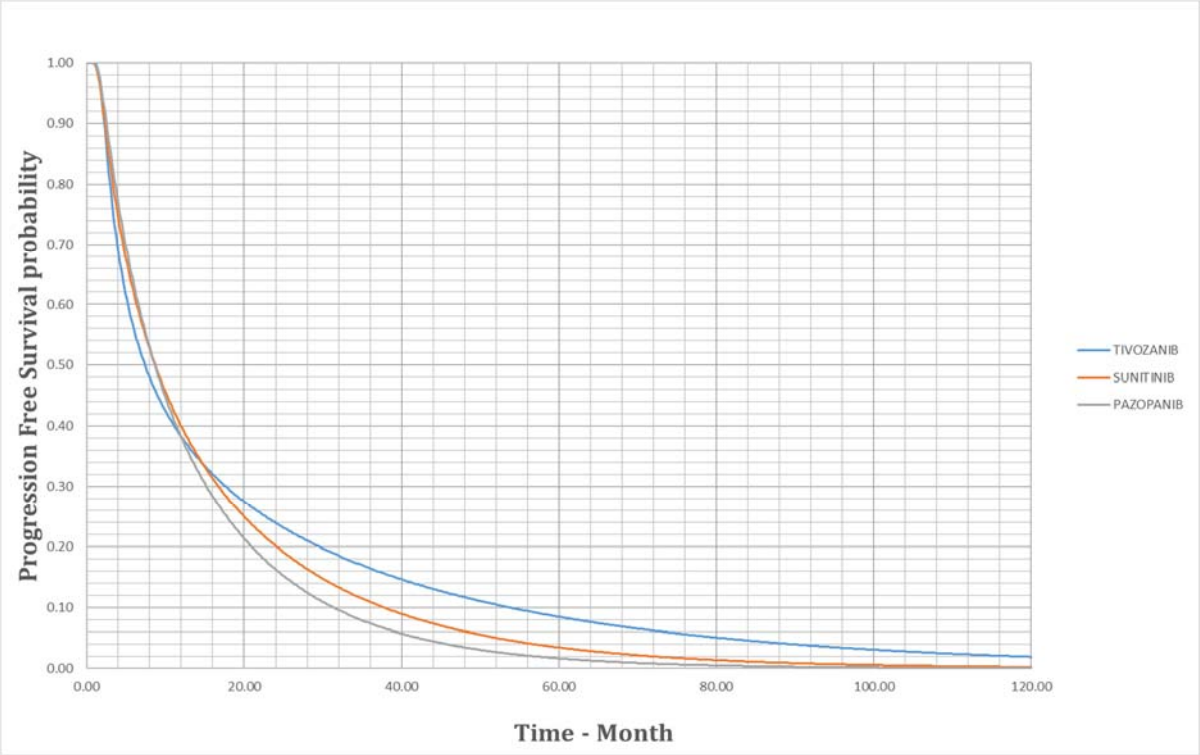


Figure 19. ERG second order FP-based NMA (P1= -2, P2= -1) OS curves

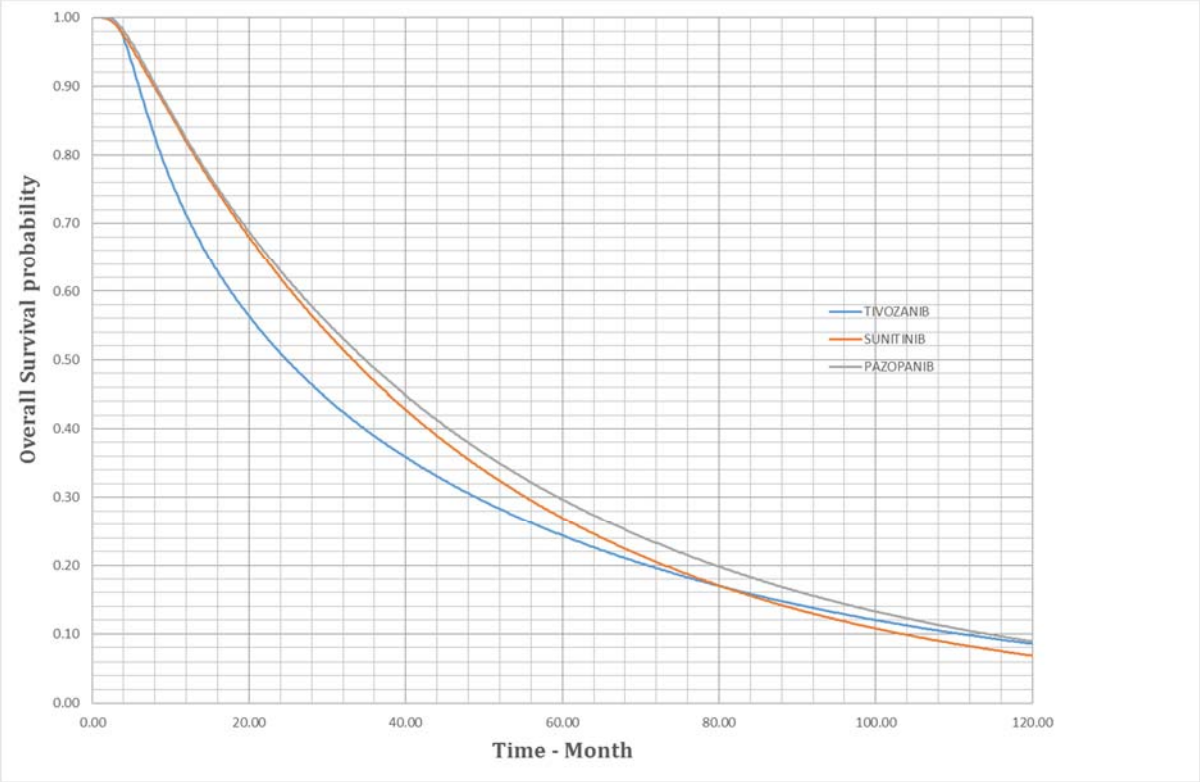


Table 44. Survival estimates based on company's and ERG's second order FP-based NMA (P1= -2, P2= -1) analyses

Treatment	Company's 2nd Order FP		ERG's 2nd Order FP	
	Median PFS (months)	Median OS (months)	Median PFS (months)	Median OS (months)
Tivozanib	9.33	24.97	7.23	24.73
Sunitinib	7.70	35.70	8.63	33.13
Pazopanib	7.47	27.77	8.63	34.77

Abbreviations in table: FP, fractional polynomial; OS, overall survival; PFS, progression-free survival.

The ERG considers that the revised estimates for the second order FP-based NMA (P1= -2, P2= -1) produces more plausible PFS and OS curves for sunitinib and pazopanib based on the order of treatment effectiveness observed in the COMPARZ trial, thus passing face validity. However, the curve for tivozanib crosses sunitinib at approximately month 77 and crosses pazopanib at approximates 114 months. In addition, 10-year OS estimates for treatments are higher than would be expected in clinical practice, with an estimated 8% of patients alive for the pazopanib and tivozanib arm and 6% for sunitinib. Estimates of PFS for tivozanib predict that 2% of patients will not have experienced progressive disease, which according to the ERG's clinical experts is not what would be seen in clinical practice as by 10 years all patients will experience progressive disease. The ERG notes that there is significant uncertainty surrounding the extrapolation of PFS and OS as presented in Figure 20 and Figure 21.

Figure 20. ERG second order FP-based NMA (P1= -2, P2= -1) PFS curves with 95% CrI

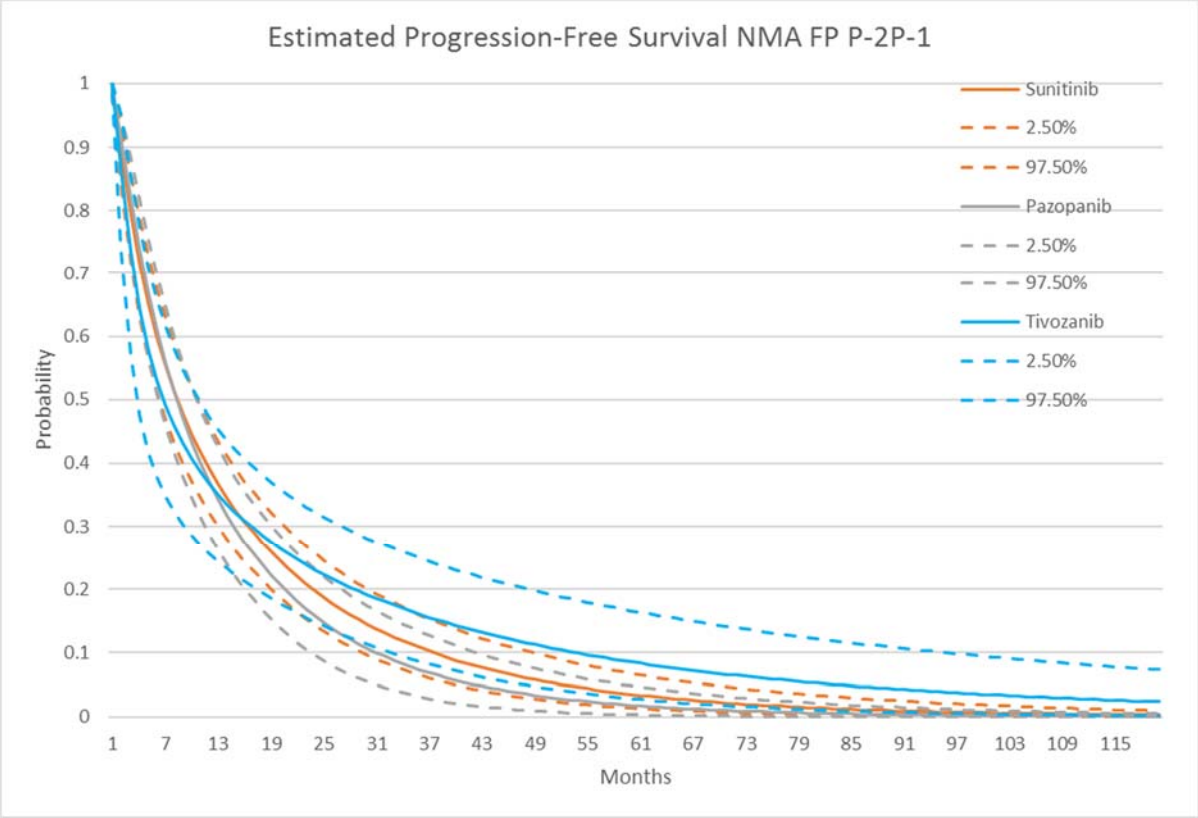
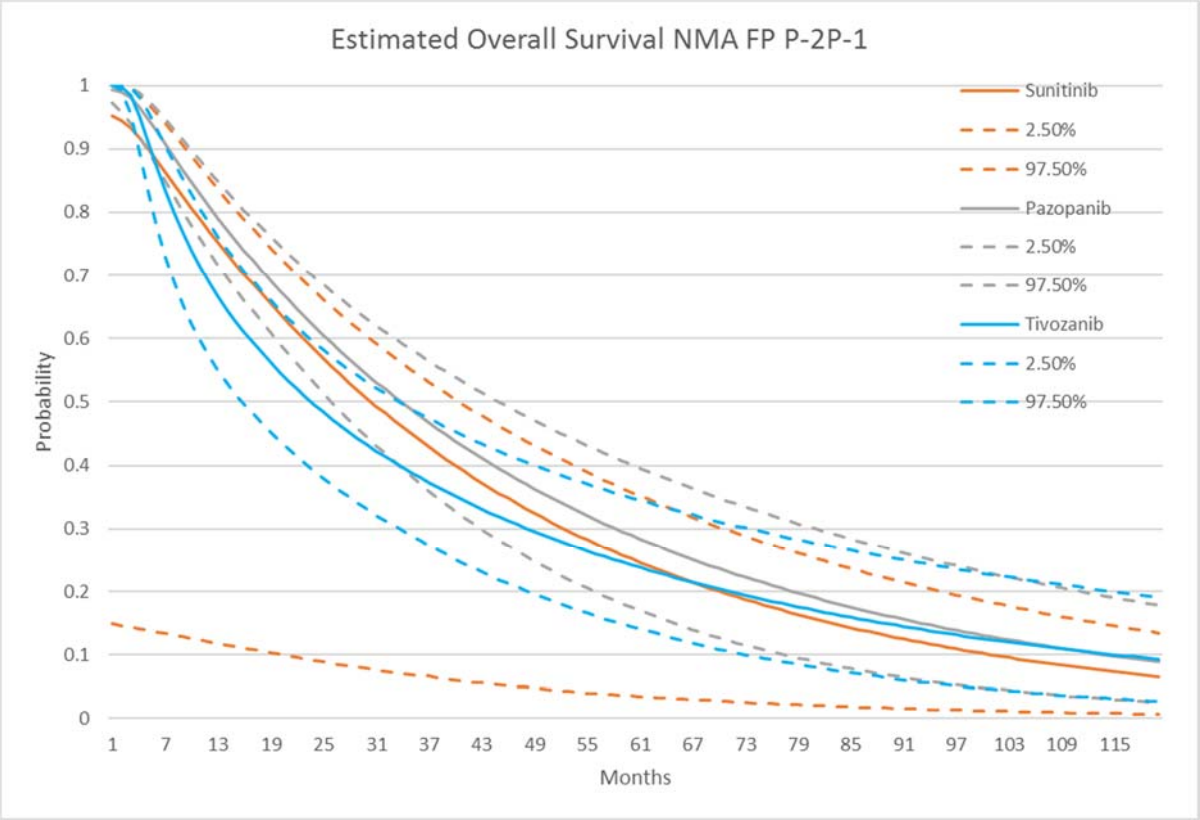


Figure 21. ERG second order FP-based NMA (P1= -2, P2= -1) OS curves with 95 CrI



To validate whether the second order FP-based NMA (P1= -2, P2= -1) was the most appropriate curve choice for the extrapolation of PFS and OS, the ERG ran a series of second order FP-based NMAs with various permutations of powers in WinBUGS. Within the FP framework, the powers were chosen from the following set of numbers: -2, -1, -0.5, 0, 0.5, 1, 2 and 3. Ideally, all the available powers would be assessed for the first and second order FP-based NMAs and DIC statistics obtained to assess goodness of fit to the data. In the additional analyses submitted by the company, no justification for selecting only a subset of the available powers was presented. This is especially relevant when considering that only one permutation of powers was reported for the second order FP-based NMA. Second order FP-based NMAs tend to produce a better fit to the data as there is an additional parameter added to the calculation increasing the flexibility of the curve. Thus, it is perhaps not surprising that the second order FP-based NMA was found to be the best fitting curve compared to all the first order FPs assessed. Due to time constraints, the ERG could not run all permutations of powers for the second order FP-based NMA and instead reviewed a plausible range around the company's base case option.

To select the permutations of powers to be assessed for curve fit, as a rule-of-thumb" the ERG considered any DIC compared to the company's base case + 4 points was a similar curve fit. Any DIC less than the company's curve fit would be considered a better statistical fit. Table 45 and Table 46 presents the ERG's DIC estimates for the fixed effects FP models for the various permutations of powers of P1 and P2 for PFS and OS.

Table 45. ERG DIC statistics for second order FP-based NMAs (PFS)

Power - P1	Power – P2	DIC
-3	-3	**781**
-3	-2.5	**781**
-3	-2	783
-3	-1.5	785
-3	-1	788
-3	-0.5	792
-2	-3	783
-2	-2.5	783
-2	-2	786
-2	-1.5	789
-2	-1	795

Abbreviations in table: DIC, Deviance Information Criterion.
Note: Highlighted cells indicated company base case curve choice. Bold cells indicate lowest DIC.

Table 46. DIC statistics for second order FP-based NMAs (OS)

Power - P1	Power – P2	DIC
-3	-2.5	857
-3	-1.5	858
-3	-1	857
-3	-0.5	855
-3	0	853
-2	-3	858
-2	-2.5	857
-2	-2	858
-2	-1.5	855
-2	-1	855
-2	-0.5	852
-2	0	**849**
-2	0.5	850
-1	-1	851
-1	0	853

Abbreviations in table: DIC, Deviance Information Criterion.
Note: Highlighted cells indicated company base case curve choice. Bold cells indicate lowest DIC.

The ERG used three criteria to determine the most appropriate curve for the NMA and so the extrapolation of PFS and OS. The first criterion was the visual fit of the baseline tivozanib KM data against the estimated FP curves based on the events and patients at risk from TIVO-1 (referred to hereafter as the unadjusted curve), the second criterion was the clinical plausibility of the extrapolation, and the third criterion was the lowest DIC. However, it should be noted that the DIC statistic is based on the fit of the curves to the entire data set used in the NMA and doesn't necessarily indicate whether the extrapolations will be clinical plausible.

Based on the three criteria, the ERG found two plausible curve choices for PFS. These were P1= -3, P2= -3 and P1= -3, P2= -2.5. Figure 22 and Figure 23 present the visual fit of the unadjusted curves

against the tivozanib PFS KM data. It should be noted that of none of the curves assessed had a good fit to the baseline KM data.

Figure 22. PFS KM curve vs unadjusted second order FP-based NMA (P1= -3, P2= -3) for tivozanib

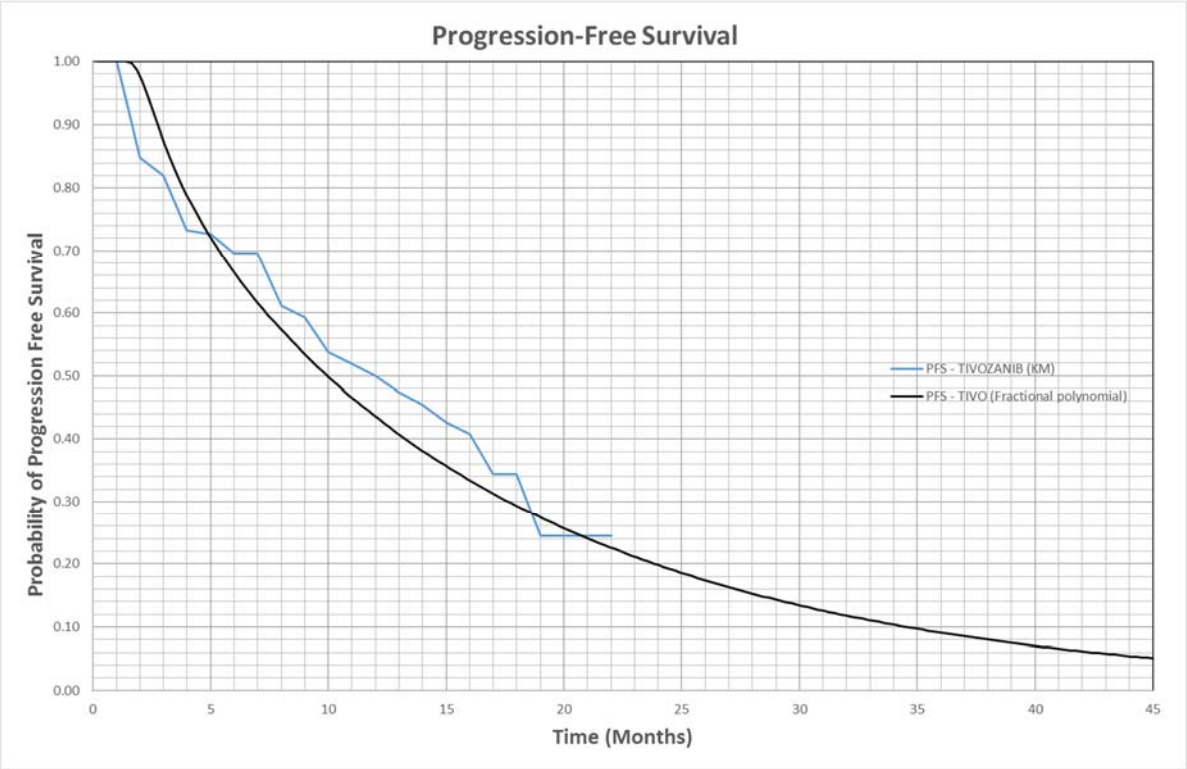
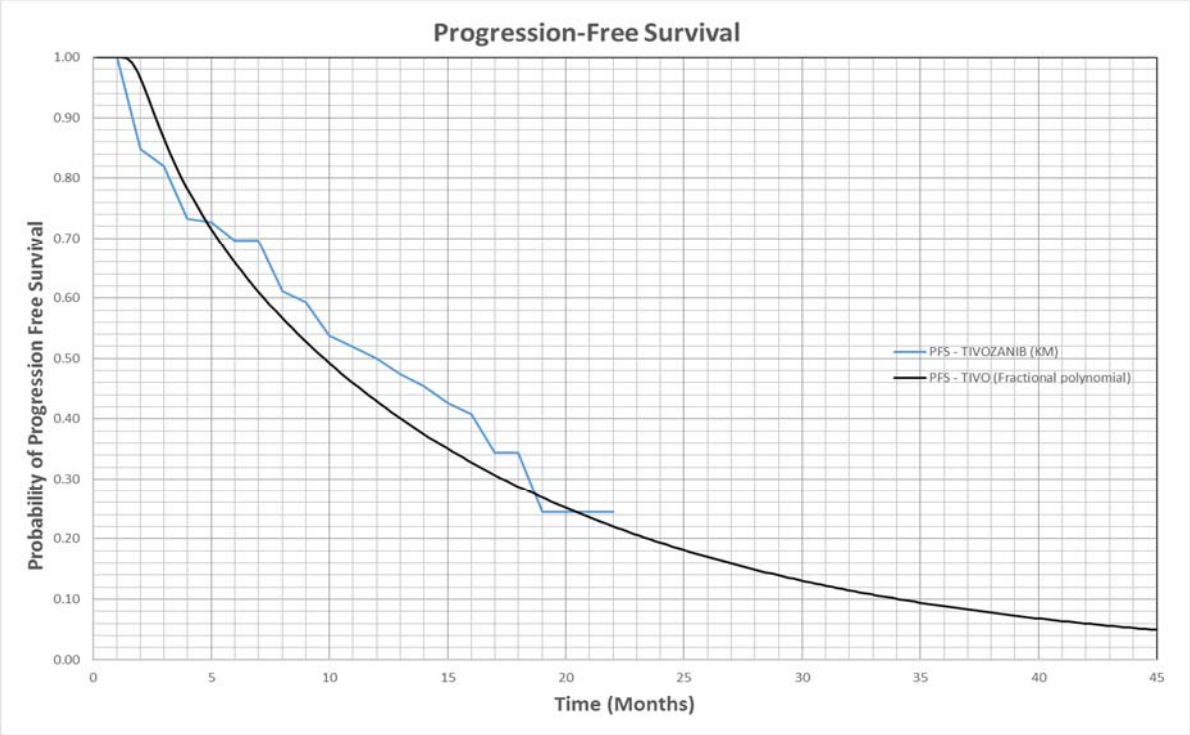


Figure 23. PFS KM curve vs unadjusted second order FP-based NMA (P1= -3, P2= -2.5) for tivozanib



However, the curves produced by the FP-based NMA passed face and clinical validity as by the end of 10 years all patients had progressed (see Figure 24 and Figure 25) and both curves presented the lowest DIC statistics out of all the FP powers assessed. It can be seen from the extrapolated curves and the median PFS estimates in Table 47 that PFS for all treatments is relatively similar, with the second order FP-based NMA (P1= -3, P2= -3) estimating a relative benefit in favour of tivozanib. Due to time constraints, the ERG was unable to capture the magnitude of the uncertainty around the curve estimates in the economic model, however Figure 26 and Figure 27 illustrate the level of uncertainty surrounding the extrapolations. These figures indicate that the uncertainty around each treatment curve is overlapping, indicating no significant difference between each treatment. Section 6 explores the impact of the two chosen PFS curves on the ICER as well as scenario assuming equal efficacy for PFS for all treatments.

Figure 24. Second order FP-based NMA (P1= -3, P2= -3) PFS adjusted curves for all treatments

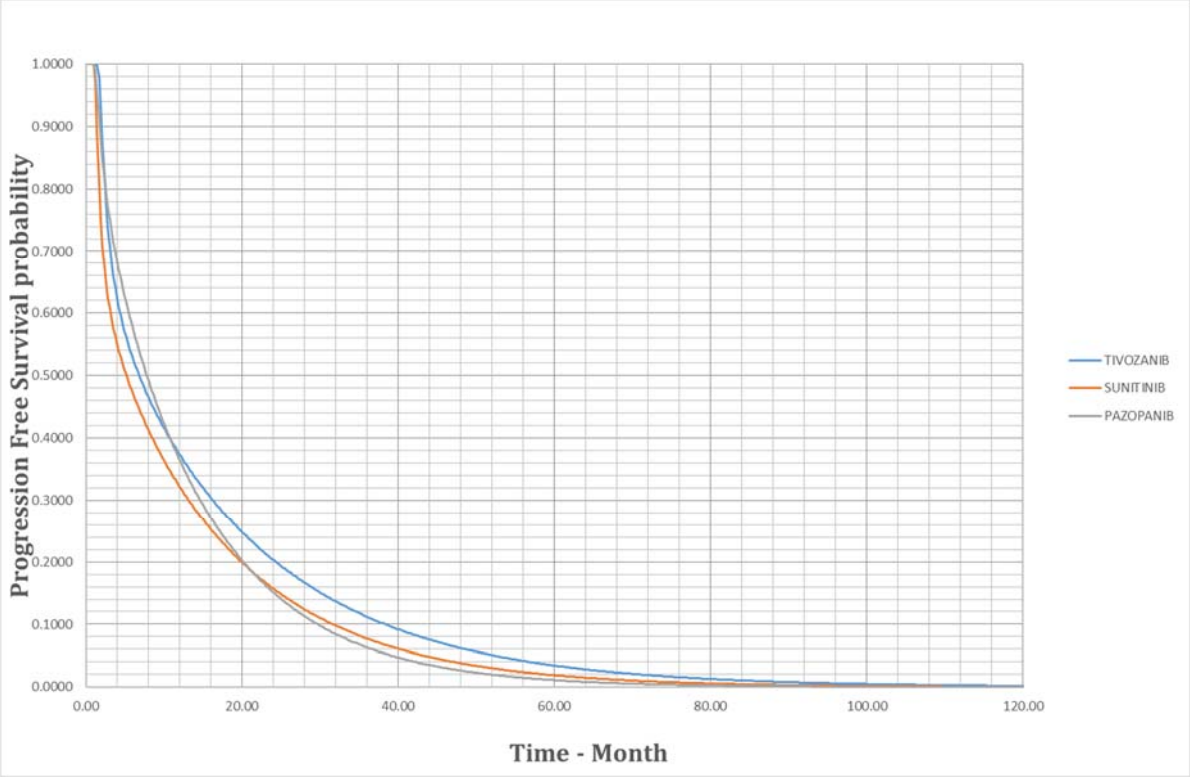


Figure 25. Second order FP-based NMA (P1= -3, P2= -2.5) PFS adjusted curves for all treatments

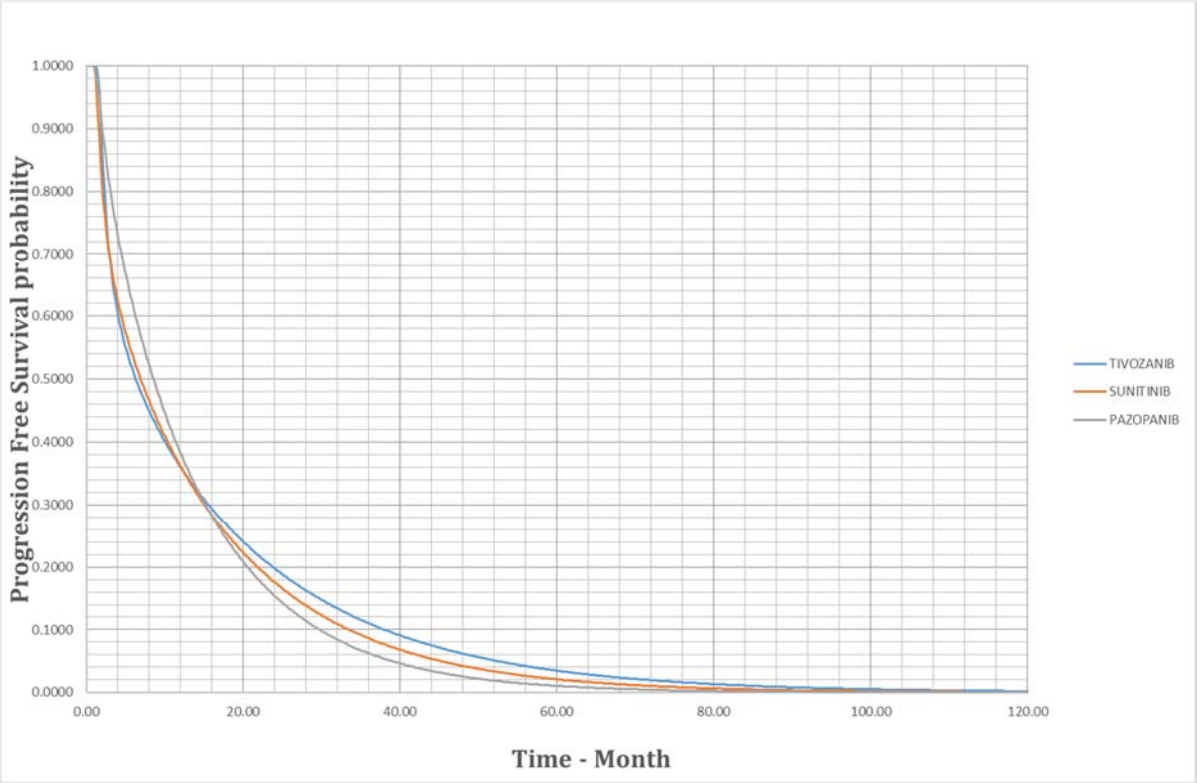


Figure 26. Second order FP-based NMA (P1= -3, P2= -3) PFS curves included 95% CrI

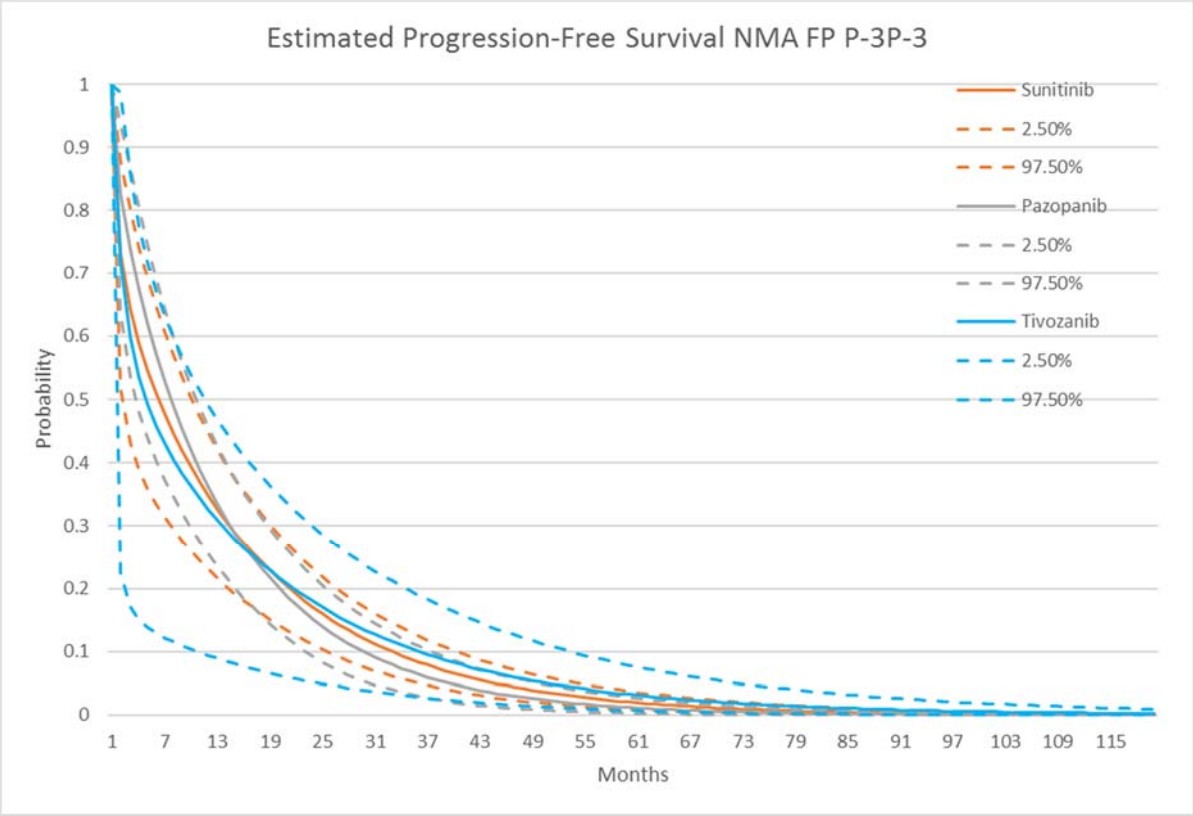


Figure 27. Second order FP-based NMA (P1= -3, P2= -2.5) PFS curves included 95% CrI

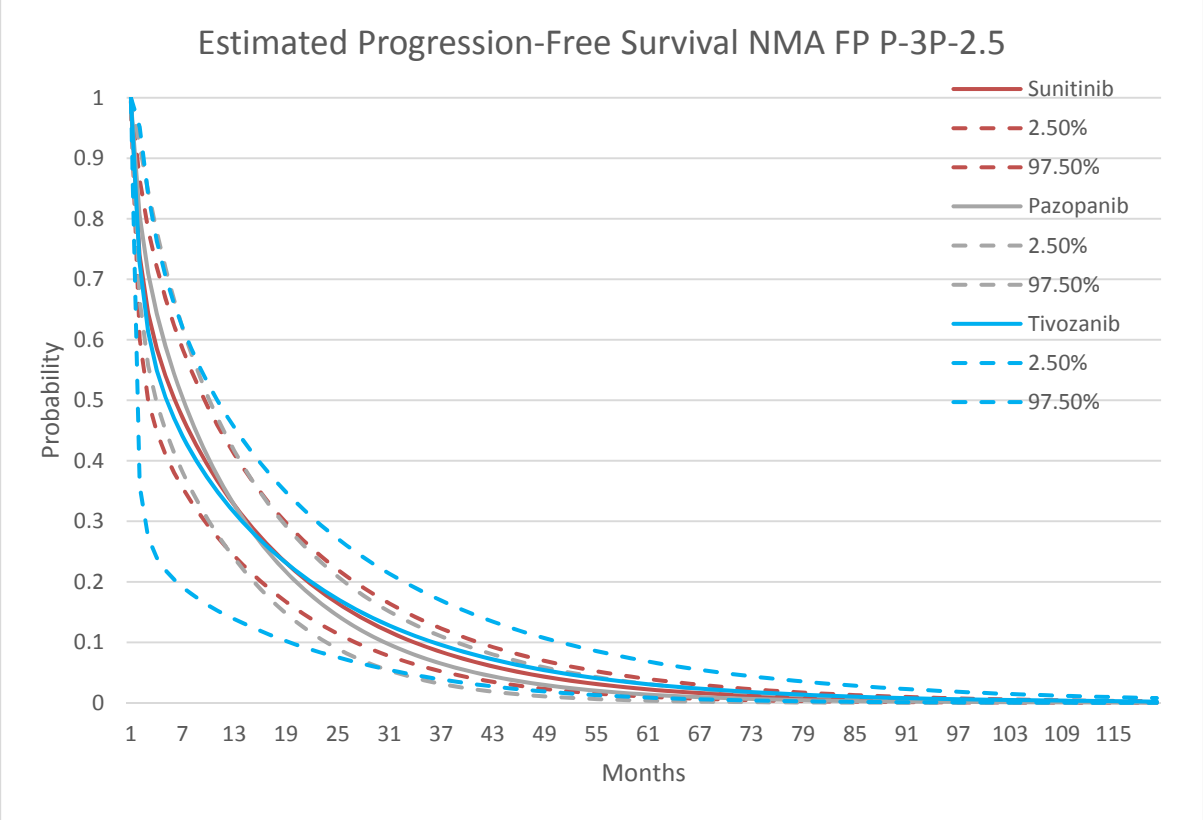


Table 47. Median PFS estimates for best fitting FP curves

Treatment	Median PFS (months)	
	Second order FP-based NMA (P1= -3, P2= -3)	**Second order FP-based NMA (P1= -3, P2= -2.5)**
Tivozanib	6.77	6.07
Sunitinib	5.13	6.77
Pazopanib	7.70	8.40
Abbreviations in table: PFS, progression-free survival; FP, fractional polynomial.		

The ERG determined that the most appropriate second order FP-based NMA for OS was for P1= -2 and P2= -1.5. Figure 28 presents the visual fit of the unadjusted extrapolated second order FP-based NMA (P1= -2 and P2= -1.5) against the OS KM data for tivozanib, which shows the extrapolated curve has a good fit to the baseline data. OS estimates at 10 years predict that approximately 6% of tivozanib and sunitinib patients and 8% of pazopanib patients will still be alive (Figure 29). The OS DIC statistic for the second order FP-based NMA (P1= -2 and P2= -1.5) is the same as the company base case choice (855). The ERG considers that while the 10-year OS estimates may still be considered high and the DIC statistic is the same as the company base case curve, the ERG's preferred choice corrects the issue of the tivozanib curve crossing the sunitinib and pazopanib curves (as seen in Figure 19), which cannot be clinically justified, while maintaining face validity based on the modelled benefit for pazopanib compared to sunitinib being consistent with that observed in the COMPARZ trial. As with PFS, the uncertainty around the estimates for OS for all treatments is overlapping indicating no significant difference between each treatment (Figure 30). The ERG explores the impact of the change in curve choice for OS, as well as equal efficacy for all treatments for OS on the ICER in Section 6.

Figure 28. OS KM curve vs unadjusted second order FP-based NMA (P1= -2, P2= -1.5) for tivozanib

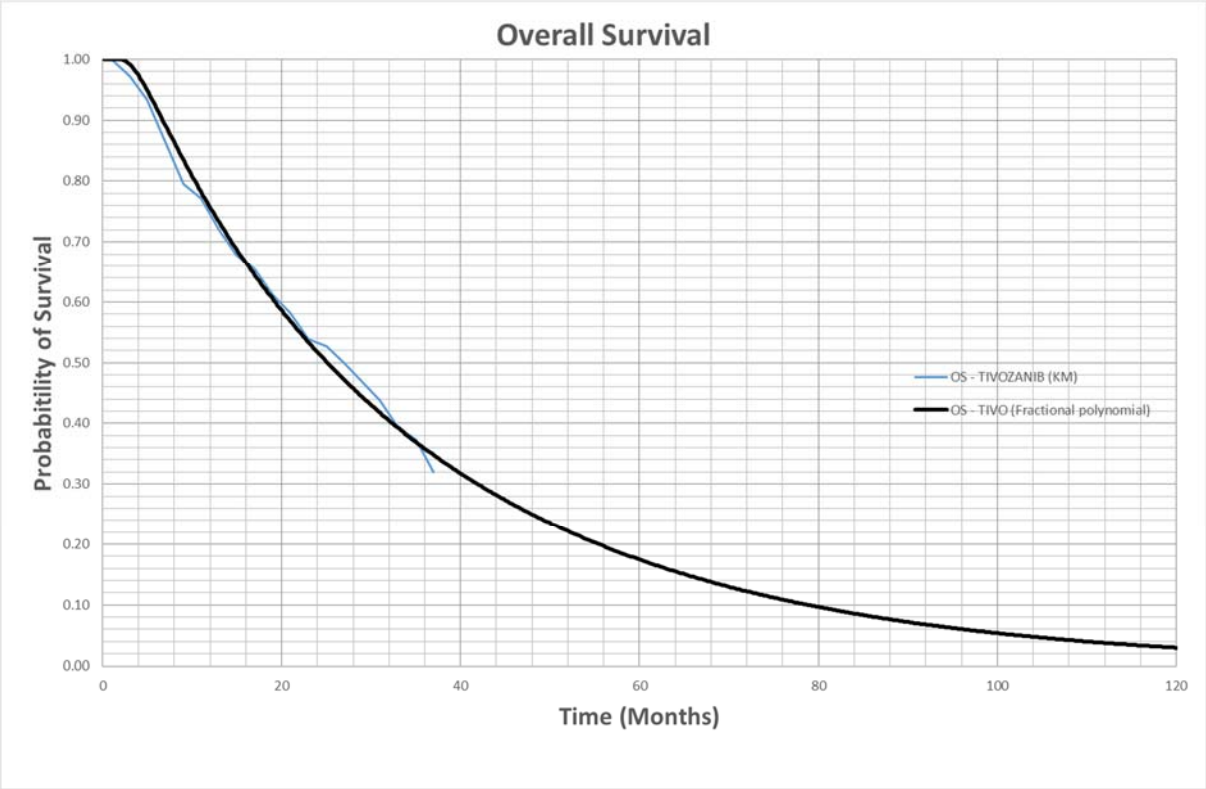


Figure 29. Second order FP-based NMA (P1= -2, P2= -1.5) OS adjusted curves for all treatments

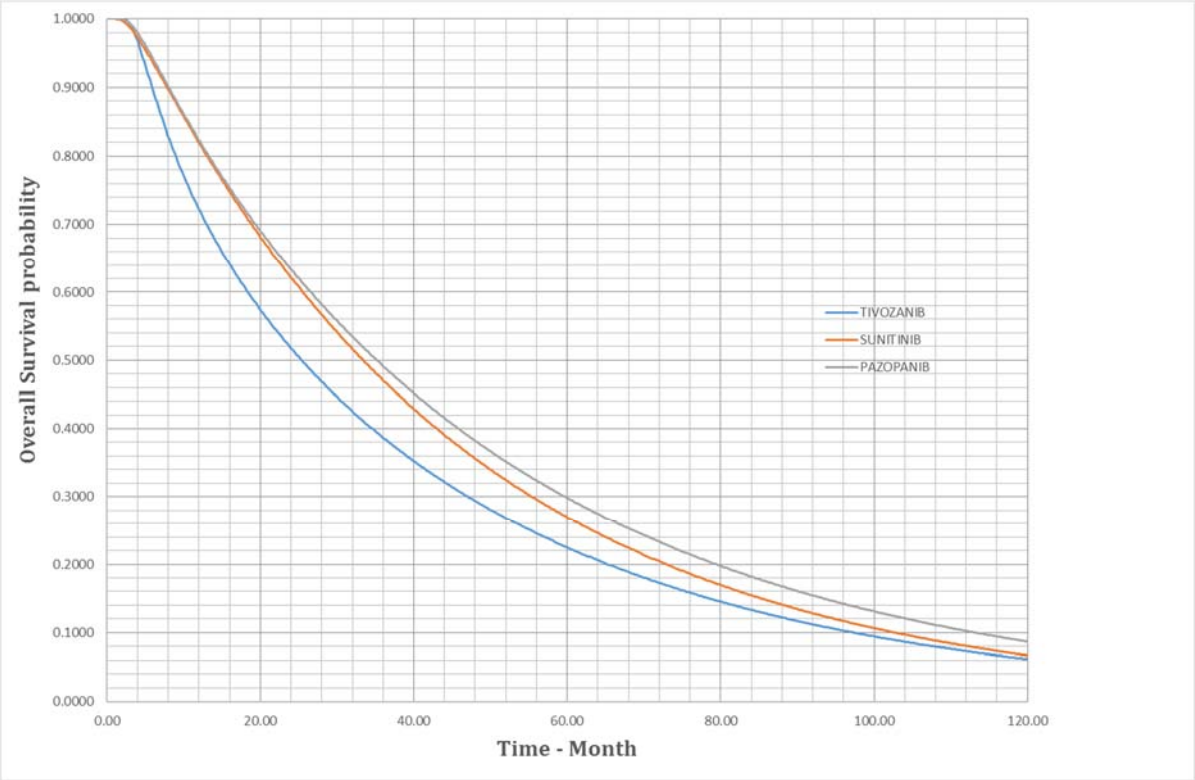


Figure 30. Second order FP-based NMA (P1= -2, P2= -1.5) OS curves included 95% CrI

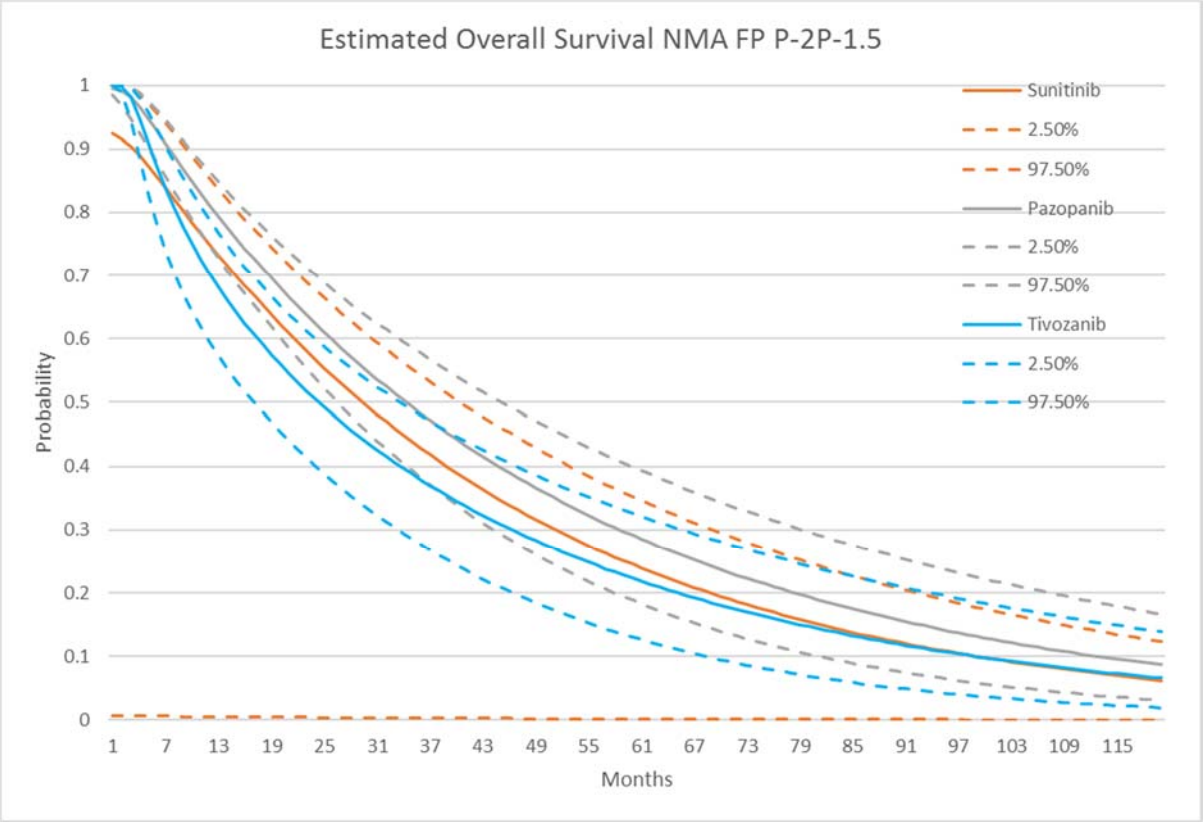


Table 48. Median OS estimates for second order FP-based NMA (P1= -2, P2= -1.5)

Treatments	Median OS (months)
Tivozanib	24.97
Sunitinib	27.53
Pazopanib	29.17
Abbreviations in table: OS, overall survival; FP, fractional polynomial.	

Aside from the implementation of treatment effectiveness in the model, the issue of confounding seen for OS in the TIVO-1 should not be overlooked when interpreting the results of the analyses carried out by the ERG and the company. As mentioned in Section 4.2, TIVO-1 was a one-way crossover designed trial, with patients on sorafenib given the option to receive tivozanib upon disease progression. Observed OS in TIVO-1 is expected to be confounded by imbalance in subsequent targeted therapies (66.3% in the sorafenib group; 20.3% in the tivozanib group) caused by the one-way crossover allowing patients who progressed on sorafenib access to tivozanib. The imbalance was exacerbated because there was no provision of subsequent therapy for the tivozanib group and access to therapies was lower than would be expected in the UK. Analyses presented by the company to adjust OS for crossover showed inconsistent results with varying levels of uncertainty, and the company chose not to incorporate crossover-adjusted results in the NMA (see Section 4.2). This issue is discussed further in Section 4.3. During the clarification stage, the ERG suggested that the company explore the use of matched adjusted indirect comparisons (MAIC), which would overcome the issue of confounding in the underlying OS

TIVO-1 data. The ERG recognises that this approach has several limitations, but prefers this method as all the methods explored by the company (PHs, parametric NMA and FP-based NMA) do not correct the fundamental issue with the OS TIVO-1 data creating significant uncertainty around cost-effectiveness results.

5.4.6 Adverse events

The company applied the odds ratios for treatment-emergent adverse events (TEAEs) from the original NMA described in Section 4.3 to the rates observed in the tivozanib arm of TIVO-1 to calculate the comparable incidence for pazopanib and sunitinib. The company considered Grade 3 or higher TEAEs that had an incidence of 5% or more in any treatment arm in the cost-effectiveness analysis. The company's justification for these inclusion criteria in the model is that it considers it unlikely that the cost and utility impact of less severe adverse events and less frequently occurring adverse events would have a significant impact in terms of costs or quality of life.

The TEAEs included in the model for the base case analysis are anaemia, asthenia, fatigue, and hand-foot syndrome (HFS). The ORs calculated in the NMA and the incidence rates, based on the TIVO-1 overall population, derived and used in the company's model are presented in Table 49 and Table 50, respectively.

Table 49. Pairwise estimates of treatment effects (OR) for grade 3 or more AEs derived from NMA (CS, pg 132, Table 52)

AE	Tivozanib vs Sunitinib		Tivozanib vs Pazopanib		Tivozanib vs IFN-α	
	OR	95% CI	OR	95% CI	OR	95% CI
Anaemia	0.028	[0;47.690]	0.106	[0;176.000]	0.037	[0;64.430]
Asthenia/ Fatigue	0.953	[0.245;4.014]	1.699	[0.417;7.420]	1.000	[0.255;4.252]
HFS	0.186	[0.033;0.835]	0.407	[0.069;1.935]	1.838	[0.278;11.390]
Hypertension	1.148	[0.458;2.951]	1.141	[0.447;3.091]	12.800	[3.688;51.910]
Note: These values were confirmed to be the correct values during clarification stage, and not the values reported in Table 31 in the CS.						

Table 50. Incidence rates of treatment-emergent adverse events used in the model (CS, pg 132, Table 53)

AE	Tivozanib		Sunitinib		Pazopanib		IFN-α	
	% of patients	95% CI	% of patients	95% CI	% of patients	95% CI	% of patients	95% CI
Anaemia	4	0.016 – 0.064	60	0.538 – 0.658	28	0.267 – 0.297	53	0.469 – 0.590
Asthenia/ Fatigue	10	0.064 – 0.137	10	0.067 – 0.142	6	0.052 – 0.071	10	0.063 – 0.137
HFS	2	0.003 – 0.037	10	0.063 – 0.135	5	0.021 – 0.074	1	0.000 – 0.024
Hypertension	27	0.216 – 0.324	24	0.191 – 0.296	24	0.185 – 0.305	3	0.008 – 0.048
Abbreviations in table: CI, confidence interval; HFS, Hand-Foot Syndrome; IFN, interferon.								

The impact of TEAEs on quality of life of patients, and the costs of managing adverse events are described in Section 5.4.7 and Section 5.4.8, respectively. The mean durations of adverse events in the model that were used to estimate the impact of adverse events on quality of life were obtained from the VEG105192 trial and are described in greater detail in Section 5.4.7.

5.4.6.1 ERG critique

The company state in the CS that one of the main benefits of tivozanib is that it is well tolerated, with lower rates of TEAEs than pazopanib and sunitinib, which it claims is supported by the results of the NMA carried out to estimate adverse events for the comparator treatments. However, the company used the original NMA for TEAEs rather than the simplified NMA from which effectiveness results are derived. The ERG had several issues with the NMA carried out originally by the company as described previously in Section 4.3. The simplified NMA requested by the ERG included only the four studies required to link tivozanib with sunitinib and pazopanib: TIVO-1,[41] COMPARZ,[9] SWITCH[72] and CROSS-J-RCC[71] to estimate both treatment effectiveness and TEAEs considered to be of relevance by the ERG's clinical experts. Even though the company reran the NMA for TEAEs and stated in its additional analysis document that AE estimates were based on the new NMA, the ORs and rates of adverse events used in its updated economic model submitted post clarification stage were still based on the original NMA. The results of the company's updated NMA for adverse events are presented in Table 51.

Table 51. Results of company's updated NMA for adverse events for the treatment naïve population (Company's clarification response)

AE	Tivozanib vs Sunitinib		Tivozanib vs Pazopanib	
	Median	95% CI	Median	95% CI
Asthenia/ Fatigue	0.685	[0.173; 2.849]	1.220	[0.294; 5.294]
Hypertension	1.422	[0.639; 3.182]	1.421	[0.598; 3.391]
Diarrhoea	0.113	[0.025; 0.430]	0.097	[0.020; 0.399]
ALT increased	0.231	[0; 7.128]	0.058	[0; 1.873]
AST increased	0.134	[0; 3.215]	0.030	[0; 0.753]
Abbreviations in table: CI, confidence interval; ALT, alanine aminotransferase; AST, aspartate aminotransferase				

As seen in Table 51, the median ORs estimated for tivozanib relative to sunitinib and pazopanib for asthenia/fatigue and hypertension in the new NMA are less favourable for tivozanib than those reported in the original NMA and used in the updated model.

As mentioned previously, to produce the incidence of AEs for the comparators, the ORs were applied to the incidence rates of AEs for tivozanib observed in the TIVO-1 trial for the overall population instead of incidence rates observed for the treatment naïve population. This is a significant oversight by the company, given that data for the TIVO-1 treatment-naïve population were available and were used to produce the original treatment naïve NMA. Table 52 presents the TIVO-1 treatment naïve incidence rates of the AEs of interest for the economic model. The ERG explored the impact of changing the

incidence rates to reflect the treatment naïve population and found it had a negligible impact, however the ERG has included this in the ERG alternative base case, presented in Section 6.3, as it more appropriately reflects the population of interest for the model.

Table 52. Incidence rates of AEs (tivozanib, TIVO-1) – overall vs treatment naïve

AE	Tivozanib (TIVO-1)	
	% - overall population	% - treatment naïve population
Anaemia	4	0.6
Asthenia/ Fatigue	10	5
HFS	2	2
Hypertension	27	25
Diarrhoea	2	2.2

The ERG considers that the ORs produced by the original NMA are associated with a significant amount of uncertainty. During clarification stage, the ERG requested that the company carry out a scenario analysis using the actual rates of Grade 3 and above AEs affecting more that 5% observed for each of the comparator treatments as observed in the published trials included in the simplified NMA. The company responded to the request stating they were unable to complete the analysis with timeframe given for clarification responses. As such, the ERG obtained the rates observed in the trials included in the simplified NMA and used the estimates to validate the rates of adverse events derived from the company's original NMA (and subsequently used in the economic model).

The incidence of AEs reported in the trials included in the simplified NMA, and the rates used in the economic model based on the original NMA are presented in Table 54. As seen in Table 54, there is inconsistency between the incidence rates of anaemia observed in the trials for sunitinib and pazopanib and the rates assumed in the model. In the model, 60% of patients in the sunitinib arm are assumed to experience anaemia of a severity of Grade 3 or higher while the corresponding observed rates across the COMPARZ and CROSS-J-RCC trials were 7%, and 12% respectively.[9, 82] The ERG's clinical expert also considered an incidence rate of 60% for Grade 3 and higher anaemia in patients receiving sunitinib to be too high and not reflective of clinical practice. As for pazopanib, the assumed rate in the model is 28% while only 2% of patients in the pazopanib arm of the COMPARZ trial experienced Grade 3 and higher anaemia.[82] The rates of the other adverse events compared to the COMPARZ and CROSS-J-RCC trials are also inconsistent with those assumed in the model but to a lesser extent.[9, 82]

Generally, whether using trial data or the estimates produced from the original NMA, tivozanib is shown to be more favourable that the comparators, except for hypertension. The company state in the CS that hypertension is a biomarker of efficacy for VEGFR-TKIs and present a retrospective analysis demonstrating that patients with hypertension experience significantly longer PFS (Table 45, CS, page 110). However, given the significant uncertain around the ORs from the original NMA and discrepancies with the observed rates in the trials, the ERG considers that it would be more appropriate

to use either estimates from the simplified NMA based only on the four trials of interest, or simply the incidence of AEs obtained from the trials. The company did state that their revised base case should include OR estimates from the simplified NMA and estimated new ORs for fatigue/asthenia, hypertension and diarrhoea (not for anaemia and HFS), but did not update their base case analyses. Thus, the ERG reran the simplified NMA based on data from the published trials to obtain ORs for all the key AEs, which are presented in Table 53. The ERG was unable to replicate the results produced by the company. As such the ERG has implemented its own OR estimates in the ERG alternative base case presented in Section 6.3. In addition, the ERG explored a scenario of assuming ORs of one for all AEs as the results from the ERG NMA indicated that there was no significant difference between treatments (i.e 95% CrI crossed one). Results are presented in Section 6.2.

Table 53. ERG's odds ratio estimates for key adverse events (simplified NMA)

Adverse event	Tivozanib vs. sunitinib	Tivozanib vs. pazopanib
Anaemia	0.02	0.06
Asthenia/Fatigue	0.56	0.91
Hand-foot syndrome	0.20	0.42
Hypertension	1.25	1.25
Diarrhoea	0.67	0.56

A secondary issue related to the NMA is the use of TEAEs for the analysis instead of treatment-related adverse events (TRAEs), which are adverse events that are attributed to treatment received while TEAEs are any adverse events that occur from the initiation of treatment. The ERG requested a scenario using rates of TRAEs instead of TEAEs to be produced by the company at clarification stage, but due to lack of time the company were unable to deliver the analysis.

The ERG's clinical experts said that in addition to the adverse events included in the company's analysis, they would expect Grade 3 diarrhoea and liver impairment to be included. The company stated during clarification stage that, based on the incidence rates estimated in the original NMA, the incidence rates of severe diarrhoea did not reach the level of 5% that was pre-specified for inclusion of AEs. They also stated that based on feedback from their clinical experts, diarrhoea is managed by stopping the treatment drug and only a few patients would require GP and hospital visits. However, the economic model submitted at clarification with the additional analyses does include diarrhoea as an AE. The ERG is satisfied with the inclusion of diarrhoea based on the estimates observed in the trials, presented in Table 54. Furthermore, diarrhoea has been included as an adverse event in previous NICE technology appraisals for the treatment of first-line RCC and a cost was assumed for managing it in these analyses.[25, 107]. However, it should be noted that the OR estimated for diarrhoea was obtained from the new NMA rather than the old NMA, which the other estimates used in the model are based on.

Due to the implementation of data for the TIVO-1 overall population instead of the treatment-naïve population, and use of estimates from the original NMA rather than the simplified one underlying the

clinical effectiveness inputs as reported by the company in the additional analyses document, the ERG has limited confidence in the validity and robustness of the way AEs have been implemented in the economic model. Moreover, the ERG requested several scenarios (as outlined above) to be performed during clarification stage that the company were unable to complete due to time constraints. As such the ERG implemented the scenarios in the economic model and found that individually they had minimal impact, but has included the changes in the ERG preferred base case to aid completeness and accuracy of the analysis, presented in Section 6.

Table 54. Adverse event rates observed in trials included in the simplified NMA

% of patients with Grade 3 or 4 AEs	Tivozanib	Sorafenib			Sunitinib			Pazopanib
	TIVO-1 naïve (N=181)	TIVO-1 naïve (N=181)	CROSS-J-RCC (N=63)	SWITCH (N=177)	CROSS-J-RCC (N=57)	SWITCH (N=176)	COMPARZ (N=548)	COMPARZ (N=554)
Anaemia	0.6	1.7	5	NR	12	NR	7	2
Fatigue/asthenia	5	2.8	2	4.5	16	7.4	20	13
HFS	2	16	25	12	12	5.7	12	6
Hypertension	25	16	17	9	18	12	15	15
Diarrhoea	2.2	6.1	6	5.1	0	2.8	8	9

Notes: TIVO-1 data are for the 70% in each group that were naïve to systemic therapy. Data for CROSS-J-RCC and SWITCH are first-line therapy experience only (i.e. not post-crossover)
Abbreviations in table: AE, adverse effects; HFS, hand-foot syndrome; N, number of patients; NR, not reported

5.4.7 Health-related quality of life

Systematic literature review

The company searched for studies reporting quality of life and health state utility values (HSUVs) in patients with metastatic RCC, as part of the search described and critiqued in Section 5.3.

The inclusion and exclusion criteria applied for quality of life studies are summarised in Table 55. A total of 58 studies were identified by the search that were considered relevant to patients with advanced or metastatic RCC who were either treatment naïve or receiving first-line VEGFR-TKI after prior cytokines. Fifteen studies reported HSUVs, and are summarised in Table 56.

Table 55. Inclusion and exclusion criteria applied in quality of life search (CS, pg 134, Table 54)

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Aged ≥ 18 years Any gender Any race Has locally advanced/advanced/metastatic/stage III/stage IV disease	No data reported on relevant population
Intervention	Any intervention included in the efficacy review Surgery if reports follow-up of more than 3 months Radiotherapy if reports follow-up of more than 3 months Placebo Best supportive care No intervention	No data reported on relevant intervention
Comparators	Any of the included interventions No comparator	No data reported on relevant comparator
Outcomes	Utility values Other quality of life measures	No data reported on a relevant outcome
Study design	Randomised controlled trials Observational studies Systematic reviews will be used for citation chasing only Studies only available as conference abstracts will be included if they report sufficient relevant data to allow analysis	Other study design
Language restrictions	English only	Full text publication in other language
Publication dates	1995 onwards (journal articles) Last 2 years of conference abstracts	Published outside relevant dates

Table 56. Summary of included quality of life studies and assessment of their appropriateness for cost-effectiveness analysis (Adapted from CS, pg 135-140, Table 55 and Table 56)

Study	Population/ Recruitment	Interventions	Sample size/ Results	Results	Consistency with reference case	Appropriateness for cost-utility model
Castellano 2009[108]	MRCC, France, Germany, Italy, Spain, UK, Poland; mean age 60-61 yrs; 72% male (Motzer 2007 trial) RCT participants	IFN-α Sunitinib	304 (European subgroup)	**EQ-5D index**: sunitinib 0.72 (0.24); IFN 0.74 (0.25); difference -0.02, p=0.41 **EQ-VAS**: sunitinib 68.57 (18.39); IFN 65.95 (19.32); difference 2.63, p=0.23	High (study included in ITC)	Moderate: values not reported for all health states
Cella 2008[109]	MRCC, US, Europe, Canada, Australia, Russia, Brazil; median 59-62 yr; 71% male (Motzer 2007 trial) RCT participants	IFN-α Sunitinib	750	**EQ-5D index** Baseline, mean (SD): sunitinib 0.76 (0.23) IFN-α. 0.76 (0.23) End of treatment (Least squares mean): sunitinib 0.762 IFN-α. 0.725 **EQ-VAS** Baseline, mean (SD): sunitinib 73.8 (18.5) IFN 71.43 (19.51) End of treatment (Least squares mean): sunitinib 73.4 IFN-α. 68.7	High (study included in ITC)	Moderate: values not reported for all health states
Cella 2010[110]	MRCC, US, Europe, Canada, Australia, Russia, Brazil; median 59-62 yr; 71% male (Motzer 2007 trial) RCT participants	IFN-α Sunitinib	750 total; 347 from US; 274 from Europe	Mean scores of all post-baseline observations in European group **EQ-5D Index:** sunitinib 0.72 IFN-α. 0.71 **EQ-VAS:** sunitinib 72.55 IFN-α. 67.22	High (study included in ITC)	Moderate: values not reported for all health states

Cella 2012[111]	Advanced/ mRCC receiving 1st-2nd line therapy, US, Canada, Italy; mean 59 yr; 70% male (Sternberg 2010 trial) RCT participants	Pazopanib Placebo	435	**EQ-5D Index values**, mean (SD) Baseline: placebo 0.73 (0.24); pazopanib 0.72 (0.25) *Change from baseline with complete/partial response (CR/P)* Placebo: 0.03 (0.11) Pazopanib: -0.01 (0.15) *Change from baseline in stable disease (SD)* Placebo: 0.01 (0.17) Pazopanib: -0.05 (0.25) *Change from baseline in progressive disease (PD)* Placebo: -0.15 (0.32) Pazopanib: -0.14 (0.26) **EQ-5D VAS values**, mean (SD) Baseline: placebo 65.9 (23.84); pazopanib 64.6 (23.69) *Change from baseline in CR/PR* Placebo: 6.3 (20.7) Pazopanib: 1.6 (23.1) *Change from baseline in SD* Placebo: 3.6 (23.8) Pazopanib: 2.5 (21.3) *Change from baseline in PD* Placebo: -9.6 (18.4) Pazopanib: -7.7 (21.1)	Moderate (study included in ITC; includes 2nd line)	High: values can be determined for all health states
Cohen 2012[112]	MRCC, newly diagnosed, US; mean 59 yrs; 77% male Patients attending cancer centre	Not specified	217	**SF-36 values at baseline**: SF-36 MCS: mean 52.1 (SD9.9) SF-36 PCS: mean 34.7 (SD 11.9)	Moderate (treatment unclear)	Moderate: values not reported for all health states
De Groot 2014[113]	MRCC, Netherlands; mean 63yr; 77% male Dutch RCC registry	Not specified	100	**EQ-5D values at diagnosis**: 0.73 (95%CI 0.64 to 0.82) EQ-5D values after 2-6 months: 0.75 (0.66 to 0.84)	Moderate (treatment unclear)	Moderate: values not reported for all health states
Escudier 2009[114]	MRCC, 2nd line after cytokines, US, Europe; median 59 yrs; 82%	Sunitinib regimen comparisons	107	**EQ-5D values**, median Baseline: 0.8 for both treatment arms; no significant change over up to 29 cycles of therapy	High	Moderate: values not reported for all health states

	male RCT participants			**EQ-VAS scores**, median Baseline: 70 for both treatment arms; no significant change over up to 29 cycles of therapy		
Goebell 2014[115]	MRCC, 64% receiving 1st line therapy, Germany; median 70 yrs; 72% male (FAMOUS study) Patients recruited by clinicians to German RCC registry	Sunitinib (51%), sorafenib (15%), temsirolimus (16%), bevacizumab+ IFN-α. (11%), everolimus (5%), IFN-α (1%)	98	**EQ-5D values** Patients with fatigue: 0.76 (SD 0.23) Patients without fatigue 0.89 (SD 0.12)	High	Moderate: values not reported for all health states
Hagiwara 2016[116]	MRCC, 1st line therapy, setting, age, gender NR (COMPARZ trial) RCT participants	Pazopanib Sunitinib	NR	**Regression model-derived EQ-5D utility values during PFS**, mean (95%CI): Pazopanib: 0.709 (0.67 to 0.75) Sunitinib: 0.683 (0.64 to 0.73) **Published estimates of EQ-5D utility values during PFS**, mean (95%CI): Pazopanib: 0.739 (0.73 to 0.75) Sunitinib: 0.708 (0.70 to 0.72)	High (study included in ITC)	High
Hutson 2013[117]	Metastatic RCC, receiving 1st line therapy; International; median 58 yrs; 72% male (Hutson 2013 study) RCT participants	Axitinib Sorafenib	288	**EQ-5D values,** mean (SD) Axitinib: baseline 0.71 (0.25); end of treatment 0.64 (0.27) Sorafenib: baseline 0.71 (0.27); end of treatment 0.59 (0.29)	High (study included in ITC)	Moderate: values not reported for all health states
Litwin 1997[118]	Advanced RCC 1st line, US; mean 58 yrs; 100% male Patients who had received treatment at cancer centre	Infiltrating lymphocytes + Interleukin-2	25	**RAND-36 mean scores** (95% confidence interval) in all mRCC patients (100=best, 0=worst): Physical function: 65 (53-76) Social function: 69 (58-80) Bodily pain: 70 (58-81) Emotional well-being: 74 (66-82)	Moderate (not all treatments relevant)	Moderate: values not reported for all health states

				Energy/fatigue: 47 (37-57) General health perceptions: 52 (42-62) Physical role limitations: 36 (16-57) Emotional role limitations: 53 (32-75) **RAND-36 scores by number of comorbidities in mRCC patients (4 patients had no comorbidities, 5 had one, 6 had 2, 5 had 3 or more)** Physical function: None: 76; 1: 75; 2: 70; 3+: 39 Social function: None: 78; 1: 83; 2: 65; 3+: 53 Bodily pain: None: 60; 1: 86; 2: 75; 3+: 54 Emotional well-being: None: 77; 1: 88; 2: 71; 3+: 59 Energy/fatigue: None: 55; 1: 55; 2: 51; 3+: 28 General health perceptions: None: 63; 1: 55; 2: 58; 3+: 32 Physical role limitations: None: 44; 1: 50; 2: 38; 3+: 15 Emotional role limitations: None: 50; 1: 100; 2: 39; 3+: 27		
Motzer 2013[41]	Recurrent/ mRCC, 1st line or after cytokines; International median 59yrs; 72% male (TIVO-1 trial) RCT participants	Tivozanib Sorafenib	517	**EQ-5D:** Baseline: Tivozanib 0.73, SD 0.25; Sorafenib 0.73, SD 0.26 Change from baseline, LS mean: Tivozanib -0.05, SE 0.02; Sorafenib -0.06, SE 0.02, p=0.391	High (TIVO-1 trial)	High
Sternberg 2010[74]	Advanced/ mRCC, 1st line or after cytokines; US; median 59-60 yrs; 71% male (Sternberg 2010 trial) RCT participants	Pazopanib Placebo	435	**EQ-5D Index** (values less than 0 = advantage for placebo; minimal clinically important difference= 0.08) Baseline values NR Week 6: 0.01 (-0.04 to 0.05), p=0.84 Week 12: -0.04 (-0.09 to 0.01), p=0.08 Week 18: -0.02 (-0.08 to 0.04), p=0.5 Week 24: -0.03 (-0.09 to 0.04), p=0.44 Week 48: 0.03 (-0.03 to 0.1), p=0.33 **EQ-VAS** (values less than 0 = advantage for placebo; minimal clinically important difference= 7) Baseline values NR Week 6: 1.85 (-2.41 to 6.12), p=0.39	High (study included in ITC)	Moderate: values not reported for all health states

				Week 12: 0.06 (-4.79 to 4.91), p=0.98 Week 18: -0.08 (-5.04 to 4.89), p=0.98 Week 24: -0.15 (-4.83 to 4.53), p=0.95 Week 48: -1.97 (-9.02 to 5.09), p=0.58		
Yang 2010[119]	Advanced/recurrent RCC, 1st line therapy, setting NR; mean 59 yrs; 68% male (ARCC trial) RCT participants	IFN-α Temsirolimus	270 subgroup	**Baseline values, mean (SD)**: EQ-5D: 0.62 (0.24) EQ-VAS: 64.03 (17.17) **Least square mean on-treatment values**, up to week 32, mean (SE): EQ-5D: IFN 0.492 (0.031); temsirolimus 0.590 (0.026), p for difference=0.0022 EQ-VAS: IFN 58.83 (1.83); temsirolimus 63.33 (1.56), p=0.0168	High (study included in ITC)	Moderate: values not reported for all health states
Zbrozek 2010[120]	Advanced/recurrent RCC, 1st line therapy, setting NR; mean 59 yrs; 69% male (ARCC trial) RCT participants	IFN-α Temsirolimus	626	**Baseline EQ-5D values** (median) IFN-α: 0.656; Temsirolimus: 0.689 **EQ-5D values by health state** (median) TOX: 0.585; TWiST: 0.689; REL: 0.587	High (study included in ITC)	High

Abbreviations in table: EQ-5D, EuroQoL -5Dimensions; EQ-VAS, Visual Analogue Scale; IFN, interferon; ITC, indirect treatment comparison; MCS, Mental Component summary; mRCC, metastatic renal carcinoma; NR, not reported; PCS, Physical Component summary; RCT, randomised clinical trial; SD, standard deviation; SE, standard error.

Health-related quality of life data used in cost-effectiveness analysis

The HSUVs used in the model are based on EQ-5D data collected in the TIVO-1 trial for the overall population.

[redacted][12]

Mean utility values of 0.726 and 0.649 are assumed for patients in the model regardless of treatment arm prior to progression and after progression, respectively. The HSUVs used in the model and are presented in Table 4.

Table 57. Health state utility values used in the model

Health state	Mean utility (SE)	95% CI
Pre-progression	0.726 (0.011)	0.705 – 0.748
Post-progression	0.649 (0.019)	0.612 – 0.686
Abbreviations in table: AE: Adverse event, CI, confidence interval; HFS: Hand-foot syndrome		

The company applied a utility decrement attributable to adverse events in the model to reflect the impact of these events on patients' quality of life. The company reports that it was unable to directly derive these decrements from the TIVO-1 trial, and therefore used the values of utility decrements reported in the company's submission in the single technology appraisal (TA215). The CS states that the utility decrements estimated were based on quality of life data collected in the VEG105192 trial assessing the efficacy of pazopanib compared to placebo. The durations of adverse events used to estimate quality-adjusted life year (QALY) decrements in the model are also based on the durations observed in the VEG105192 trial.[25] The mean durations of adverse events, and utility decrements estimated for patients experiencing adverse events are reported in Table 58 and Table 59, respectively. The utility decrements

were deducted from the HSUV for pre-progression (i.e. 0.726) to estimate the mean utility values for patients experiencing the specific adverse events reported in Table 59.

It should be noted that, during clarification stage, the ERG queried the exclusion of diarrhoea from AEs of interest in the original NMA and found through consultation with clinical experts this was a clinically important omission (see Section 5.4.6 for more detail). The company submitted an updated economic model with estimates for diarrhoea included, however, no description of where the estimates came from or justification for their use were submitted by the company. Thus, the ERG was unable to validate the estimates for diarrhoea against the published literature.

Table 58. Mean duration of Grade 3 adverse events assumed in the model to estimate QALY decrement (CS, pg 142, Table 58)

Duration of AEs	Mean days	95% CI
Anaemia	37.5	19.1 – 55.9
Fatigue	56.9	29.0 – 84.8
HFS	60.5	30.9 – 90.2
Hypertension	40.2	20.5 – 59.9
Diarrhoea	29.1	14.8 – 43.4
Abbreviations in table: AE: Adverse event, CI, confidence interval; HFS: Hand-foot syndrome		

Table 59. Mean utility values assumed for patients experiencing adverse events in the model (CS, pg 141-142, Table 57 and Table 59)

State	Utility decrement	Utility value: mean (standard error)	95% confidence interval
Anaemia	0.12	0.61 (0.020)	0.525; 0.765
Asthenia/Fatigue	0.13	0.60 (0.026)	0.517; 0.777
HFS	0.05	0.68 (0.006)	0.638; 0.738
Hypertension	0.07	0.66 (0.007)	0.600; 0.740
Diarrhoea	0.02	0.71 (0.01)	0.710; 0.750

5.4.7.1 ERG critique

The HSUVs used for patients in the pre-progression (without adverse events) and post-progression health states are based on EQ-5D data collected from the ITT population of the TIVO-1 trial. Given that 30% of patients in the TIVO-1 trial were not treatment-naïve, the ERG considers that using values based on the overall population and not the treatment-naïve population maybe inaccurate for the purposes of this appraisal; since tivozanib is being assessed as a first-line treatment. According to the ERG's clinical experts, patients with prior cytokine treatment would have a lower quality of life compared to patients who are treatment-naïve but considered the HSUVs used in the model to be reflective of patients encountered in UK clinical practice. The company did identify published utility values in the systematic literature review that it carried out and stated the values estimated in the model are in line with published HSUVs in the identified studies. However, the studies were carried out in various geographical contexts and in the studies, that did include UK patients, the mean utility values were not reported separately for the UK patient subgroup. Overall, in the absence of more appropriate

data, the ERG is satisfied with the company's approach of using conservative utility estimates for PFS and post-progression survival (PPS) in the economic model.

Limited details on the statistical analysis of the utility data from TIVO-1 were reported in the CS. The ERG requested additional data related to the statistical analysis from the CSR during the clarification stage. The company provided the ERG with model estimates for each treatment at each time point, with the difference between least squared means at each time point and corresponding 95% CIs and p-values. However, there were no details in the CSR on the steps taken to select the covariates that were included in the regression model, particularly if other covariates like line of therapy were considered. The ERG considers that this information would have been useful to aid the assessment of the robustness of the methods, and the validity of the final selected model. However, after reviewing the additional information provided, the ERG considers that the approach taken to analyse the utility data to be appropriate.

The company assumed that utility values are the same regardless of treatment arm based on the results of the linear-regression model, which found the difference between least squared means in EQ-5D across the tivozanib and sorafenib arms was not statistically significant. The ERG considers the company's assumption is reasonable.

The company applies utility decrements in the model for patients experiencing adverse events. The company reports that the values obtained from the company submission in the pazopanib STA are from the VEG105192 trial.[25] Upon review of the ERG report for the pazopanib STA, the ERG found that the information the company used in this submission was incorrect as the utility decrements used in the pazopanib submission were estimated from a vignette study carried out on a sample from the UK general population and not from the VEG105192 trial.[25] Therefore, using these values is not in line with the NICE reference case which stipulates that utility estimates should be obtained from patients experiencing the health states.[104]

Furthermore, the EQ-5D data collected in the TIVO-1 trial are likely to include the impact of adverse events experienced by patients receiving tivozanib and sorafenib on quality of life. Removing the utility decrement associated with adverse events in the model has a negligible impact on the resulting ICERs, and as such will be removed for the ERG base case presented in Section 6.3.

5.4.8 Resources and costs

Systematic literature review

The systematic literature search carried out by the company to identify studies reporting resource use and costs of managing RCC is described and critiqued in Section 5.3. The inclusion criteria applied for studies on resource use and costs are summarised in Table 60.

Table 60. Inclusion and exclusion criteria applied for studies on resource use and costs

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Aged ≥ 18 years Any gender Any race Has locally advanced/advanced/metastatic/stage III/stage IV disease	No data reported on relevant population
Intervention	Any intervention included in the efficacy review Best supportive care No intervention	No data reported on relevant intervention
Comparators	Any of the included interventions No comparator	No data reported on relevant comparator
Outcomes	Direct costs Indirect and informal costs Resource use	No data reported on a relevant outcome
Study design	Randomised controlled trials Observational studies Database studies Systematic reviews will be used for citation chasing only Studies only available as conference abstracts will be included if they report sufficient relevant data to inform model development or parameterisation	Other study design
Language restrictions	English only	Full text publication in other language
Publication dates	2000 onwards (journal articles) Last 2 years of conference abstracts	Published outside relevant dates

The search identified a total of five studies,[9, 121-124] two of which considered costs specifically in a UK setting. The studies identified are summarised in Table 61.

Table 61. Summary of studies identified reporting resource use and costs (CS, pg 144, Table 61)

Study	**Hansen *et al.* 2015[124]**	**Hill *et al*. 2016[121]**	**James *et al.* 2009[122]**	**Mickisch *et al.* 2010[123]**	**Motzer *et al.* 2013[9]**
Country	Europe, Asia, Australia, North America	International	UK	UK, Germany, France, Italy	North America, Europe, Australia, Asia
Date	US$, 2013	US$ 2014-15	GBP 2008	NR	NR
Population	Advanced or metastatic RCC, 1110 patients receiving 1st line pazopanib or sunitinib, Karnofsky performance status 70% or more; mean age 61yrs (COMPARZ trial)	Theoretical cohort of patients with cancer, including those receiving sorafenib for RCC	Patients attending tertiary cancer centre with mRCC and applying for sorafenib or sunitinib funding as first (33%) or second-line (51%); median age 56-63 yrs, 75% male	Hypothetical cohort of patients with metastatic RCC, receiving 1st line therapy with bevacizumab + IFN-α or sunitinib	Advanced or metastatic RCC, 1110 patients with clear cell histology, receiving 1st line therapy with pazopanib or sunitinib (COMPARZ trial)
Applicability to England	Moderate	Moderate	High	High	Moderate
Cost valuations	Resource use from COMPARZ trial; total healthcare costs; unit costs of managing Grade 3+ AEs	Sorafenib product costs	Mean cost of inpatient episodes	Costs per adverse event, Grade 3-4 (Grade 2) in UK	Medical resource use over first 6 months of treatment
Costs for use in economic analysis	Average total health care resource use, mean unadjusted costs by component Providers: pazopanib $963; sunitinib $1,007, Diagnosis: pazopanib $161; sunitinib $235 Hospitalisations: pazopanib $426; sunitinib $1,198 Procedures: pazopanib $601; sunitinib $713 Unit costs of managing grade 3-4 adverse events (mean) Hypertension: $190.51;		£2,246 total costs for funded patients vs £2,332 for unfunded patients. Mean 19 outpatient episodes for unfunded vs 22 episodes for funded patients	Cost per adverse event grade 3-4 (grade 2), all Euros Anaemia: 2494 (112) Anorexia: 70 (70) Arterial thromboembolism: 2494 (112) Bleeding: 637 (637) Chills: 42 (42) Reduced cardiac ejection fraction: 1123 (1123) Depression: 224 (224) Diarrhoea: 3207 (112) Dry skin: 0 (112) Dyspnoea: 42 (42) Epistaxis: 1084 (112) Fatigue/ aesthenia: 372 (372)	Cumulative mean (SD) medical resource use per patient per month over first 6 months for study participants Non-study medical visits: pazopanib 0.726 (1.472); sunitinib 0.779 (1.690) Telephone consultations: pazopanib 0.279 (0.718); sunitinib 0.312 (0.656) Number of days in hospital: pazopanib 0.402 (2.273); sunitinib 0.562 (2.187) Emergency department visits: pazopanib 0.037 (0.156); sunitinib 0.067 (0.195)

	Fatigue: $131.14; Diarrhoea: $174.29; Palmar-plantar erythrodysesthesia: $112.04; Headache: $250.61; Nausea/vomiting: $174.55; Arthralgia: $127.16; Dyspnoea: $235.61; Asthenia: $131.60; Anorexia: $138.45; Mucositis: $171.42; Dehydration: $195.79; Syncope: $203.84; Pleural effusion: $229.81			GI perforation: 5929 (112) Hair colour changes: 70 (70) HFS: 2589 (112) Headache: 274 (274) Heart failure: 3293 (112) Hypertension: 21 (21) Influenza-like syndrome: 42 (42) Leucopenia: 1792 (112) Lymphopenia: 1792 (1792) Mucosal inflammation: 495 (495) Myalgia: 274 (274) Nausea: 2803 (112) Neutropenia: 1792 (70) Pain in extremity: 274 (274) Proteinuria: 3929 (112) Pyrexia: 42 (42) Rash: 148 (148) Skin discolouration: 70 (70) Stomatitis: 495 (88) Thrombocytopenia: 3372 (112) VTE: 2246 (112) Vomiting: 2803 (112) Wound healing complications: 148 (148)	
Technology costs	Study drug: pazopanib $69,417; sunitinib $74,433, Non-study drug: pazopanib $9,118; sunitinib $9.091	Sorafenib - product costs API/tablet: 200mg Tablets/month: 112 API price/kg: $3000 API cost/tablet: $0.60 Add costs of excipients, formulation: $0.62 Add costs of tableting: $0.66 Cost per month: $73.83			

		Add cost of bottle, packaging, shipping, duties: $74.18 Add 50% mark-up: $111.27 Target price: $1,450/patient/yr Lowest available price of sorafenib in UK: $58,027			
Abbreviations in table: GI, gastro-intestinal; HFS, hand-foot syndrome; IFN, interferon; kg, kilogramme; mRCC, metastatic renal cell carcinoma; RCC, renal cell carcinoma; SD, standard deviation; VTE, venous thromboembolism.					

Resource use and costs included in the model

The costs considered in the model are pharmacological costs, disease management costs, cost of managing adverse events, and subsequent therapy costs and are described below.

Pharmacological costs

The pharmacological costs included in the model are drug acquisition and administration costs. To estimate the total pharmacological costs for patients, the costs were applied to all patients who were in the progression-free health state for each cycle in the model. The doses and costs per cycle applied in the model are summarised in Table 62. The costs for sunitinib and pazopanib in the base case analysis incorporate the publicly available and nationally implemented patient access schemes (PAS). The PAS for sunitinib is the provision of the first six-week cycle of treatment for free with the list price charged for all subsequent cycles, while for pazopanib it is a simple discount of 12.5% on list price. It should be noted that after clarification stage, the company changed the list price of their treatment from [redacted] to [redacted].

Table 62. Drug acquisition costs applied in the model (Adapted from CS, pg 146, Table 62)

Treatment	Dose regimen	PAS discount	List price	Mean cost per week (on treatment)
Tivozanib	1,340µg daily for 3 weeks followed by 1 week rest	None	[redacted]	[redacted]
Sunitinib	50mg daily for 4 weeks followed by 2 weeks rest	No charge for first cycle. List price thereafter	50mg caps x 28: £3,138.80[125]	First 6 weeks: nil Thereafter: 784.70**
Pazopanib	800mg daily administered continuously	12.5% discount on all doses	400mg tabs x 30: £1,121[125]	£457.74

Abbreviations in table: µg; microgramme; mg, milligramme; MU, mega unit; PAS, patient access scheme.
*This is the updated list price provided by the company during clarification stage.
** This cost is the correct cost per week on treatment that is used in the model.

Disease management costs

Resource use for disease management is assumed to constitute oncologist visits and computerised tomography (CT) scans in line with the assumptions made in the STAs for pazopanib and sunitinib.[23, 25] The company assumes that patients have monthly oncologist visits prior to and after progression and CT scans every 3 months as long as they are receiving active treatment. The resource use assumed in the model is summarised in Table 63. It is assumed that 60% of patients in the model who progress on first-line treatment go on to receive axitinib as a second-line treatment, and therefore the cost of the CT scan after progression is applied to these patients. The remaining 40% of progressed patients are

assumed to be on BSC, which consists of monthly oncologist visits. The company state this assumption is based on clinical advice and recommendations presented in TA333. [26]

Table 63. Disease management costs (CS, pg 147, Table 63)

Cost Item	Frequency	Unit cost[126]	Reference[126]
Stable Disease			
Oncologist Examination (first visit)	First visit	£197	NHS Reference Costs 2015/6 HRG WF01B: service code 370 Medical Oncology
Oncologist Examination (subsequent visits)	Monthly	£163	NHS Reference Costs 2015/6 HRG WF01A: service code 370 Medical Oncology
CT Scan	Every 3 months	£115	RD27Z Computerised Tomography Scan of more than three areas (Source: NHS Reference costs 2015/16)
Progressive Disease			
Oncologist Examination	Monthly	£163	NHS Reference Costs 2015/6 HRG WF01A: service code 370 Medical Oncology
CT Scan (for patients on subsequent active therapy only)	Every 3 months	£115	RD27Z Computerised Tomography Scan of more than three areas (Source: NHS Reference costs 2015/16)

Abbreviations in table: GP, General Practitioner; HFS: Hand-foot syndrome; HRG, Health Resources Group; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.

Adverse event costs

The costs of managing Grade 3 or higher anaemia, fatigue, hand-foot syndrome, and hypertension are included in the model as the company considers them to be the key adverse events of interest as described in Section 5.4.6. The proportion of patients in the model who experience adverse events are assumed to experience one episode per adverse event. The company reports that the resource use assumed for managing these adverse events, as summarised in Table 64, is based on feedback from a UK clinician.

At the clarification stage, the ERG queried the exclusion of diarrhoea from AEs of interest in the original NMA and through consultation with a clinical expert this was found to be an omission (see Section 5.4.6 for more detail). The company submitted an updated economic model including estimates for diarrhoea, but no description of where the estimates came from or justification for their use were submitted by the company. Thus, the ERG was unable to validate these costs.

Table 64. Costs of managing adverse events (CS, pg 148, Table 64)

Adverse event	Service	Proportion of patients	Unit cost	Reference
Anaemia	Day case	50%	£306	NHS reference costs 2015/6

	transfusion			Weighted mean of HRG SA04G-SA04L[126]
	Short stay transfusion	50%	£509	
	Mean expected cost:		£407.50	
Fatigue	Additional outpatient attendance	50%	£163	NHS Reference Costs 2015/6 HRG WF01A: service code 370 Medical Oncology[126]
	Mean expected cost		£81.50	
HFS	Additional outpatient attendance	60%	£163	NHS Reference Costs 2015/6 HRG WF01A: service code 370 Medical Oncology[126]
	Short stay admission	30%	£526	NHS reference costs 2015/6 Weighted mean of HRG SA04G-SA04L[126]
	Mean expected cost		£255.60	
Hypertension	GP attendance x3	100%	£109	PSSRU Costs of health and social care 2016[127]
	Treatment with antihypertensive	100%	£28	Assumes treatment with Ramipril 5mg + bendroflumethiazide 2.5mg for 1 year[125]
	Mean expected cost		£137	
Diarrhoea	Not reported	100%	£752	Not reported
Abbreviations in table: HFS: Hand-foot syndrome				

Subsequent therapy costs

The only subsequent treatment considered in the model is axitinib, which is assumed to be received by 60% of patients who progress, while remaining 40% of patients go on to BSC, which consists of monitoring visits with oncologists. Patients are assumed to receive axitinib upon progression for the remaining duration of the model time horizon (10 years). The dosage and drug costs per cycle applied in the model are summarised in Table 65.

Table 65. Dose and cost of axitinib in the model (CS, pg 148, Table 65)

Treatment	Dose regimen	List price	Mean cost per week
Axitinib	5mg, twice a day	5mg tabs x 56: £3,517	£879.25
Abbreviations in table: mg, milligramme.			

5.4.8.1 ERG critique

Resource use is estimated for the base case analysis mainly based on previous NICE technology appraisals for sunitinib and pazopanib.[23, 25] The ERG's clinical experts confirmed that the resource use assumed in the model is reflective of UK clinical practice. However, even though the company stated in Section 2.4 of the CS that patients would require liver tests and thyroid function tests prior to treatment, and periodically thereafter, the company did not include blood tests in its resource use assumptions. The ERG's clinical experts said that patients would have monthly blood tests (full blood count and liver function tests) and thyroid function tests every 3 months. Therefore, the ERG asked the company to run a scenario analysis in which these blood tests are included for patients who are receiving treatment during the clarification stage. The company did not carry out this analysis, and provided the

following justification for not including blood tests in the model, "*Clinical advice from our advisors was that there would be no difference in blood tests across the VEGFR-TKIs and that therefore they would not be required in the resource use assumptions*." The ERG disagrees with this justification for the exclusion of blood tests since all resource use components for managing disease are the same across VEGFR-TKIs with the difference being the length spent by patients in health states because of receiving different treatments. As such the ERG obtained the cost of a blood test from NHS reference costs (£3, HRG code DAPS05) and included it in the ERG alternative base case reported in Section 6.3.

In addition, the ERG's clinical experts also disagreed with the assumptions made surrounding resource use for managing anaemia, fatigue and hand-foot syndrome (HFS). The proposed changes to resource use assumed for adverse events by the ERG's clinical expert are summarised in Table 66. The ERG carried out a scenario analysis assuming resource use for adverse events based on clinical expert opinion and found this had a negligible impact on the ICER (refer to Section 6.2).

Table 66. Resource use assumptions for managing adverse events based on ERG's clinical expert opinion

Adverse event	Service	Company's assumption	ERG's clinical expert
Anaemia	Day case transfusion	50%	80%
	Short stay transfusion	50%	20%
Fatigue	Additional outpatient attendance	50%	20%
HFS	Additional outpatient attendance	60%	60%
	Short stay admission	30%	0
Abbreviations in table: HFS, hand-foot syndrome			

The ERG considers that subsequent therapy costs assumed in the model are not reflective of the current treatment pathway for patients with recurrent or metastatic RCC. Currently in the NHS, patients can receive axitinib, nivolumab and everolimus if they progress after first line of therapy. However, the company assumes that 60% of patients receive axitinib after discontinuing treatment based on feedback from clinical experts and TA333,[26] while the remaining patients receive BSC. The ERG's clinical experts stated that based on the current treatment options available they would expect patients to be split across the treatment options as summarised in Table 67 with only 10% of patients receiving BSC. This is in line with the views held by clinical experts in the appraisal committee of the NICE STA of cabozantinib, and that only a very small group of patients considered unfit for treatment would receive BSC after discontinuing treatment.[29] Therefore, the company's assumption that 40% of patients receive BSC is not reflective of UK clinical practice. The company did carry out two scenario analyses related to the cost of subsequent therapies, the first assumed that the mean cost of subsequent therapy is reduced by 50%, and the second scenario assumed that 90% of patients receive axitinib. However, they are both of limited values as neither reflects UK clinical practice.

Table 67. Subsequent therapies proposed by ERG's clinical expert

Subsequent therapy	Proportion of patients
Axitinib	50%
Everolimus	10%
Nivolumab	30%
BSC	10%
Abbreviations in table: BSC, best supportive care	

Furthermore, the company assumes that the patients in the model who go on to receive axitinib, continue receiving it until they die, resulting in the cost of axitinib making up more than 50% of total costs for all treatments. This assumption does not reflect clinical reality based on feedback from the ERG's clinical experts. Furthermore, the mean duration of treatment for patients receiving axitinib as a second-line treatment of RCC as reported in the technology appraisal for axitinib was 220.8 days.[26, 27, 29] The ERG, therefore, asked the company to carry out a scenario analysis using data on the actual subsequent treatments received in the drugs' respective trials and the mean durations of subsequent therapy received. The company responded with the following, "*There is a paucity of data on the use of next line therapy; data on the proportion of patients receiving subsequent therapy and the type of therapy used next-line is only available for TIVO-1 and SWITCH. The duration of next-line therapy is only available for SWITCH (Table 3 of the clinical paper). All four studies in the revised mixed treatment comparison (TIVO-1, SWITCH, Cross J RCC and COMPARZ) were carried out more than 5 years ago and are therefore are unlikely to reflect clinical practice today. We used the 60%/40% split on advice from our clinical advisor, which we believe reflects current clinical practice*". Lastly, the company did not discount subsequent treatment disease management costs in the model. The ERG corrected this and results of the corrected company base case are presented in Section 6.1.

The ERG disagrees with the way subsequent therapy costs have been implemented in the model and thus implemented a more plausible approach to modelling subsequent therapy costs by calculating the proportion of patients who are newly progressed in a cycle and multiplying this proportion by a one-off total weighted cost of subsequent therapy (presented in Table 72). The total weighted cost is based on the distribution of patients across second line treatments in presented in Table 67, mean duration, list price, recommended dose and RDI of treatments obtained from the published literature (Table 68, Table 69 and Table 70, respectively). Costs for nivolumab include wastage. Disease management costs were estimated based on the company's original costs (Table 63) and the mean duration of treatment to create a one-off cost and then this was applied to the proportion who are newly progressed in a cycle.

Table 68. Duration of second line treatment

Subsequent therapy	Mean Duration of treatment (days)	Source
Axitinib	220.8	TA333 CS based on AXIS trial[128]
Everolimus	167.6	Cabozantinib STA based on METEOR trial[129]

Nivolumab	167.3*	Motzer 2015[130]
Abbreviations in table: CS, company submission; STA; single technology assessment. Note: mean duration was not available for nivolumab and instead median duration was applied.		

Table 69. Second line treatment costs

Subsequent therapy	Formulation (mg)	Dose (mg)	Units (per pack)	List price (per pack)	Source
Axitinib	5	10	56	£3,517	BNF[125]
Everolimus	10	10	30	£2,673	BNF[125]
Nivolumab	100	3mg/kg*	1	£1,097	BNF[125]
	40		1	£439	BNF[125]
Abbreviations in table: mg, milligram; kg, kilogram. Note: mean weight observed in the TIVO-1 trial was 80.7kg.					

Table 70. Relative dose intensity for second line treatment

Subsequent therapy	Relative dose intensity (RDI)	Source
Axitinib	102%	TA333 [128]
Everolimus	94%	TA417[131]
Nivolumab	98%	TA417[131]

As nivolumab is an immunotherapy delivered intravenously every 14 days (one cycle of treatment), administration costs of the first and subsequent visits have been included in total cost of treatment based on median duration of treatment, presented in Table 72.

Table 71. Administration costs for nivolumab

Description	Administration costs	Source
First visit (Deliver Simple Parenteral Chemotherapy at First Attendance (OP))	£199	NHS reference costs 2015/6 (HRG code SB12Z)[132]
Subsequent visit (Deliver Subsequent Elements of a Chemotherapy Cycle (OP))	£212	NHS reference costs 2015/6 (HRG code SB15Z)[132]

Table 72. Total weighted cost of second line treatment

Subsequent therapy	Weighted cost
Axitinib	£14,819
Everolimus	£1,506
Nivolumab	£9,692
Total weighted cost	**£26,017**

The ERG found that implementing its own assumptions for subsequent therapy has a substantial impact on the ICER (refer to Section 6.2) and has included this alternative scenario in the ERG base case, presented in Section 6.3. However, it should be noted that the modelling of subsequent therapies does not include any assumptions around the treatment effectiveness of each of the subsequent therapies on OS for tivozanib, sunitinib or pazopanib.

The ERG also requested the company to carry out a scenario analysis adjusting the costs of drug acquisition based on relative dose intensity. However, the company did not carry out the analysis and provided the following justification, "*Data on dose intensity is only available for tivozanib and sorafenib in the TIVO-1 study (94% for tivozanib versus 80%). Data on dose intensity is not available for pazopanib (COMPARZ study) or sunitinib (COMPARZ study, Cross J RCC and SWITCH)".* The ERG considers that dose intensities used in previous NICE technology appraisals to be relevant even if they were based on different trials (Table 73). The ERG implemented the RDIs for each treatment in the model and found this had a significant impact on the ICER (refer to Section 6.2) and as such included this assumption in the ERG alternative base case presented in Section 6.3.

Table 73. Relative dose intensities from previous TAs

Treatment	Trial	Mean	Estimation	Source
Pazopanib	VEG 105192 trial[74]	0.86[25]	Ratio of mean daily dose on treatment to planned daily dose	NICE TA 215 ERG report[25]
Sunitinib	Motzer *et al.* 2007[133]	0.86[107]	Dose intensity was calculated as the amount of drug administered versus the amount that should have been administered over the course of treatment.	NICE TA178 ERG report[23, 107]

Abbreviations: ERG, Evidence Review Group; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.

NHS Reference Costs and Personal Social Services Research Unit (PSSRU) costs are used where available, in line with the NICE reference case.[126, 127] The ERG identified an error in the way monthly disease management costs were adjusted to be applied as weekly (per cycle) costs in the model. A month was assumed to have 4 weeks instead of 4.35 weeks when converting monthly costs of managing patients during pre-progression and post-progression to weekly costs. The ERG corrected this error in model and the corrected base case results are reported in Section 6.1.

Overall, the ERG considers that the calculation of costs for the PPS health state to be inappropriately modelled and as such grossly overestimated for all treatments. Economic modelling of costs should closely match what would be seen in clinical reality for the results produced by the economic model to be appropriate for decision making. The company cite lack of data availability as one of the main reasons for not performing the scenario analyses requested by the ERG. However, consideration should have been made of data available in the published STAs for the comparator treatments and employed in scenarios to provide some indication of how changing these assumptions impact the ICER.

5.5 Results included in company's submission

5.5.1 Base case results

As mentioned previously, the company has submitted three iterations of the economic model employing three different methods to estimate treatment effectiveness including proportional hazards modelling, a parametric NMA and finally the FP-based NMA. Each model produced vastly different results with ICERs ranging from £19,480 to £71,104 (SW quadrant of the cost-effectiveness plane) for tivozanib versus sunitinib and £36,757 to £97,130 (SW quadrant of the cost-effectiveness plane) for tivozanib versus pazopanib. The wide-ranging results demonstrates the uncertainty around the cost effectiveness results. The company's pairwise analysis results of the original submission base case analysis, the parametric NMA, and the FP-based NMA (revised base case) are presented in Table 74, Table 75, and Table 76, respectively. The corresponding fully incremental analyses are presented in Table 77, Table 78, and Table 79, respectively.

Table 74. Original submission base case pairwise analysis results (CS, pg 152, Table 68-70)

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Tivozanib	£86,176	2.085			
IFN	£59,585	1.864	£26,591	0.221	£120,303
Sunitinib	£84,199	1.983	£1,976	0.101	£19,480
Pazopanib	£85,094	2.063	£1,082	0.022	£49,955
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; IFN: Interferon; QALY, Quality-adjusted life year.					

Table 75. Parametric NMA pairwise analysis results (Company's updated clarification responses, Table 13 and 14)

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Tivozanib	£72,592	1.893			
Sunitinib	£92,965	2.180	-£20,373	-0.287	£71,104 (SW quadrant)
Pazopanib	£83,541	2.006	-£10,949	-0.113	£97,138 (SW quadrant)
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; IFN: Interferon; QALY, Quality-adjusted life year, SW, south-west.					

Table 76. Revised base case – Second order FP-based NMA (P1= -2, P2= -1) pairwise analysis (Company's additional analysis results document, Table 4 and 5)

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Tivozanib	£70,476	1.757	-	-	-
Sunitinib	£105,566	2.425	-£35,091	-0.668	£52,533 (SW Quadrant)
Pazopanib	£58,537	1.432	£11,938	0.325	£36,757
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; IFN: Interferon; QALY, Quality-adjusted life year; SW, south-west.					

Table 77. Fully incremental cost-effectiveness results results of original submission base case results (CS, pg 153, Table 71)

Therapy	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER vs IFN	ICER incremental
IFN	£59,585	2.756	1.864	-	-	-	-	-

Sunitinib	£84,199	2.876	1.983	£24,615	0.120	0.120	£205,840	£205,840
Pazopanib	£85,094	2.997	2.063	£25,509	0.241	0.199	£128,228	£11,272
Tivozanib	£86,176	3.028	2.085	£26,591	0.272	0.221	£120,303	£48,955
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; IFN: Interferon; LYG, Life years gained; QALY, Quality-adjusted life year.								

Table 78. Fully incremental cost-effectiveness results of parametric NMA (Company's updated clarification responses, Table 15)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Tivozanib	£72,592	2.692	1.893	-	-	-	-
Pazopanib	£83,541	2.930	2.006	£10,949	0.238	0.113	£97,138
Sunitinib	£92,965	3.172	2.180	£21,373	0.479	0.287	£38,942
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

Table 79. Fully incremental cost-effectiveness results of revised base case – Second order FP-based NMA (P1= -2, P2= -1) (Company's additional analysis results document, Table 6)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Pazopanib	£58,537	2.076	1.432	£11,938	-	-	-
Tivozanib	£70,476	2.543	1.757	£35,091	0.467	0.325	£52,533
Sunitinib	£105,566	3.586	2.425	£11,938	1.043	0.668	£47,361
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

5.5.2 Sensitivity analysis

The company carried out deterministic (scenario analysis and one-way sensitivity analyses), and probabilistic sensitivity analyses to assess the uncertainty surrounding the results of the revised base case second-order FP (P1= -2, P2= -1) model. However, it did not report the results of the one-way sensitivity analysis to the ERG. The ERG notes that since there were major errors in the company's revised base case model as reported throughout this report with corrections by the ERG described in Section 6.1, the results of the company's scenario analysis and probabilistic sensitivity analysis are of limited value in terms of assessing the uncertainty surrounding the cost-effectiveness results.

5.5.2.1 Scenario analysis

The company carried out scenario analyses, testing assumptions in the revised base case second-order FP (P1= -2, P2= -1) model surrounding the following parameters:

- Effectiveness estimates: using a first-order FP (p1=-2) instead of a second-order FP;
- Discounting of costs and outcomes: removing discounting for costs and outcomes from the model;
- HSUVs: using alternative values for HSUVs from previous technology appraisals;

- Subsequent therapies: assuming a higher proportion of patients in the model receive second-line treatment with axitinib, and assuming a lower mean cost of subsequent treatments.

The results of the analysis are reported in Table 80.

Table 80. Results of scenario analysis carried out on company's revised base case – Second order FP-based NMA (P1= -2, P2= -1) (Company's scenario analysis results document, Table 10, Table 11, Table 13, Table 14, Table 16, Table 17, Table 19, Table 20)

Base case assumption	Scenario	Tivozanib vs Sunitinib ICER	Tivozanib vs Pazopanib ICER
Base case ICER	-	**£52,533 (SW Quadrant)**	**£36,757**
Second-order fractional polynomial-based NMA	First-order fractional polynomial-based NMA	£59,247 (SW Quadrant)	£70,865
Discount rate of 3.5% for costs and outcomes	No discounting applied to costs and outcomes	£51,379 (SW Quadrant)	£37,211
Pre-progression utility of 0.73 Post-progression utility of 0.65	Pre-progression utility of 0.78, Post-progression utility of 0.70 based on values used in TA169[23]	£48,728 (SW Quadrant)	£34,292
	Pre-progression utility of 0.70, Post-progression utility of 0.59 based on values used in TA215[25]	£58,060 (SW Quadrant)	£39,275
Second-line treatment received by 60% patients with axitinib being the only second-line treatment option	Proportion of patients receiving second-line therapy with Axitinib is increased to 90%	£74,977(SW Quadrant)	£46,526
	Mean cost of second-line treatment reduced by 50%	£30,371 (SW Quadrant)	£27,124
Abbreviations in table: ICER, incremental cost-effectiveness ratio; SW, south-west; TA, technology appraisal.			

5.5.2.2 One-way sensitivity analysis

The company did not report one-way sensitivity analysis for the revised base case.

5.5.2.3 Probabilistic sensitivity analysis

The company performed a probabilistic sensitivity analysis (PSA) to assess the joint parameter uncertainty around the base case results across 1,000 iterations. The mean probabilistic ICERs are presented in Table 81. The difference between the deterministic and probabilistic ICERs for tivozanib relative to sunitinib, and pazopanib is £2,506 and -£4,421 per QALY, respectively. The ERG reran the PSA and obtained similar probabilistic results for tivozanib relative to sunitinib (£55,601 per QALY), while the mean probabilistic ICER for tivozanib relative to pazopanib was £29,952 per QALY which is a difference of -£6,805 per QALY. This indicates that there is substantial uncertainty surrounding the results of tivozanib relative to pazopanib in the company's model.

The resultant scatterplots from the PSA for tivozanib relative to sunitinib, and pazopanib are presented in Figure 31 and Figure 32, respectively. The cost-effectiveness acceptability curves (CEACs) are

presented in Figure 33. At a willingness-to-pay (WTP) threshold of £30,000 per QALY, the probability of tivozanib being cost-effective compared to sunitinib and pazopanib is 89.6% and 43.3%, respectively.

Table 81. Mean probabilistic ICERs (Company's scenario analysis document, Table 25 and Table 26)

Therapy	Tivozanib versus sunitinib	Tivozanib versus pazopanib
Deterministic ICER	£52,533 (SW Quadrant)	£36,757
Mean probabilistic ICER	£55,039 (SW Quadrant)	£32,336
Abbreviations: ICER, incremental cost-effectiveness ratio; SW, south west		

Figure 31. Distribution of cost-effectiveness simulations on the cost-effectiveness plane for tivozanib compared to sunitinib (Company's additional analysis document, Figure 3)

Figure 32. Distribution of cost-effectiveness simulations on the cost-effectiveness plane for tivozanib compared to pazopanib (Company's additional analysis document, Figure 4)

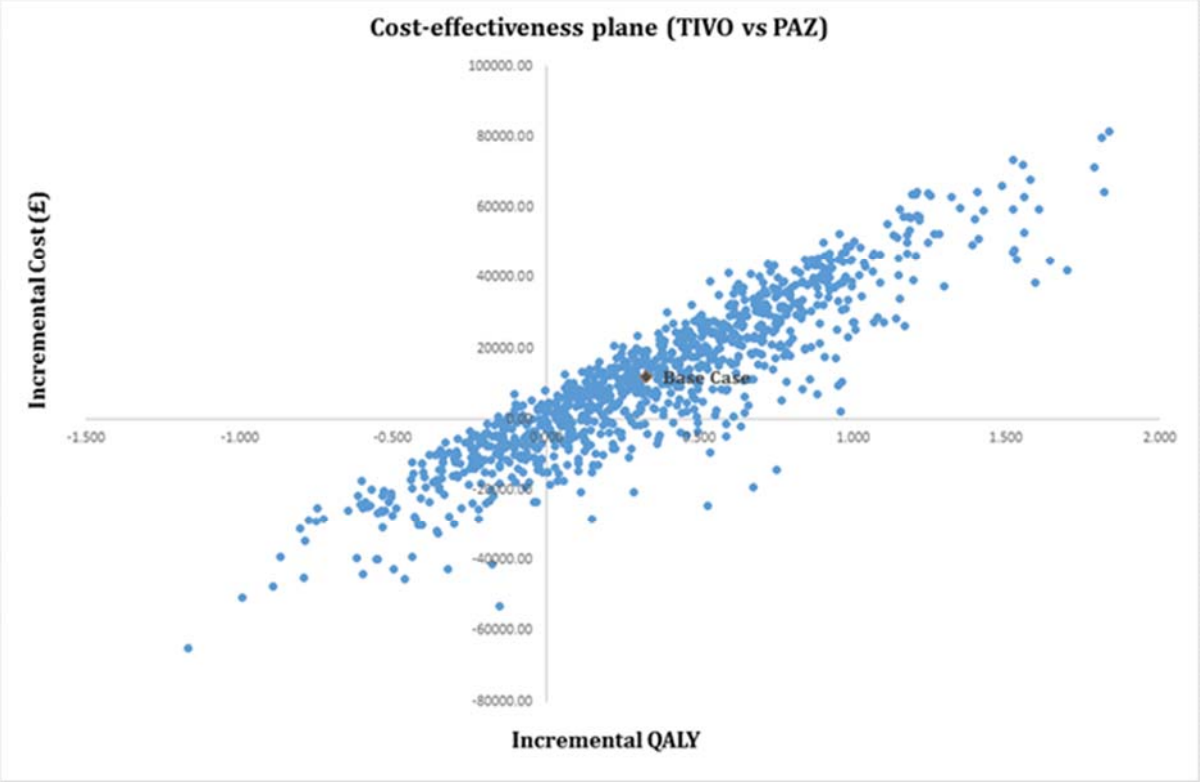
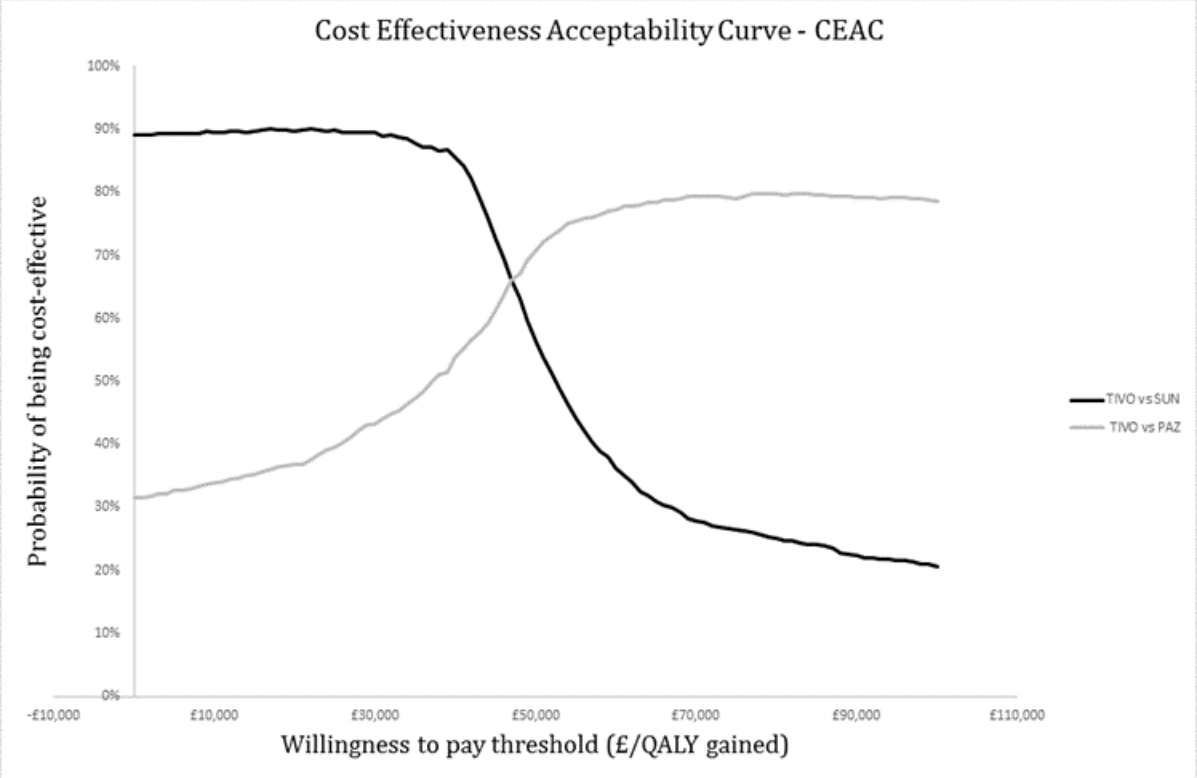


Figure 33. Cost-effectiveness acceptability curves (Company's additional analysis document, Figure 5)



5.5.3 Model validation

The company report using a similar approach to model validation used in the STAs for pazopanib and sunitinib, but did not go on to describe this further. Box 8 outlines the model validation described in the company's submission for pazopanib.[25]

Box 8. Model validation from the company's submission for pazopanib[25]

> Model validation was undertaken by Professor Steve Morris (University College, London). The validation process had two parts, described below.
>
> Firstly, the reviewer examined an earlier version of the model User Guide and Draft Report to test the model for face validity. The focus in this part of the validation process was whether or not the model was consistent with the Draft Scope produced by NICE ("Single Technology Appraisal: Pazopanib for the first-line treatment of advanced and/or metastatic renal cell carcinoma"), and whether or not the methods underpinning the model and the results produced were appropriate. The latter focused on whether or not the approaches taken to model cost-effectiveness were clearly described and plausible. -206- The outcome of this external review can be found in appendix 17. GSK and PAI (who undertook the modelling work) responded to each comment on a point-by-point basis, highlighted in grey in the Appendix. In some cases, the model or the description of the model in the User Guide and Draft Final Report was amended in the light of the comments received. In some cases the comments were noted but no further action was required or undertaken. The responses were fed back to the reviewer, who was content with the responses received.
>
> Secondly, the external health economics reviewer examined the technical validity of the Excel workbook containing the model to try and identify any flaws in the model structure. This was undertaken by looking at all the inputs and calculations to ensure that the calculations were undertaken correctly and that cells are linked properly within the model. In addition, the reviewer went through the input worksheets in the Excel workbook, modified the input parameter values, and tested if the resulting changes to the results are as expected. No significant issues were identified, and the reviewer was content with the technical validity of the model.

Given the numerous errors the ERG has discovered, not only with the original economic model, but the subsequent models submitted after and the lack of description of the company's own validation process regardless if it was based on other STAs, the ERG has limited confidence that the company performed a thorough model validation.

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

As reported in Section 5.4.5.3, the ERG corrected the fundamental flaw in the calculation of treatment effectiveness based on the parameters generated in the FP analysis. In addition to this, the weekly costs (per cycle) for disease management during pre-progression and post-progression were estimated incorrectly. Monthly costs were converted to weekly costs by dividing by 4, instead of 4.35 (365 days/12 months/7 days) which is the correct estimate of number of weeks per month. The ERG corrected this accordingly. Lastly, the company did not discount costs for subsequent therapy disease management and this has been rectified by the ERG.

The company's corrected base case ICERs for the revised base case second order FP-based NMA (P1= -2, P2= -1) analyses are reported in Table 82. The ERG also reran the scenario analyses carried out by the company except for the scenario related to subsequent treatment as this is included in the exploratory analyses reported in Section 6.3, using an alternative approach. The results of the scenario analysis are reported in Table 83. The result for the first order FP scenario should be treated with caution, as mentioned previously, the ERG does not believe the parameter estimates generated by the company are correct as they could not be validated.

Table 82. Company's corrected base case ICERs in the revised base case – Second order FP-based NMA (P1= -2, P2= -1) analysis

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Tivozanib	£71,281	4.839	-	-	-
Sunitinib	£99,073	2.415	-£27,792	-0.576	£48,222 (SW Quadrant)
Pazopanib	£71,369	1.783	-£88	0.056	Dominant

Abbreviations in table: ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; SW, south-west.

Table 83. Scenario analysis results based on company's corrected base case ICERs for the revised base case – Second order FP-based NMA (P1= -2, P2= -1) analysis

Base case assumption	Scenario	Tivozanib vs Sunitinib ICER(£)	Tivozanib vs Pazopanib ICER(£)
Base case ICER	-	**£48,222 (SW Quadrant))**	**Dominant**
Second-order fractional polynomial	First-order fractional polynomial	£56,176	£74,693
Discount rate of 3.5% for costs and outcomes	No discounting applied to costs and outcomes	£47,623	£10,751
Pre-progression utility of 0.73 Post-progression utility of 0.65	Pre-progression utility of 0.78, Post-progression utility of 0.70 based on values used in TA169[23]	£44,678	Dominant
	Pre-progression utility of 0.70, Post-progression utility of 0.59	£53,700	Dominant

	based on values used in TA215[25]		
Abbreviations in table: ICER, incremental cost-effectiveness ratio; SW, south-west; TA, technology appraisal.			

6.2 ERG scenario analysis

Throughout Section 5 the ERG have raised several issues with the economic model produced by the company and have described scenarios that warrant further exploration. The scenarios that the ERG have produced are applied to the corrected revised company base case and are as follows:

1) Implementation of the alternative second order fractional polynomial (FP) (P1= -2, P2= -1.5) for overall survival (OS);

2) Implementation of the following alternative second order FP-based NMAs for progression-free survival (PFS);

   a) Second order FP-based NMA (P1= -3, P2= -3);

   b) Second order FP-based NMA (P1= -3, P2= -2.5);

3) Scenario 1 + scenario 2a;

4) Scenario 1 + scenario 2b;

5) Equal efficacy for OS and PFS based on the ERG's estimates of the company preferred second order FP-based NMA (P1= -2, P2= -1) using the ERG estimates;

6) Use of treatment naïve adverse event (AE) incidence for tivozanib (from the TIVO-1 trial) based on Table 52;

7) ERG estimates of AE odds ratios (ORs) based on the simplified network meta-analysis (NMA) based on Table 53;

8) ERG clinical expert resource use assumptions for AEs, based on Table 66;

9) Removal of AE health state utility value (HSUV) decrements. HSUVs for PFS are based on the TIVO-1 trial which did not distinguish patients who were experiencing AEs and therefore inclusion of AE utility decrements is potentially double counting the impact of these on quality of life;

10) Scenarios 6 to 9;

11) Equal incidence of AEs based on the tivozanib incidence;

12) Inclusion of blood tests for PFS disease management costs;

13) Inclusion of relative dose intensities (RDI) for treatments based on Table 73; and

14) ERG's remodelling of subsequent therapy costs as described in Section 5.4.8.1.

The results for all the scenarios outlined above are presented in Table 84. The results should be interpreted with caution as the company's parameter estimates used to extrapolate OS and PFS could not be validated by the ERG and thus may not be correct.

Table 84. Results of ERG's scenario analyses

	Results per patient	Tivozanib (1)	Sunitinib (2)	Pazopanib (3)	Incremental value	
					(1-2)	(1-3)
0	**Corrected company base case**					
	Total costs (£)	£71,281	£99,073	£71,369	-£27,792	-£88
	QALYs	1.84	2.42	1.78	-0.58	0.06
	ICER				**£48,222 (SW quadrant)**	**Dominant**
1	**Second order FP-based NMA (P1= -2, P2= -1.5) for OS**					
	Total costs (£)	£76,997	£91,154	£94,896	-£14,156	-£17,899
	QALYs	1.97	2.23	2.34	-0.25	-0.36
	ICER				**£55,586 (SW quadrant)**	**£49,094 (SW quadrant)**
2a	**Second order FP-based NMA (P1= -3, P2= -3) for PFS**					
	Total costs (£)	£71,489	£98,686	£71,375	-£27,197	£114
	QALYs	1.83	2.40	1.78	-0.57	0.05
	ICER				**£47,746 (SW quadrant)**	**£2,311**
2b	**Second order FP-based NMA (P1= -3, P2= -2.5) for PFS**					
	Total costs (£)	£71,556	£98,916	£71,328	-£27,361	£228
	QALYs	1.83	2.41	1.79	-0.58	0.04
	ICER				**£47,180 (SW quadrant)**	**£5,161**
3	**Scenario 1+2a**					
	Total costs (£)	£77,205	£90,767	£94,903	-£13,561	-£17,697
	QALYs	1.97	2.22	2.34	-0.25	-0.37
	ICER				**£54,691 (SW quadrant)**	**£47,709 (SW quadrant)**
4	**Scenario 1+2b**					
	Total costs (£)	£77,272	£90,997	£94,855	-£13,725	-£17,583
	QALYs	1.97	2.22	2.34	-0.26	-0.38
	ICER				**£53,144 (SW quadrant)**	**£46,763 (SW quadrant)**
5	**Equal efficacy for OS and PFS based on company preferred second order FP (ERG estimates)**					
	Total costs (£)	£79,425	£83,374	£80,931	-£3,949	-£1,506
	QALYs	2.06	2.06	2.06	0.01	0.002
	ICER				**Dominant**	**Dominant**

6	**Treatment naïve AE incidence for tivozanib**					
	Total costs (£)	£71,228	£99,020	£71,336	-£27,791	-£108
	QALYs	1.84	2.42	1.79	-0.58	0.05
	ICER				**£47,823 (SW quadrant)**	**Dominant**
7	**ERG estimates of AE ORs based on the simplified NMA**					
	Total costs (£)	£71,281	£99,131	£71,413	-£28,665	-£594
	QALYs	1.84	2.41	1.78	-0.57	0.06
	ICER				**£48,540 (SW quadrant)**	**Dominant**
8	**ERG clinical expert resource use assumptions for AEs**					
	Total costs (£)	£71,278	£99,057	£71,361	-£27,779	-£84
	QALYs	1.84	2.42	1.78	-0.58	0.06
	ICER				**£48,200 (SW quadrant)**	**Dominant**
9	**Removal of AE health state utility value decrements**					
	Total costs (£)	£71,281	£99,073	£71,369	-£27,792	-£88
	QALYs	1.84	2.43	1.79	-0.58	0.05
	ICER				**£47,609 (SW quadrant)**	**Dominant**
10	**Scenarios 6 to 9**					
	Total costs (£)	£71,225	£99,035	£71,351	-£27,810	-£125
	QALYs	1.84	2.43	1.79	-0.58	0.05
	ICER (compared with corrected company base case)				**£47,640 (SW quadrant)**	**Dominant**
11	**Equal incidence of AEs**					
	Total costs (£)	£71,281	£99,054	£71,405	-£27,773	-£124
	QALYs	1.84	2.42	1.79	-0.58	0.05
	ICER				**£47,577 (SW quadrant)**	**Dominant**
12	**Inclusion of blood tests for PFS disease management costs**					
	Total costs (£)	£71,3225	£99,113	£71,405	-£27,787	-£79
	QALYs	1.84	2.42	1.78	-0.58	0.06
	ICER				**£48,214 (SW quadrant)**	**Dominant**
13	**Inclusion of relative dose intensities for treatments**					
	Total costs (£)	£69,587	£95,222	£68,045	-£25,634	£1,542
	QALYs	1.84	2.42	1.78	-0.58	0.06
	ICER				**£44,478 (SW quadrant)**	**£27,756**
14	**ERG's remodelling of subsequent therapy costs**					
	Total costs (£)	£46,821	£49,796	£45,011	-£2,975	£1,810
	QALYs	1.84	2.42	1.78	-0.58	0.06
	ICER				**£5,162 (SW quadrant)**	**£32,570**

Abbreviations in table: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; FP, fractional polynomial; PFS, progression-free survival; OS, overall survival; SW, south-west; AE, adverse event; OR, odds ratio;

6.3 ERG base case ICER

The ERG's preferred base case ICERs for tivozanib versus sunitinib and pazopanib, respectively, incorporates the following changes and assumptions made to the corrected company's base case ICER:

- Implementation of the alternative second order FP-based NMA (P1= -2, P2= -1.5) for OS. This was found to be the best fitting curve out of the options assessed by the ERG based on face validity and clinical validity;
- Implementation of the alternative second order FP-based NMA (P1= -3, P2= -2.5) for PFS. This curve was selected out of the two best fitting options available as it produces conservative estimates for PFS. Implementation of the alternative second order FP-based NMA (P1= -3, P2= -3) is explored in a scenario analysis around the ERG preferred base case in Section 6.3.1
- Alternative modelling of AEs, which include the following changes:
    - Use of treatment naïve adverse event (AE) incidence rates for tivozanib (from the TIVO-1 trial) based on Table 52;
    - ERG estimates of AE odds ratios (ORs) based on the simplified network meta-analysis (NMA) based on Table 53;
    - ERG clinical expert resource use assumptions for AEs, based on Table 66; and
    - Removal of AE health state utility value (HSUV) decrements.
- Inclusion of blood tests for PFS disease management costs;
- Inclusion of relative dose intensities (RDI) for treatments based on Table 73; and
- ERG's alternative modelling of subsequent therapy costs as described in Section 5.4.8.1

The estimates produced by the economic model for the ERG's preferred base case ICERs (and indeed all other analyses presented throughout Section 5) should be viewed with caution as there is a sunstantial amount of uncertainty surrounding the underlying data, particularly the survival data, used to populate the model. The ERG have attempted to be conservative in its assumptions to reduce the uncertainty, however, as crossover adjusted data for OS were not available for use in the analysis. The confounding of the OS data from TIVO-1 is likely to bias the results from the FP-based NMA and so the results of the cost-effectiveness analysis. As mentioned throughout the report, the ERG are unable to predict the direction and magnitude of the bias on the ICERs.

Results of the ERG's preferred base case ICERs are presented in Table 85. Fully incremental analysis of the ERG preferred base case ICERs are presented in Table 86.

Table 85. Results of ERG preferred base case (pairwise analysis)

Results per patient	Tivozanib (1)	Sunitinib (2)	Pazopanib (3)	Incremental value	
				(1-2)	(1-3)
Corrected company base case					
Total costs (£)	£71,281	£99,073	£71,369	-£27,792	-£88
QALYs	1.84	2.42	1.78	-0.58	0.06
ICER				**£48,222 (SW quadrant)**	**Dominant**
Second order FP-based NMA (P1= -2, P2= -1.5) for OS					
Total costs (£)	£76,997	£91,154	£94,896	-£14,156	-£17,899
QALYs	1.97	2.23	2.34	-0.25	-0.36
ICER				**£55,586 (SW quadrant)**	**£49,094 (SW quadrant)**
ICER with all changes incorporated				**£55,586 (SW quadrant)**	**£49,094 (SW quadrant)**
Second order FP-based NMA (P1= -3, P2= -2.5) for PFS					
Total costs (£)	£71,556	£98,916	£71,328	-£27,361	£228
QALYs	1.83	2.41	1.79	-0.58	0.04
ICER				**£47,180 (SW quadrant)**	**£5,161**
ICER with all changes incorporated				**£53,144 (SW quadrant)**	**£46,763 (SW quadrant)**
Alternative modelling for AEs					
Total costs (£)	£71,225	£99,035	£71,351	-£27,810	-£125
QALYs	1.84	2.43	1.79	-0.58	0.05
ICER				**£47,640 (SW quadrant)**	**Dominant**
ICER with all changes incorporated				**£51,729 (SW quadrant)**	**£46,585 (SW quadrant)**
Inclusion of blood tests for PFS disease management costs					
Total costs (£)	£71,325	£99,113	£71,405	-£27,787	-£79
QALYs	1.84	2.42	1.78	-0.58	0.06
ICER				**£48,214 (SW quadrant)**	**Dominant**
ICER with all changes incorporated				**£51,717 (SW quadrant)**	**£46,576 (SW quadrant)**
Inclusion of relative dose intensities for treatments					
Total costs (£)	£69,587	£95,222	£68,045	-£25,634	£1,542
QALYs	1.84	2.42	1.78	-0.58	0.06
ICER				**£44,478 (SW quadrant)**	**£27,756**
ICER with all changes incorporated				**£43,981 (SW quadrant)**	**£41,583 (SW quadrant)**
Alternative modelling of subsequent therapy costs					
Total costs (£)	£46,821	£49,796	£45,011	-£2,975	£1,810
QALYs	1.84	2.42	1.78	-0.58	0.06

ICER	**£5,162 (SW quadrant)**	**£32,570**
ICER with all changes incorporated	**£1,624 (SW quadrant)**	**Dominated**
ERG's preferred base case ICER	**£1,624 (SW quadrant)**	**Dominated**
Abbreviations in table: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; FP, fractional polynomial; PFS, progression-free survival; OS, overall survival; SW, south-west; AE, adverse event.		

Table 86. Results of the ERG preferred base case (incremental)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Pazopanib	£43,644	3.49	2.35	-	-	-	-
Tivozanib	£43,742	2.89	1.97	£98	-0.59	-0.38	Dominated
Sunitinib	£44,174	3.31	2.24	£43	-0.17	-0.11	Dominated
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

6.3.1 Scenario analysis (ERG preferred base case ICER)

The ERG found there were two potential second order FP curve choices for PFS that were assessed to be a good fit to the underlying data. The second order FP-based NMA (P1= -3, P2= -2.5) was implemented in the ERG preferred base case as it produced conservative estimates for PFS. The ERG explored a scenario using the alternative second order FP-based NMA (P1= -3, P2= -3), which was also found to be an equally good fit to the underlying data. Table 87 presents the results of this scenario.

Table 87. Results of alternative PFS scenario (pairwise analysis)

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Tivozanib	£44,111	1.97	-	-	-
Sunitinib	£42,228	1.23	£1,884	-0.42	Dominated
Pazopanib	£43,019	2.35	£1,093	-0.37	Dominated
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year.					

As mentioned previously, there is a sunstantial amount of uncertainty around the survival data and thus the ERG explored a second scenario assuming equal efficacy for PFS and OS for all treatments (cost minimisation scenario). No ICERs were produced for this scenario as the ERG base case removes AE utility decrements, resulting in no differences in QALYs. Results of this scenario are presented in Table 88.

Table 88. Results of alternative equal efficacy scenario (cost minimisation)

Therapy	Total costs	Incremental costs
Tivozanib	£43,742	-
Sunitinib	£43,736	£6
Pazopanib	£42,656	£1,087

7 OVERALL CONCLUSIONS

Tivozanib (Fotivda®; EUSA Pharma Ltd), which has not been granted European marketing authorisation at the time of writing this report, is likely to have a similar benefit for progression-free survival (PFS) as the NICE-approved first-line treatments for renal cell carcinoma (RCC). Overall survival (OS) with tivozanib may be shorter than has been observed for pazopanib and sunitinib, but estimates of comparative effectiveness may be biased against tivozanib by unadjusted treatment crossover. NMA results did not provide robust evidence that response to treatment is better or worse with tivozanib, or that it has a differential safety profile, than pazopanib and sunitinib; study results did not support NMA to compare quality of life on the three treatments.

The company submission (CS) was based on a randomised controlled trial (RCT) trial, TIVO-1,[41] which provides relevant evidence for tivozanib in a population with treatment-naïve metastatic RCC. TIVO-1 does not provide evidence for tivozanib in a pretreated population because prior treatments received in the TIVO-1 (primarily cytokines) do not reflect current UK practice. TIVO-1 was open-label but was otherwise judged to be largely free from internal biases. The sorafenib comparator group means the trial does not provide head-to-head evidence relevant to the NICE final scope, so NMA was required to provide estimates of comparative effectiveness.

The one-way crossover design of TIVO-1 and related imbalance between groups in access to subsequent targeted therapies confounded the within-trial estimate of OS. There may be less uncertainty in the TIVO-1 OS estimate if a range of crossover-adjustments had been conducted and compared for the treatment-naïve population, as recommended by the NICE Decision Support Unit[84] (and carried out in the submission for pazopanib[86]). However, even with appropriate crossover-adjusted results for the treatment-naïve population of TIVO-1, the estimates of OS in trials providing a link between tivozanib, pazopanib and sunitinib, are likely to be similarly confounded, which cannot be adjusted without individual patient data for those studies. A matched-adjusted indirect comparison (MAIC) matching the TIVO-1 tivozanib group to the COMPARZ trial, suggested to the company as an option at the clarification stage, may provide more reliable results for OS because it would not rely on the within-study comparison with sorafenib.

The company conducted a large amount of additional analyses suggested by the ERG during the clarification stage to provide more robust comparative clinical effectiveness results. Key aspects of the new analyses included restricting them to four studies required to link tivozanib with pazopanib and sunitinib to reduce clinical heterogeneity in the NMA, and implementing the fractional polynomial (FP) approach to the NMA to better model survival once proportional hazards was found not to hold. The ERG considers the estimates provided during clarification more reliable than those in the original submission, but identified a series of errors and inconsistencies that required further exploration. The

company reported methods with sufficient transparency to enable the ERG to critique and validate the findings, and provide what it considers more reasonable alternatives to inform the economic model.

The ERG has concerns that the methods implemented by the company to evaluate cost-effectiveness are not based on current guidance for good practice when carrying out such analyses. The ERG's main concern with the CS was that not enough was done to explore appropriate methods for estimating PFS and OS. The ERG considers that if the company had referred to the DSU TSD 14 document, used the recommended Survival Model Selection Process Algorithm and completed the Survival Model Selection for Economic Evaluations Process (SMEEP) chart when preparing the CS, that the company would have identified that their initial choice of modelling was inappropriate for the data being used and then other methods (such as a parametric NMA and FP-based NMA) could have been explored more thoroughly.[134] The ERG raised these issues during the clarification stage, and appreciates the company had limited time implement more appropriate methods. The ERG received the company's revised economic model using the FP-based NMA two weeks before the ERG report was due to be submitted to NICE.

Despite the limited time to review the model, the ERG discovered a fundamental flaw with the survival calculation the company used to generate the PFS and OS curves based on the parameters generated by the selected FP-based NMA. The company's calculation estimated the within period hazard rather than calculating the cumulative hazard within a model cycle, which would produce area under the curve estimates. The incorrect calculation resulted in implausible OS curves, rendering any estimates of cost-effectiveness produced by the model to be meaningless. The ERG considers that this error could have been spotted by the company and rectified if curves produced by the model had been visually inspected.

Aside from the flaw in calculating treatment effectiveness, the ERG discovered numerous data errors, not only in the initial model submitted by the company, but with the subsequent submitted models. A particular issue was with the lack of consistency and the admitted oversight of the company with using data for the overall ITT population instead of the treatment naïve population, which was the focus of the company's analysis. Moreover, the ERG had difficulty validating the key parameter estimates generated by the company using the supplied WinBUGSs code for the FP analysis. The parameters used by the company produced OS curves that did not pass face validity or clinical validity. Notably, the relative effectiveness between pazopanib and sunitinib observed in the COMPARZ trial was not maintained and the curves produced implausibly long tails which would not be seen in clinical practice. As such the ERG implemented its own FP based NMA in the model, which produced significantly different curves that, although better reflections of the underlying data, still produced implausibly long tails. The company stated they performed a model validation that was in line with methods used in the STAs for pazopanib and sunitinib. However, given the data and calculation errors not identified by the

company during their validation process, the ERG is concerned that the clinical effectiveness analyses and the economic models submitted were not rigorously validated.

The company explored a range of first order FP-based NMAs and one second order FP-based NMA to select the best fitting curve for NMA and the subsequent extrapolation of PFS and OS for all treatments. The ERG considers that the company should have explored further second order FP-based NMAs as the nature of the second order FP-based NMA means that it has greater flexibility and so will produce better fitting curves compared with the first order. As only one second order FP-based NMA was considered (P1= -2, P2= -1), it is not definitive that this permutation would be the best fit out of all the second order FP permutations available. As such, the ERG explored a range of other second order FP-based NMAs and found two second order FP curves for PFS (P1= -3, P2= -3 and P1= -3, P2= -2.5) and one second order FP curve for OS (P1= -2, P2= -1.5) that had a better fit than the company's selection for the base case. However, the uncertainty around the PFS and OS estimates for each treatment have 95% credible intervals that are overlapping, indicating no significant difference between the treatments. Moreover, the issue of confounding seen for OS in the TIVO-1 trial, described previously should not be overlooked when interpreting the results of the analyses carried out by the ERG and the company. Any treatment effectiveness estimates produced either by the company or the ERG will be subject to a high degree of uncertainty as the company did not implement crossover adjusted data in the NMA and the ERG was unable to modify this in the exploratory analyses.

A secondary issue, but nonetheless important to highlight, is the inappropriate method for modelling subsequent therapies. The company did not take into account how second line therapy in the UK has changed with treatments newly introduced into routine clinical practice such as everolimus and nivolumab. Also, the company assumed that patients will be treated with second-line active therapy (axitinib) for the remainder of their lives, which does not reflect clinical reality and grossly overestimates post-progression costs. The company cite lack of data from the included trials in the network as the reason behind the assumptions made for the modelling. The ERG considers that the company could have gone further by enlisting clinical experts to develop realistic assumptions. While this proposed method isn't as robust as trial data, it does aid making the analysis and the results more relevant to the UK context and thus more appropriate for decision making.

7.1 Implications for research

Pazopanib and sunitinib are established in England for first-line treatment of metastatic RCC. The company propose tivozanib as an alternative to these two treatments on the basis that it has similar efficacy. The lack of direct evidence for tivozanib compared with pazopanib and sunitinib mean the evidence to support this claim is based on one or more methods for indirectly comparing treatments. The lack of direct evidence is particularly problematic when deriving comparative estimates for OS

from trials with crossover designs. If treatment switching is planned in one or both groups, exploring a range of methods to adjust for possible confounding would aid decision-making in the technology appraisal process. When this is not possible, methods that do not rely on the confounded within-study comparison, such as MAIC, may be more appropriate.

The ERG considers that no relevant evidence was submitted for tivozanib in a pretreated population, but notes an ongoing RCT that may provide evidence for patients who have failed treatment with therapies likely to be given first line in the UK. The trial, AV-951-15-303, was due to begin recruitment in June 2017.

8 REFERENCES

1. National Institute for Health and Care Excellence. Tivozanib for treating renal cell carcinoma. Final Scope.2017 24th April 2017. Available from: https://www.nice.org.uk/guidance/GID-TA10123/documents/final-scope.

2. Atkins MB, Bukowski RM, Escudier BJ, Figlin RA, Hudes GH, Kaelin WG, Jr., et al. Innovations and challenges in renal cancer: summary statement from the Third Cambridge Conference. Cancer. 2009;115(10 Suppl):2247-51.

3. Ljungberg B, Albiges L, Bensalah K, Bex A, Giles R, Hora M, et al. Renal cell carcinoma2017 24th April 2017. Available from: http://uroweb.org/guideline/renal-cell-carcinoma/.

4. Cancer Research UK. Kidney cancer. Statistics2016 24th April 2017. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/kidney-cancer/incidence.

5. National Cancer Institute. Staging. 2015.

6. Escudier B, Porta C, Schmidinger M, Rioux-Leclercq N, Bex A, Khoo V, et al. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology. 2016;27(Supplement 5):v58-v68.

7. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. Journal of Clinical Oncology. 2009;27(22):3584-90.

8. Sternberg CN, Hawkins RE, Wagstaff J, Salman P, Mardiak J, Barrios CH, et al. A randomised, double-blind phase III study of pazopanib in patients with advanced and/or metastatic renal cell carcinoma: final overall survival results and safety update. European Journal of Cancer. 2013;49(6):1287-96.

9. Motzer RJ, Hutson TE, Cella D, Reeves J, Hawkins R, Guo J, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. New England Journal of Medicine. 2013;369(8):722-31.

10. Heng DY, Xie W, Regan MM, Warren MA, Golshayan AR, Sahi C, et al. Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. Journal of Clinical Oncology. 2009;27(34):5794-9.

11. Motzer RJ, Mazumdar M, Bacik J, Berg W, Amsterdam A, Ferrara J. Survival and prognostic stratification of 670 patients with advanced renal cell carcinoma. Journal of Clinical Oncology. 1999;17(8):2530-40.

12. AVEO Pharmaceuticals I. Clinical study report protocol AV-951-09-301. A phase 3, randomized, controlled, multi center, open-label study to compare tivozanib (AV 951) to sorafenib in subjects with advanced renal cell carcinoma. 2012.

13. Mekhail TM, Abou-Jawde RM, Boumerhi G, Malhi S, Wood L, Elson P, et al. Validation and extension of the Memorial Sloan-Kettering prognostic factors model for survival in patients with previously untreated metastatic renal cell carcinoma. Journal of Clinical Oncology. 2005;23(4):832-41.

14. Karnofsky DA, Graef I, Smith HW. Studies on the mechanism of action of the nitrogen and sulfur mustards in vivo. American Journal of Pathology. 1948;24(2):275-91.

15. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. American Journal of Clinical Oncology. 1982;5(6):649-55.

16. Yang L, Li Y, Wang L, Zhang Y, Ma X, Ye Z. Preparation and adsorption performance of a novel bipolar PS-EDTA resin in aqueous phase. J Hazard Mater. 2010;180(1-3):98-105.

17. Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. Current Medical Research & Opinion. 2010;26(5):1091-6.

18. Cella D. Beyond traditional outcomes: improving quality of life in patients with renal cell carcinoma. The oncologist. 2011;16 Suppl 2:23-31.

19. Health and Social Care Information Centre. Hospital Episode Statistics, Admitted Patient Care - England, 2014-15 20152014-2015 25th April 2017. Available from: http://www.hscic.gov.uk/hesdata.

20. Hagiwara M, Hackshaw MD, Oster G. Economic burden of selected adverse events in patients aged >/=65 years with metastatic renal cell carcinoma. J Med Econ. 2013;16(11):1300-6.

21. Office of National Statistics. Cancer registration statistics, England: first release, 20152015 25th April 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/firstrelease2015#2015-cancer-registrations.

22. National Institute for Health and Care Excellence. Renal cancer overview: pathway2017 27th April 2017. Available from: https://pathways.nice.org.uk/pathways/renal-cancer.

23. National Institute for Health and Care Excellence. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma2009 27th April 2017. Available from: http://www.nice.org.uk/Guidance/TA169.

24. National Institute for Health and Care Excellence. Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma2009 27th April 2017. Available from: https://www.nice.org.uk/Guidance/TA178.

25. National Institute for Health and Care Excellence (NICE). Pazopanib for the first-line treatment of advanced renal cell carcinoma,. 2013.

26. National Institute for Health and Care Excellence. Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment2015 27th April 2017. Available from: https://www.nice.org.uk/Guidance/ta333.

27. National Institute for Health and Care Excellence. Nivolumab for previously treated advanced renal cell carcinoma2016 27th April 2017. Available from: https://www.nice.org.uk/guidance/TA417/chapter/1-Recommendations.

28. National Institute for Health and Care Excellence. Everolimus for advanced renal cell carcinoma after previous treatment2017 27th April 2017. Available from: https://www.nice.org.uk/guidance/TA432/chapter/1-Recommendations.

29. National Institute for Health and Care Excellence. Cabozantinib for treating renal cell carcinoma [ID931]2017 27th April 2017. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10075/consultation/html-content-2.

30. National Cancer Registration and Analysis Service. NHS treated cancer patients receiving major surgical resections - NCIN Data Briefing2011 27th April 2017. Available from: http://www.ncin.org.uk/publications/data_briefings/major_resection.

31. Chae EJ, Kim JK, Kim SH, Bae SJ, Cho KS. Renal cell carcinoma: analysis of postoperative recurrence patterns. Radiology. 2005;234(1):189-96.

32. Janzen NK, Kim HL, Figlin RA, Belldegrun AS. Surveillance after radical or partial nephrectomy for localized renal cell carcinoma and management of recurrent disease. Urologic Clinics of North America. 2003;30(4):843-52.

33. National Institute for Health and Care Excellence. Lenvatinib with everolimus for previously treated advanced renal cell carcinoma2017 2nd May 2017. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10125.

34. Electronic Medicines Compendium (eMC). Votrient 200 mg and 400 mg film coated tablets2016 28th April 2017. Available from: https://www.medicines.org.uk/emc/medicine/23148.

35. Electronic Medicines Compendium (eMC). Afinitor Tablets. 2016.

36. Electronic Medicines Compendium (eMC). Opdivo 10 mg/mL concentrate for solution for infusion2017 28th April 2017. Available from: https://www.medicines.org.uk/emc/medicine/30476.

37. Zhu X, Stergiopoulos K, Wu S. Risk of hypertension and renal dysfunction with an angiogenesis inhibitor sunitinib: systematic review and meta-analysis. Acta Oncologica. 2009;48(1):9-17.

38. Qi WX, Lin F, Sun YJ, Tang LN, He AN, Yao Y, et al. Incidence and risk of hypertension with pazopanib in patients with cancer: a meta-analysis. Cancer Chemotherapy and Pharmacology. 2013;71(2):431-9.

39. Y W, R K, P R, A L, Z I. Hypertension in cancer patients treated with anti-angiogenic based regimens. Cardio-Oncology [Internet]. 2015 28th April 2017. Available from: https://cardiooncologyjournal.biomedcentral.com/articles/10.1186/s40959-015-0009-4.

40. KJ K, R D, RB A. Chapter 7. Pharmacogenomics. 2012. PLOS: Computational Biology. Available from: http://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1002817.

41. Motzer RJ, Nosov D, Eisen T, Bondarenko I, Lesovoy V, Lipatov O, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. Journal of Clinical Oncology. 2013;31(30):3791-9.

42. Office for National Statistics (ONS). Office for National Statistics, Cancer survival by stage at diagnosis for England. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalbystageatdiagnosisforenglandexperimentalstatistics/adultsdiagnosed20122013and2014andfollowedupto2015. (accessed on 06.12.2016). 2016.

43. National Cancer Registration and Analysis Service. Cancer breakdown by stage 201425th April 2017. Available from: http://www.ncin.org.uk/view?rid=3006.

44. Cohen HT, McGovern FJ. Renal-cell carcinoma. New England Journal of Medicine. 2005;353(23):2477-90.

45. Elson PJ, Witte RS, Trump DL. Prognostic factors for survival in patients with recurrent or metastatic renal cell carcinoma. Cancer Research. 1988;48(24 Pt 1):7310-3.

46. AVEO Pharmaceuticals I. Clinical study report protocol AV-951-09-301. A phase 3, randomized, controlled, multi center, open-label study to compare tivozanib (AV 951) to sorafenib in subjects with advanced renal cell carcinoma. 2016.

47. AVEO Pharmaceuticals I. Clinical study report AV-951-07-201 A phase 2, placebo-controlled, randomized, discontinuation trial of tivozanib (AV-951) in patients with renal cell carcinoma. 2011.

48. AVEO Pharmaceuticals I. Clinical study report Protocol AV-951-10-202. A Phase 2 and Biomarker Study of Tivozanib in Subjects With Advanced Renal Cell Carcinoma. 2015.

49. Nosov DA, Esteves B, Lipatov ON, Lyulko AA, Anischenko AA, Chacko RT, et al. Antitumor activity and safety of tivozanib (AV-951) in a phase II randomized discontinuation trial in patients with renal cell carcinoma. Journal of Clinical Oncology. 2012;30(14):1678-85.

50. Hutson TE, Rathmell WK, Feng B, Robinson MO, Gyuris J, Lin J, et al. Phase 2 clinical evaluation of preclinically defined biomarkers for vascular endothelial growth factor tyrosine kinase inhibitor tivozanib in renal cell carcinoma. Annals of Oncology. 2014;25(Supplement 4):iv58-iv64.

51. Sternberg CN ET, Tomczak P, Strahs A, Esteves B, Berkenblit A, Motzer R, editor Tivozanib in patients treatment-naive for metastatic renal cell carcinoma: A subset analysis of the phase III TIVO-1 study [poster]. Annual Meeting of the American Society of Clinical Oncology (ASCO); May 31-June 4 2013; 2013; Chicago, Illinois.

52. Cowey CL. Profile of tivozanib and its potential for the treatment of advanced renal cell carcinoma. Drug design, development and therapy. 2013;7:519-27.

53. Bhargava P, Robinson MO. Development of second-generation VEGFR tyrosine kinase inhibitors: current status. Current Oncology Reports. 2011;13(2):103-11.

54. EUSA Pharma (UK) Limited. Draft Summary of Product Characteristics for Fotivda (tivozanib). 2017.

55. Wagstaff J, Jones R, Hawkins R, Porfiri E, Pickering L, Bahl A, et al. Treatment patterns and clinical outcomes in patients with renal cell carcinoma in the UK: Insights from the RECCORD registry. Annals of Oncology. 2016;27(1):159-65.

56. Bristol Myers Squibb Ltd. Opdivo Summary of Product Characteristics 2017 [updated 6 January 2017]. Available from: https://www.medicines.org.uk/emc/medicine/30476.

57. Novartis Pharmaceuticals UK Ltd. Afinitor Tablets Summary of Product Characteristics 2016. Available from: http://www.medicines.org.uk/emc/medicine/22281.

58. Ipsen. Cabometyx Summary of Product Characteristics 2016. Available from: http://www.medicines.org.uk/emc/medicine/32431.

59. Anderson ML, Chiswell K, Peterson ED, Tasneem A, Topping J, Califf RM. Compliance with Results Reporting at ClinicalTrials.gov. New England Journal of Medicine. 2015;372(11):1031-9.

60. Motzer RJ, Nosov D, Eisen T, Bondarenko I, Lesovoy V, Lipatov O, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial (Protocol). Journal of clinical oncology : official journal of the American Society of Clinical Oncology [Internet]. 2013. Available from: http://jco.ascopubs.org.www.socprox.net/content/suppl/2013/09/09/JCO.2012.47.4940.DC1/Protocol_JCO.2012.47.4940.pdf.

61. Armstrong AJ, Halabi S, Eisen T, Broderick S, Stadler WM, Jones RJ, et al. Everolimus versus sunitinib for patients with metastatic non-clear cell renal cell carcinoma (ASPEN): A multicentre, open-label, randomised phase 2 trial. Lancet oncology [Internet]. 2016; 17(3):[378-88 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/165/CN-01142165/frame.html.

62. Eisen T, Loembe AB, Shparyk Y, Macleod N, Jones RJ, Mazurkiewicz M, et al. A randomised, phase II study of nintedanib or sunitinib in previously untreated patients with advanced renal cell cancer: 3-year results. British journal of cancer [Internet]. 2015; 113(8):[1140-7 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/135/CN-01106135/frame.html.

63. Escudier B, Szczylik C, Hutson TE, Demkow T, Staehler M, Rolland F, et al. Randomized phase II trial of first-line treatment with sorafenib versus interferon Alfa-2a in patients with metastatic renal cell carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology [Internet]. 2009; 27(8):[1280-9 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/935/CN-00681935/frame.html.

64. Gleave ME, Elhilali M, Fradet Y, Davis I, Venner P, Saad F, et al. Interferon gamma-1b compared with placebo in metastatic renal-cell carcinoma. Canadian Urologic Oncology Group. The New England journal of medicine [Internet]. 1998; 338(18):[1265-71 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/737/CN-00149737/frame.html

http://www.nejm.org/doi/pdf/10.1056/NEJM199804303381804.

65. Hudes G, Carducci M, Tomczak P, Dutcher J, Figlin R, Kapoor A, et al. Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. New England Journal of Medicine. 2007;356(22):2271-81.

66. Hutson TE, Lesovoy V, Al-Shukri S, Stus VP, Lipatov ON, Bair AH, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. Lancet Oncology. 2013;14(13):1287-94.

67. Motzer RJ, Barrios CH, Kim TM, Falcon S, Cosgriff T, Harker WG, et al. Phase II randomized trial comparing sequential first-line everolimus and second-line sunitinib versus first-line sunitinib and second-line everolimus in patients with metastatic renal cell carcinoma. Journal of Clinical Oncology. 2014;32(25):2765-72.

68. Negrier S, Escudier B, Lasset C, Douillard JY, Savary J, Chevreau C, et al. Recombinant human interleukin-2, recombinant human interferon alfa-2a, or both in metastatic renal-cell carcinoma. Groupe Français d'Immunothérapie. New England Journal of Medicine [Internet]. 1998; 338(18):[1272-8 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/738/CN-00149738/frame.html

http://www.nejm.org/doi/pdf/10.1056/NEJM199804303381805.

69. Negrier S, Perol D, Ravaud A, Chevreau C, Bay JO, Delva R, et al. Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. Cancer. 2007;110(11):2468-77.

70. Tannir NM, Jonasch E, Albiges L, Altinmakas E, Ng CS, Matin SF, et al. Everolimus Versus Sunitinib Prospective Evaluation in Metastatic Non-Clear Cell Renal Cell Carcinoma (ESPN): A Randomized Multicenter Phase 2 Trial. European Urology. 2016;69(5):866-74.

71. Tomita Y, Naito S, Sassa N, Takahashi A, Kondo T, Koie T, et al. Sunitinib versus sorafenib as first-line therapy for patients with metastatic renal cell carcinoma with favorable or intermediate MSKCC risk factors: A multicenter randomized trial, CROSS-J-RCC. Journal of Clinical Oncology. 2014;32(4).

72. Eichelberg C, Vervenne WL, De Santis M, Fischer von Weikersthal L, Goebell PJ, Lerchenmuller C, et al. SWITCH: A Randomised, Sequential, Open-label Study to Evaluate the

Efficacy and Safety of Sorafenib-sunitinib Versus Sunitinib-sorafenib in the Treatment of Metastatic Renal Cell Cancer. European Urology. 2015;68(5):837-47.

73. Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. New England Journal of Medicine. 2007;356(2):125-34.

74. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, et al. Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. Journal of Clinical Oncology. 2010;28(6):1061-8.

75. Mulders P. Vascular endothelial growth factor and mTOR pathways in renal cell carcinoma: differences and synergies of two targeted mechanisms. BJU International. 2009;104(11):1585-9.

76. Yang JC, Haworth L, Sherry RM, Hwu P, Schwartzentruber DJ, Topalian SL, et al. A randomized trial of bevacizumab, an anti-vascular endothelial growth factor antibody, for metastatic renal cancer. New England Journal of Medicine. 2003;349(5):427-34.

77. Clark JI, Atkins MB, Urba WJ, Creech S, Figlin RA, Dutcher JP, et al. Adjuvant high-dose bolus interleukin-2 for patients with high-risk renal cell carcinoma: a cytokine working group randomized trial. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2003;21(16):3133-40.

78. Dexeus FH, Logothetis CJ, Sella A, Finn L. Interferon alternating with chemotherapy for patients with metastatic renal cell carcinoma. American Journal of Clinical Oncology: Cancer Clinical Trials. 1989;12(4):350-4.

79. Motzer RJ, Rakhit A, Thompson JA, Nemunaitis J, Murphy BA, Ellerhorst J, et al. Randomized multicenter phase II trial of subcutaneous recombinant human interleukin-12 versus interferon-α2a for patients with advanced renal cell carcinoma. Journal of Interferon and Cytokine Research. 2001;21(4):257-63.

80. Zhao J, Zhu Y, Zhang C, Wang X, He H, Wang H, et al. Sorafenib or sunitinib as postoperative adjuvant therapy for Chinese patients with locally advanced clear cell renal cell carcinoma at high risk for disease recurrence. Urol. 2013;31(8):1800-5.

81. Zhou A. Anlotinib versus sunitinib as first line treatment for metastatic renal cell carcinoma (mRCC): Preliminary results from a randomized phase II clinical trial. Journal of Clinical Oncology. 2016;34(Suppl):Abstract 4565.

82. Tomita Y NS, Sassa N, Takahashi A, Kondo T, Koie T et al, editor Sunitinib versus sorafenib as first-line therapy followed by sorafeniub and sunitinib for patients with metastatc renal cell carcinoma (RCC) with clear cell histology: A multicenter randomized trial, CROSS-J-RCC [poster]. 2017 Genitourinary Cancers Symposium; 2017: Journal of Clinical Oncology.

83. Therasse P AS, Eisenhauer EA, Wanders J, Kaplan RS, Rubenstein L, Verweij J Van Glabbeke M, van Oosterom AT, Christian MS, Gwyther SG. New Guidelines to Evaluate the Response to Treatment in Solid Tumors. Journal of the National Cancer Institute. 2000;92(3):205-16.

84. Latimer NR, Abrams KR. NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. ScHARR, University of Sheffield, 2014.

85. ClinicalTrials.gov. A Rollover Protocol to Allow Continued Access to Tivozanib (AV951) for Subjects Enrolled in Other TIvozanib Protocols 2015 [12 May 2017]. Available from: Available from: https://clinicaltrials.gov/ct2/show/study/NCT01369433.

86. Glaxo Smith Kline. Pazopanib (Votrient®) for the first-line treatment of patients with advanced renal cell carcinoma (RCC). Manufacturer's submission 2010. Available from: https://www.nice.org.uk/guidance/ta215/history.

87. Cella D, Ivanescu C, Esteves B, Krivoshik A, Motzer R. Treatment benefit of tivozanib hydrochloride vs sorafenib on health-related quality of life among patients with advanced/metastatic renal cell carcinoma (mRCC): TIVO-1 study results. 2017.

88. Cella DF TD, Gray G, Sarafian B, Linn E, Bonomi A, Silberman M, Yellen SB, Winicour P, Brannon J, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. Journal of Clinical Oncology. 1993;11(3):570-9.

89. Cella D, Yount S, Brucker PS, et al. Development and validation of a scale to measure disease-related symptoms of kidney cancer. Value in Health. 2007;10(4):285-93.

90. Dolan P. Modeling valuations for EuroQol health states. Medical Care. 1997;35(11):1095-108.

91. ClinicalTrials.gov. Comparison of Sequential Therapies With Sunitinib and Sorafenib in Advanced Renal Cell Carcinoma (CROSS-J-RCC) 2011 [7th June 2017]. Available from: https://clinicaltrials.gov/ct2/show/NCT01481870.

92. Ouwens MJ, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. Research Synthesis Methods. 2010;1(3-4):258-71.

93. Jansen JP. Network meta-analysis of survival data with fractional polynomials. BMC Med Res Methodol. 2011;11:61.

94. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9.

95. Gelman A RD. Inference from iterative simulation using multiple sequences. Statistical Science. 1992;7:457-72.

96. Dias S, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011 last updated April 2014. Report No.

97. Kilonzo M, Hislop J, Elders A, Fraser C, Bissett D, McClinton S, et al. Pazopanib for the first-line treatment of patients with advanced and/or metastatic renal cell carcinoma : a NICE single technology appraisal. Pharmacoeconomics. 2013;31(1):15-24.

98. Hoyle M, Green C, Thompson-Coon J, Liu Z, Welch K, Moxham T, et al. Cost-effectiveness of sorafenib for second-line treatment of advanced renal cell carcinoma. Value in Health. 2010;13(1):55-60.

99. Hoyle M, Green C, Thompson-Coon J, Liu Z, Welch K, Moxham T, et al. Cost-effectiveness of temsirolimus for first line treatment of advanced renal cell carcinoma. Value in Health. 2010;13(1):61-8.

100. Thompson Coon J, Hoyle M, Green C, Liu Z, Welch K, Moxham T, et al. Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation. Health Technol Assess. 2010;14(2):1-184, iii-iv.

101. Drummond MF, Jefferson TO. Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. Bmj. 1996;313(7052):275-83.

102. Health Information Research Unit (HIRU) McMaster's University. [cited 2017 26th of May]. Available from: http://hiru.mcmaster.ca/hiru/HIRU_Hedges_home.aspx.

103. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess. 2004;8(36):iii-iv, ix-xi, 1-158.

104. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013 - 5. The Reference Case 2013 [cited 2017 4th April]. Available from: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case.

105. Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Oudard S, et al. Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology [Internet]. 2009; 27(22):[3584-90 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/258/CN-00697258/frame.html.

106. Motzer RJ, Escudier B, Tomczak P, Hutson TE, Michaelson MD, Negrier S, et al. Axitinib versus sorafenib as second-line treatment for advanced renal cell carcinoma: Overall survival analysis and updated results from a randomised phase 3 trial. The Lancet Oncology. 2013;14(6):552-62.

107. National Institute for Health and Care Excellence (NICE). Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma,2009 27th April 2017. Available from: https://www.nice.org.uk/Guidance/TA178.

108. Castellano D, del Muro XG, Perez-Gracia JL, Gonzalez-Larriba JL, Abrio MV, Ruiz MA, et al. Patient-reported outcomes in a phase III, randomized study of sunitinib versus interferon-{alpha} as first-line systemic therapy for patients with metastatic renal cell carcinoma in a European population. Annals of Oncology. 2009;20(11):1803-12.

109. Cella D, Bushmakin AG, Cappelleri JC, Charbonneau C, Li JZ, Kim ST, et al. Health-related quality of life (HRQOL) in metastatic renal cell carcinoma (MRCC) patients receiving sunitinib (SU) or interferon (IFN)-ALFA in a randomized phase III trial: Updated geographic analysis. Annals of Oncology. 2008;Conference:34th Congress of the European Society for Medical Oncology (ESMO) Stockholm Sweden. Conference Start: 20080912 Conference End: 6. Conference Publication: (var.pagings). 19 (S8) (pp viii189).

110. Cella D, Michaelson MD, Bushmakin AG, Cappelleri JC, Charbonneau C, Kim ST, et al. Health-related quality of life in patients with metastatic renal cell carcinoma treated with sunitinib vs interferon-alpha in a phase III trial: final results and geographical analysis. British journal of cancer [Internet]. 2010; 102(4):[658-64 pp.]. Available from: http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/811/CN-00729811/frame.html.

111. Cella D, Pickard AS, Duh MS, Guerin A, Mishagina N, Antras L, et al. Health-related quality of life in patients with advanced renal cell carcinoma receiving pazopanib or placebo in a randomised phase III trial. European Journal of Cancer. 2012;48(3):311-23.

112. Cohen L, Cole SW, Sood AK, Prinsloo S, Kirschbaum C, Arevalo JM, et al. Depressive symptoms and cortisol rhythmicity predict survival in patients with renal cell carcinoma: role of inflammatory signaling. PLoS One. 2012;7(8):e42324.

113. DeGroot U, Redekop W, Oosterwijk E, Kiemeney LC. Patient and disease characteristics are important determinants of health-related quality of life of patients with metastatic renal cell carcinoma results from a population-based registry. Value in Health. 2014;17(7):A649.

114. Escudier B, Roigas J, Gillessen S, Harmenberg U, Srinivas S, Mulder SF, et al. Phase II study of sunitinib administered in a continuous once-daily dosing regimen in patients with cytokine-refractory metastatic renal cell carcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2009;27(25):4068-75.

115. Goebell PJ, Münch A, Müller L, Hurtz HJ, Koska M, Busies S, et al. A cross-sectional investigation of fatigue in advanced renal cell carcinoma treatment: Results from the FAMOUS study. Urologic Oncology: Seminars and Original Investigations. 2014;32(3):362-70.

116. Hagiwara M. Utility values among patients (pts) with metastatic renal cell carcinoma (mRCC) receiving first-line treatment with pazopanib (PZ) and sunitinib (SU). Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2016;34(Suppl):Abstract e21068.

117. Hutson TE, Lesovoy V, Al-Shukri S, Stus VP, Lipatov ON, Bair AH, et al. Axitinib versus sorafenib as first-line therapy in patients with metastatic renal-cell carcinoma: a randomised open-label phase 3 trial. The Lancet Oncology. 2013;14(13):1287-94.

118. Litwin MS, Fine JT, Dorey F, Figlin RA, Belldegrun AS. Health related quality of life outcomes in patients treated for metastatic kidney cancer: a pilot study. Journal of Urology. 1997;157(5):1608-12.

119. Yang S, De Souza P, Alemao E, Purvis J. Quality of life in patients with advanced renal cell carcinoma treated with temsirolimus or interferon-α. British journal of cancer. 2010;102(10):1456-60.

120. Zbrozek AS, Hudes G, Levy D, Strahs A, Berkenblit A, DeMarinis R, et al. Q-TWiST analysis of patients receiving temsirolimus or interferon alpha for treatment of advanced renal cell carcinoma. Pharmacoeconomics. 2010;28(7):577-84.

121. Hill A, Gotham D, Fortunak J, Meldrum J, Erbacher I, Martin M, et al. Target prices for mass production of tyrosine kinase inhibitors for global cancer treatment. BMJ Open. 2016;6(1).

122. James N, Pascoe J, Zachariah A, Ray D, Oldroyd A, Parry H, et al. Effect of the UK postcode lottery on survival of patients with metastatic renal cancer: an audit of outcomes in patients with metastatic renal cancer suitable for treatment with tyrosine kinase inhibitors. Clin Oncol (R Coll Radiol). 2009;21(8):610-6.

123. Mickisch G, Gore M, Escudier B, Procopio G, Walzer S, Nuijten M. Costs of managing adverse events in the treatment of first-line metastatic renal cell carcinoma: bevacizumab in combination with interferon-alpha2a compared with sunitinib. British journal of cancer. 2010;102(1):80-6.

124. Hansen RN, Hackshaw MD, Nagar SP, Arondekar B, Deen KC, Sullivan SD, et al. Health care costs among renal cancer patients using pazopanib and sunitinib. Journal of Managed Care and Specialty Pharmacy. 2015;21(1):37-44.

125. British Medical Association and Royal Pharmaceutical Society of Great Britain. British National Formulary, Issue 72. London: BMJ Group and RPS Publishing.; September 2016.

126. Department of Health. Reference Cost Collection: National Schedule of Reference Costs - Year 2015-16 - NHS trust and NHS foundation trusts. Available at https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016. 2016.

127. Curtis L, Burns A. Unit Costs of Health and Social Care 2016. Available at http://www.pssru.ac.uk/project-pages/unit-costs/2016/index.php 2017.

128. National Institute for Health and Care Excellence (NICE). NICE technology appraisal guidance TA333. Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment. February 2015. Available at: https://www.nice.org.uk/guidance/ta333. (Accessed on 01.12.2016). 2015.

129. National Institute for Health and Care Excellence (NICE). Single Technology Appraisal: Cabozantinib for previously treated advanced renal cell carcinoma [ID931] - Committee Papers. Available from: https://www.nice.org.uk/guidance/GID-TA10075/documents/committee-papers. (Accessed on: 07.03.17). 2017.

130. Motzer RJ, Escudier B, McDermott DF, George S, Hammers HJ, Srinivas S, et al. Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. New England Journal of Medicine. 2015;373:1803-13.

131. National Institute for Health and Care Excellence (NICE). NICE technology appraisal guidance TA417. Nivolumab for previously treated advanced renal cell carcinoma. Available from: https://www.nice.org.uk/guidance/ta417. (Accessed on 06.12.2016). 2016.

132. Department of Health. National Schedule of Reference Costs: The Main Schedule 2015-2016 [cited 2017 5th April]. Available from: https://www.gov.uk/government/publications/nhs-reference-costs-2015-to-2016.

133. Motzer RJ, Hutson TE, Tomczak P, Michaelson D, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. New England Journal of Medicine. 2007;356(2):115-24.

134. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. ScHARR, University of Sheffield, 2011.

9 APPENDICES

9.1 Study designs and participant flow

Figure 34. Key dates for TIVO-1 and the extension study

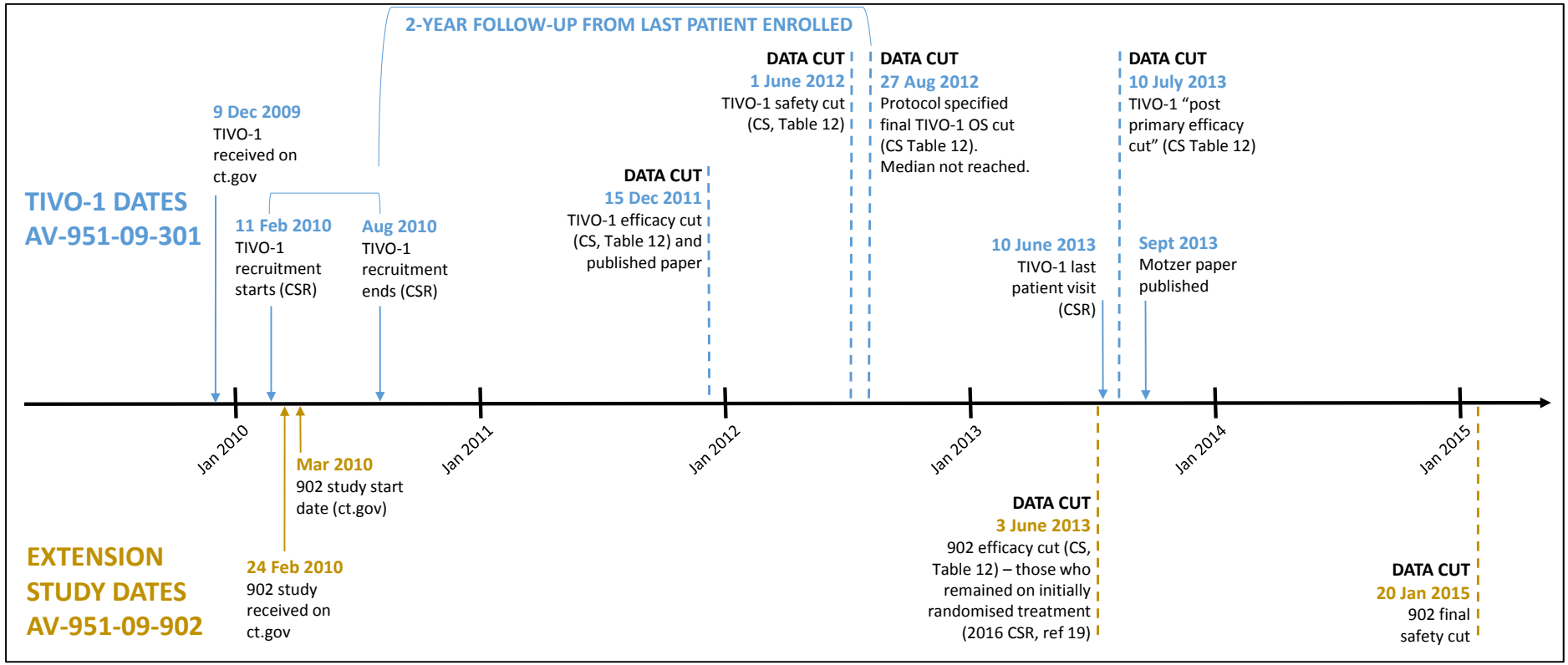


Figure 35. ERG participant flow diagram for TIVO-1 and the extension study (compiled from CS Figures 2 and 3, and final CSR Figure 16)

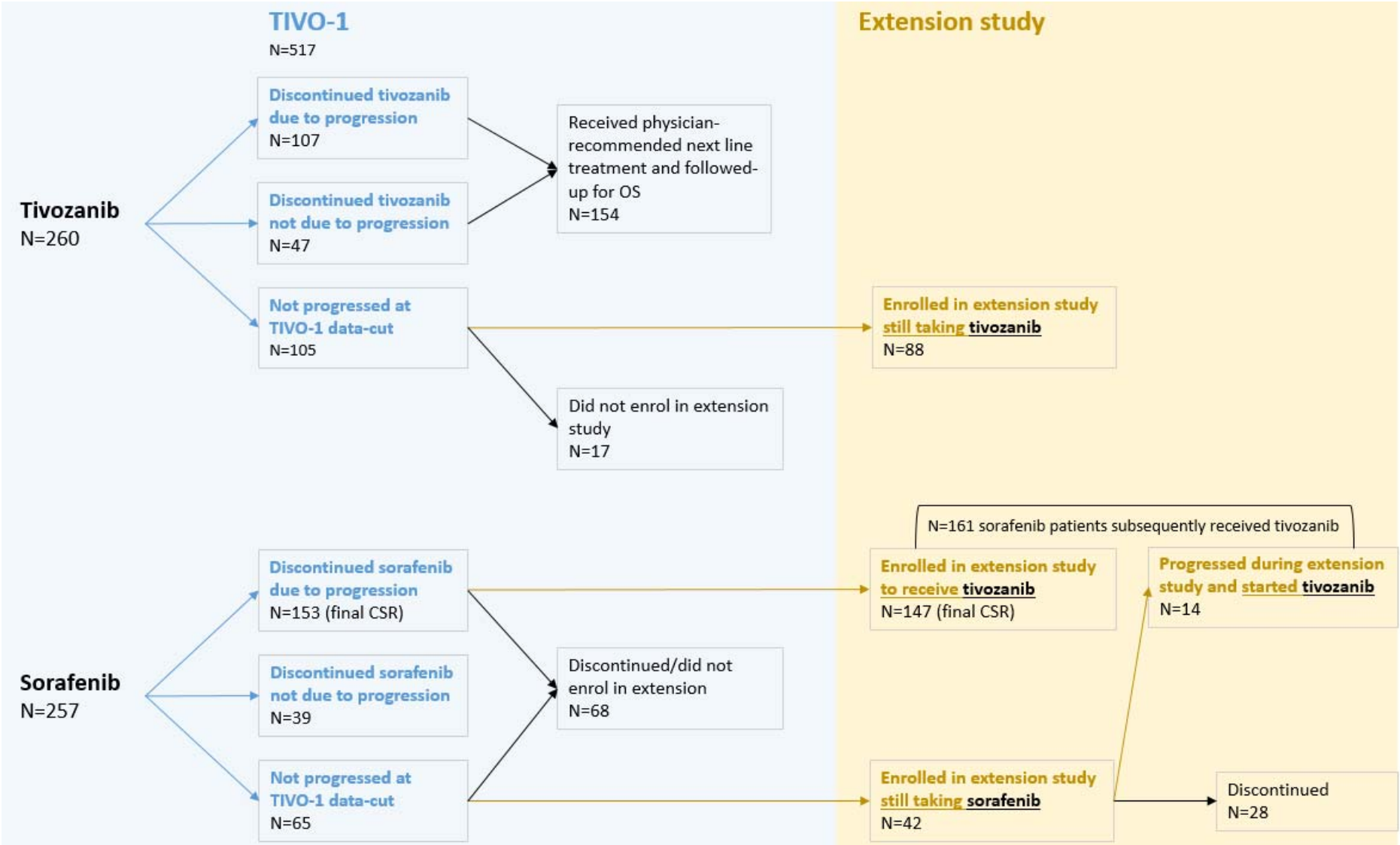


Figure 36. Design of TIVO-1 (AV-951-09-301) and the extension study (AV-951-09-902) (reproduced from CS, Figure 2, pg. 56)

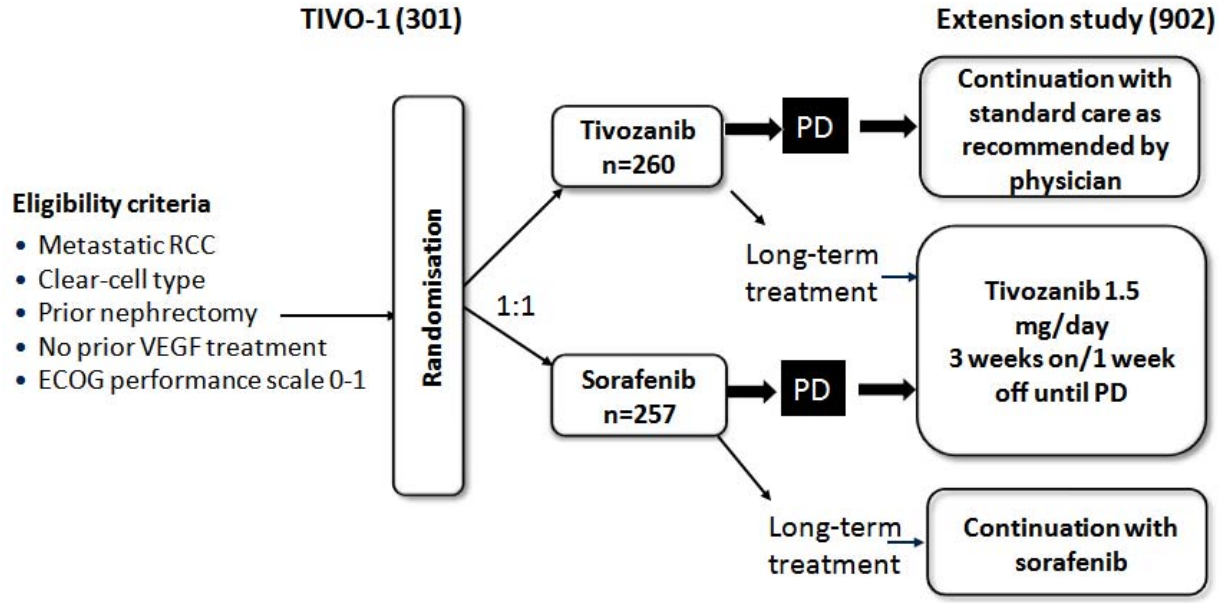


Figure 37. Design of the discontinuation study (reproduced from CS appendices Figure 3:A)

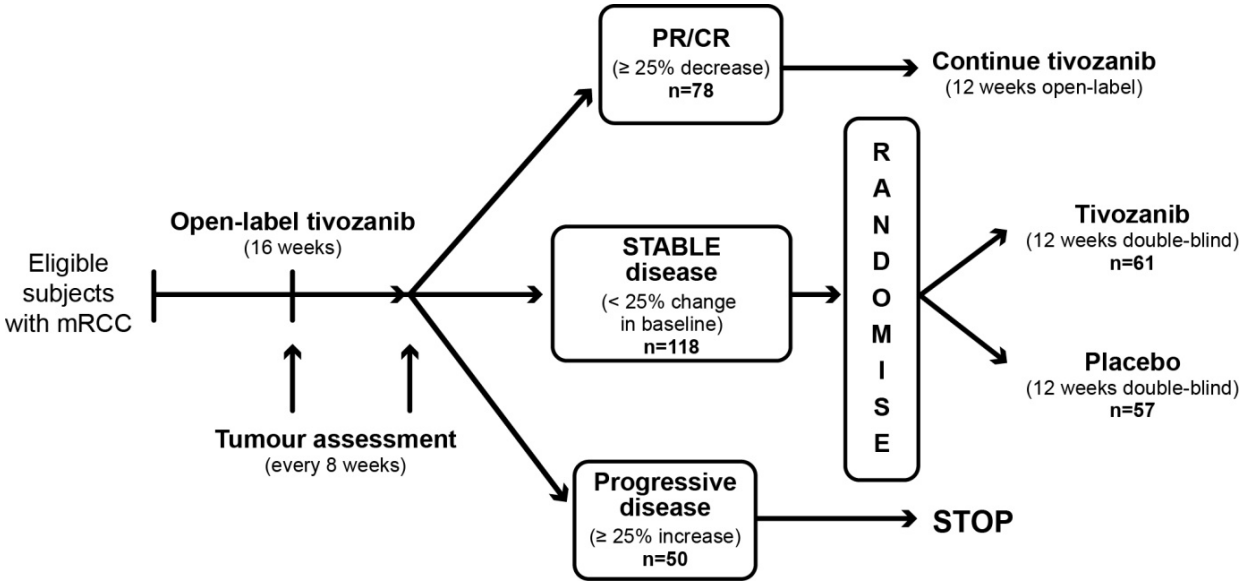
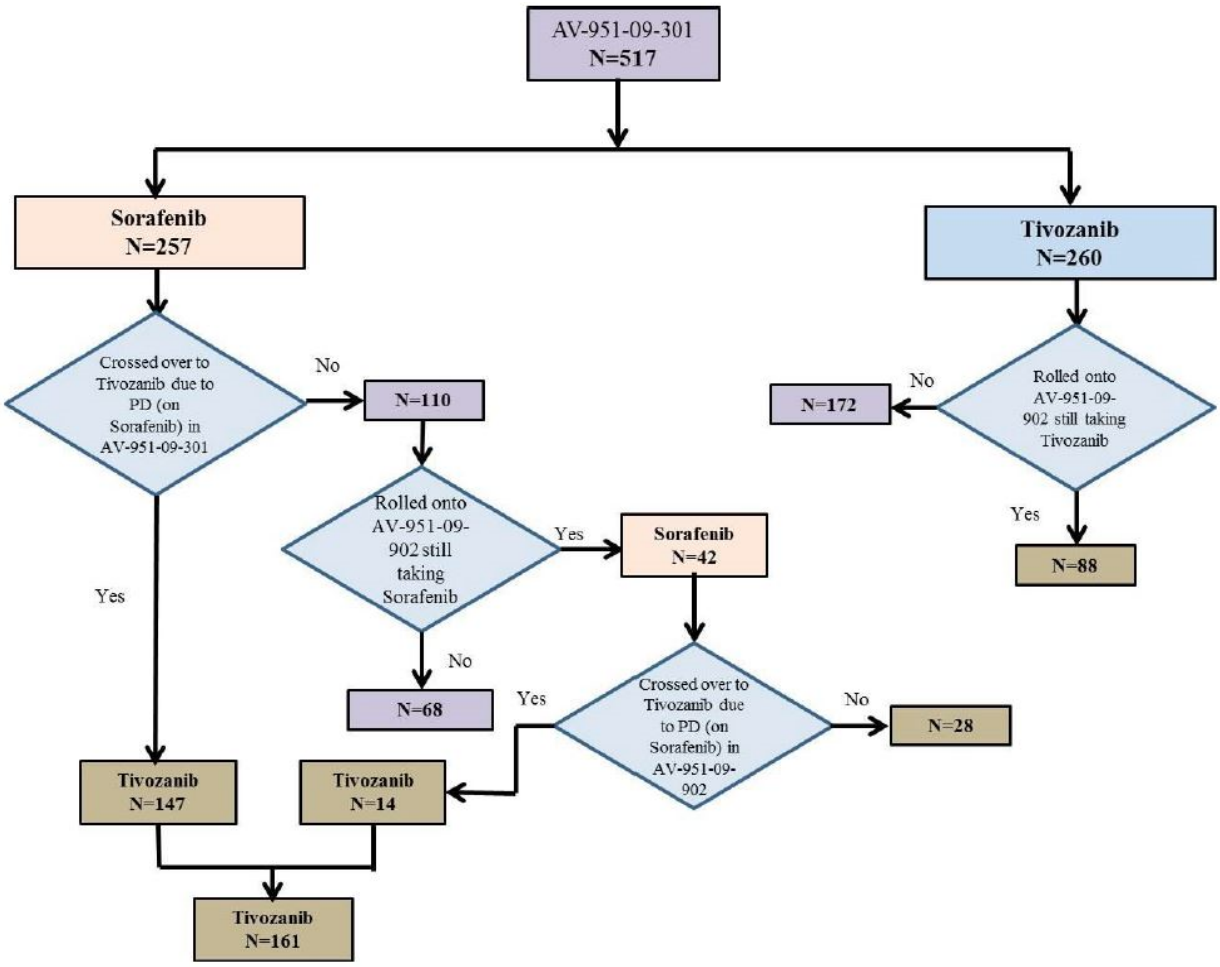


Figure 38. Participant flow diagram presented in the final CSR



9.2 Baseline characteristics

Table 89. Baseline characteristics of the Phase II discontinuation study population (reproduced from CS appendices, Table 3:A)

	Entire treated population (n=272)	
Characteristic	**No. of patients**	**%**
Gender		
Male	191	70
Female	81	30
Age, years		
Median	56	
Range	26–79	
Race		
White	254	93
Asian	18	7
ECOG performance status		
0	132	49
1	140	51
Previous nephrectomy	199	73
Histology		
Clear-cell RCC	226	83
Non-clear cell RCC	46	17
No. of previous systemic treatments		
Treatment-naïve	146	54
1	116	43
≥2	10	4
Types of previous systemic treatments10		
Interferon	102	38
Interleukin-2	20	7
Vaccine	20	7
Chemotherapy	19	7
Other agents	21	8
Most common sites of metastatic disease		
Lymph nodes	184	68
Lung	184	68
Peri-nephric tissue/kidney	106	39
Liver	66	24
Adrenal	57	21
Bone	55	20
MSKCC prognostic score		
Favourable	75	28
Intermediate	164	60
Poor	28	10
Not available/unknown	5	2

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center; RCC, renal cell carcinoma

Table 90. Baseline characteristics of the Phase II biomarker study population (reproduced from CS appendices Table 3:C)

	Number (%) of patients					
Characteristic	**Clear cell**		**Non-clear cell**		**All**	
	n	%	n	%	n	%
Gender						
Male	67	74.4	14	93.3	81	77.7
Female	23	25.6	1	6.7	24	22.9
Age, years						
Median	59.5		66.0		61.0	
Range	38, 83		42, 79		38, 83	
Mean	60 (9.99)		64.7 (9.26)		60.7 (9.98)	
Race						
White	80	88.9	13	86.7	93	88.6
Black	5	5.6	1	6.7	6	5.7
Asian	2	2.2	1	6.7	3	2.9
Other	3	3.3	0	0	3	2.9
ECOG performance status						
0	67	74.4	11	73.3	78	74.3
1	23	25.6	4	26.7	27	25.7
Previous nephrectomy						
Complete	85	94.4	12	80.0	97	92.4
Partial	5	5.6	3	20	8	7.6
No. of previous systemic treatments						
Treatment naive	75	83.3	14	93.3	89	84.8
One or more treatments	15	16.7	1	6.7	16	15.2
Most common sites of metastatic disease						
Lymph nodes	40	44.4	10	66.7	50	47.6
Lung	72	80.0	5	33.3	77	73.3
Peri-nephric tissue/kidney	8	8.9	1	6.7	9	8.6
Liver	18	20.0	2	13.3	20	19.0
Adrenal	20	22.2	5	33.3	25	23.8
Bone	15	16.7	3	20.0	18	17.1
MSKCC prognostic score						
Favourable	37	41.1	4	26.7	41	39.0
Intermediate	52	57.8	11	73.3	63	60.0
Poor	1	1.1	0		1	1.0
Not available/unknown	0	0	0	0	0	0

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center; RCC, renal cell carcinoma

9.3 Quality assessment

Table 91. Quality Assessment of TIVO-1 trial by Company and ERG (adapted from CS, Table 18, pg. 67)

Questions	TIVO-1 (Motzer et al. 2013) Company Assessment	ERG Assessment
Was randomisation carried out appropriately?	**Yes**: stratified by geographic region, number of prior treatments for metastatic disease, number of metastatic sites	**Yes**: Randomisation was stratified by geographical region, number of prior treatments for metastatic disease, number of metastatic sites/ organs involves.
Was the concealment of treatment allocation adequate?	**Yes,** randomisation was performed using an IVR/IWR (information from protocol provided as an appendix to the clinical trial publication)	**Yes**: Patients were randomly assigned 1:1 using IVR/IWR system to either tivozanib and sorafenib
Were the groups similar at the outset of the study in terms of prognostic factors?	**Yes**, baseline characteristics were well balanced, except for ECOG	**Unclear**. Small imbalance between groups for: 'Most common metastases sites', 'Organs involved', ECOG, MSKCC scores.
Were the care providers, participants and outcome assessors blind to treatment allocation?	**No**: open label, independent radiological assessors of progression were blinded	**Unclear**. This was an open label trial, patients and investigators were aware of treatment allocation. Investigators reviewed PD and were confirmed by IRR, which formed the primary analysis.
Were there any unexpected imbalances in drop-outs between groups?	**No**, CONSORT diagram shows discontinuations were well balanced other than due to disease progression	**No**. the CONSORT diagram there was a fairly equal balance of discontinuations between both treatment groups except for discontinuation due to progression where sorafenib had a higher proportion (n= 153) compared to tivozanib (n=107).
Is there any evidence to suggest that the authors measured more outcomes than they reported?	**No**, all stated outcomes are reported	**No**. all outcomes stated in methods reported (PFS, OS, ORR, safety and HRQoL).
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	**Yes**; ITT analysis included all randomised patients, safety analysis included all patients who received one or more doses	**Unclear**. ITT analysis was used for all randomised patients for efficacy. For PFS this was appropriate. However, for OS this was not appropriate due to imbalances in subsequent therapies. Also, crossover adjustments for OS data were not used. Safety analysis included patients that had received one or more doses of treatment.

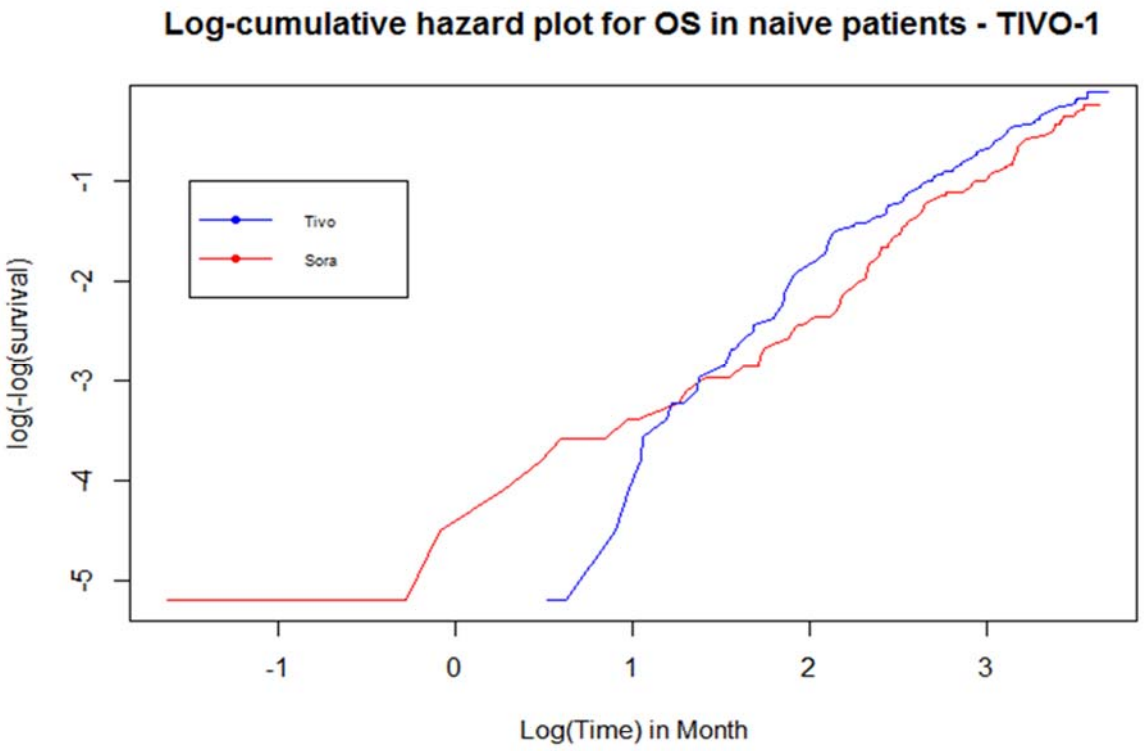
Abbreviation: CONSORT, Consolidated Standard of Reporting trials; ECOG: Eastern Cooperative Oncology Group; ERG, evidence review group; HRQoL, Health related quality of life; ITT: Intention to treat; IVR/IWR: Interactive Voice Response/Interactive Web Response; MSKCC, Memorial Sloan Kettering Cancer Center; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; OS, overall survival

Table 92. Quality assessment of comparator studies that populated the NMA (adapted from CS, Table 27, pg. 90)

Trial acronym/ reference	Randomisation appropriate	Treatment concealment adequate	Baseline comparability adequate	Researcher blinding adequate	Dropout imbalances	Outcome reporting selective	Intention to treat	Overall risk of bias
ARCC[65]	Unclear	Unclear	Yes	No	No	No	Yes	Moderate
ASPEN[61]	Yes	Yes	Yes	No	No	No	Yes	Low
COMPARZ[9]	Yes	Unclear	Yes	No	No	No	Yes	Low
CROSS-J-RCC[82]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	No	High
Eisen 2015[62]	Yes	Yes	Yes	No	No	No	Yes	Low
Escudier 2009[63]	Yes	Unclear	Yes	No	No	No	Yes	Low
ESPN[70]	Yes	Unclear	Yes	Unclear	No	No	No	Moderate
Gleave 1998[64]	Yes	Unclear	Yes	Unclear	No	No	No	Moderate
Hutson 2013[66]	Yes	Yes	Yes	No	No	No	Yes	Low
Motzer 2009[7]	Yes	Yes	Yes	Yes	No	No	Yes	Low
Mulders 2012[75]	Yes	Yes	Yes	Yes	No	No	Yes	Low
Negrier 1998[68]	Yes	Yes	Yes	Yes	No	No	Yes	Low
PERCY Quattro[69]	Yes	Yes	Yes	No	No	No	Yes	Low
RECORD-3[67]	Yes	Unclear	Yes	No	No	No	Yes	Low
Sternberg 2010[74]	Yes	Unclear	Yes	Yes	No	No	Yes	Low
SWITCH[72]	Yes	Yes	Yes	No	No	No	Yes	Low
TARGET[73]	Yes	Unclear	Yes	Yes	No	No	Yes	Low
TIVO-1[41]	Yes	Yes	Yes	Yes	No	No	Yes	Low
Yang 2003[76]	Yes	Unclear	Yes	Yes	No	No	Yes	Low

9.4 Proportional hazards tests for OS and PFS in the TIVO-1 treatment-naïve population

Figure 39. Log-cumulative hazards plots for OS and PFS in the TIVO-1 treatment-naive population (from the company's clarification responses)



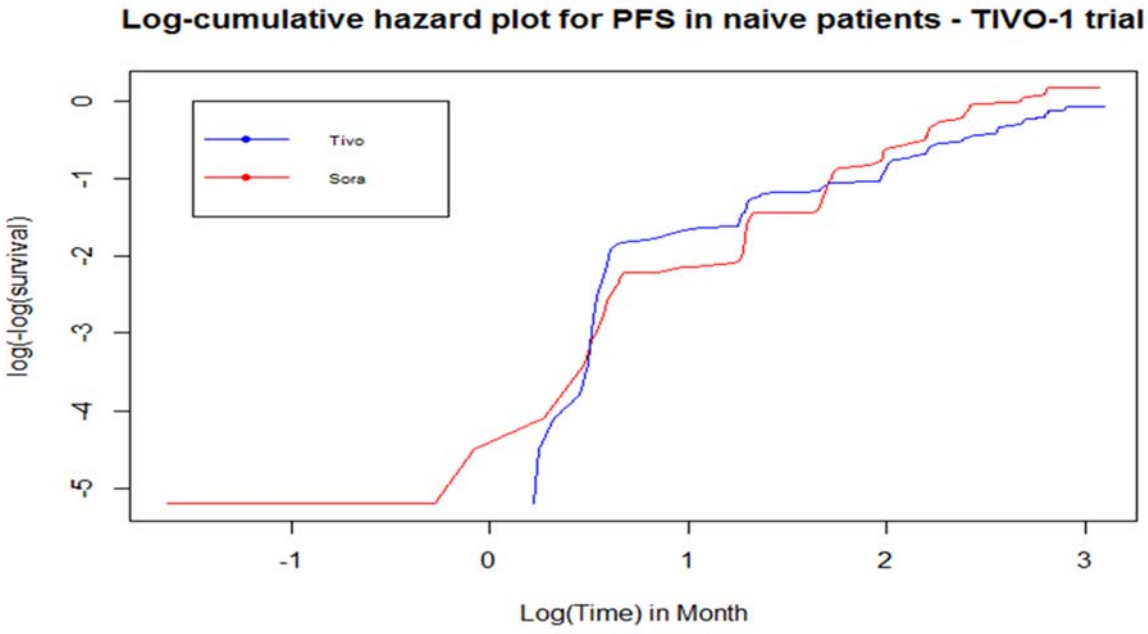


Figure 40. Log(survival/(1-survival)) plot for OS in the TIVO-1 treatment-naive population (from the company's clarification responses)

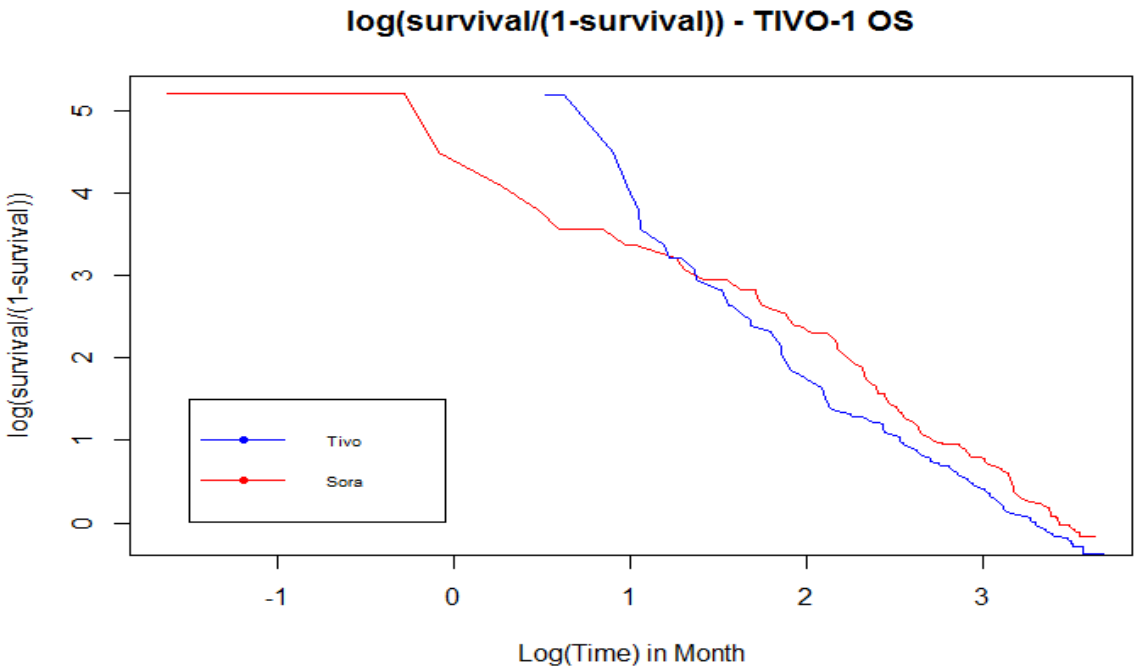


Figure 41. Log(survival/(1-survival)) plot for PFS in the TIVO-1 treatment-naive population (from the company's clarification responses)

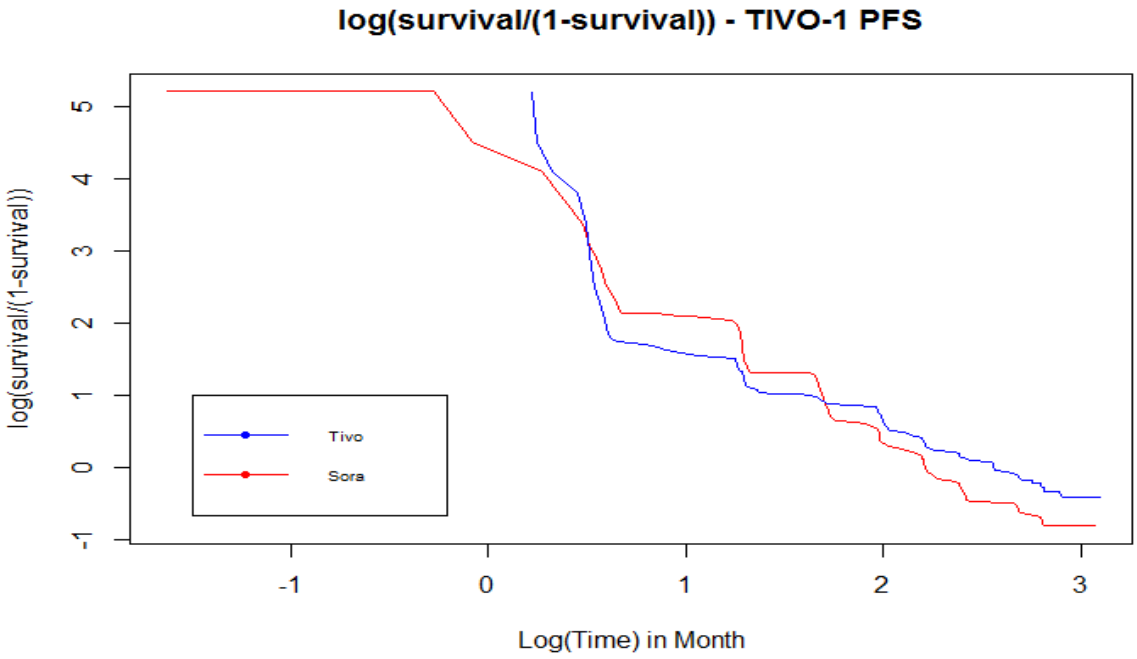


Figure 42. Log (inverse standard normal distribution function (1-survival Function)) plots versus Log (time) for OS in the TIVO-1 treatment-naive population (from the company's clarification responses)

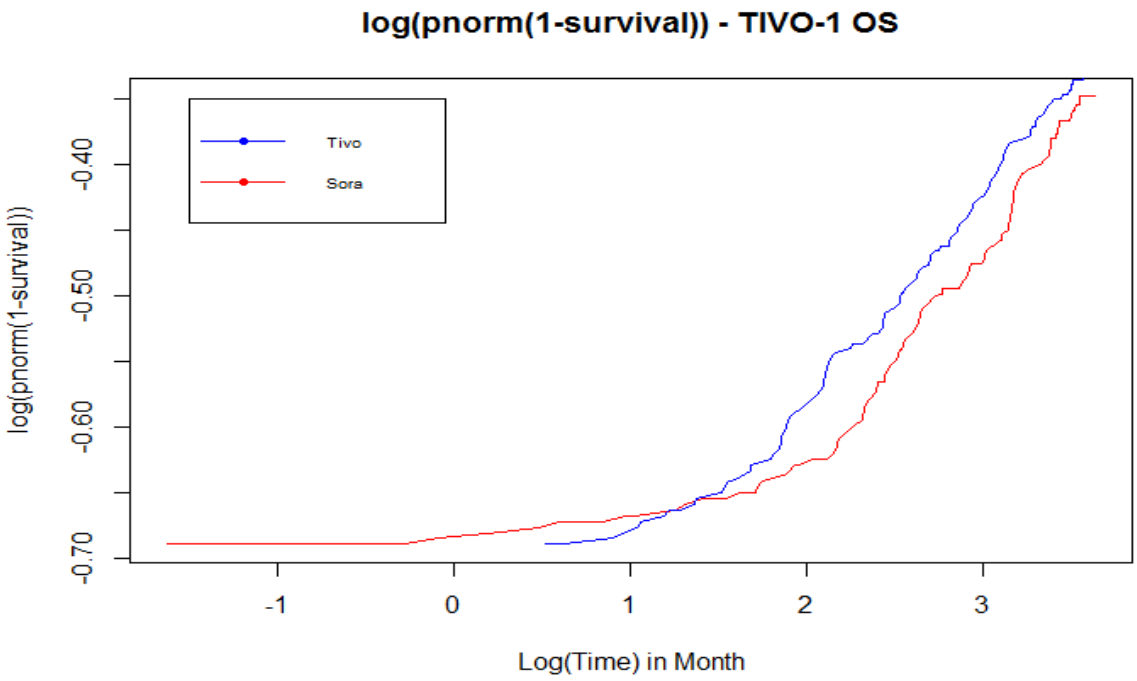
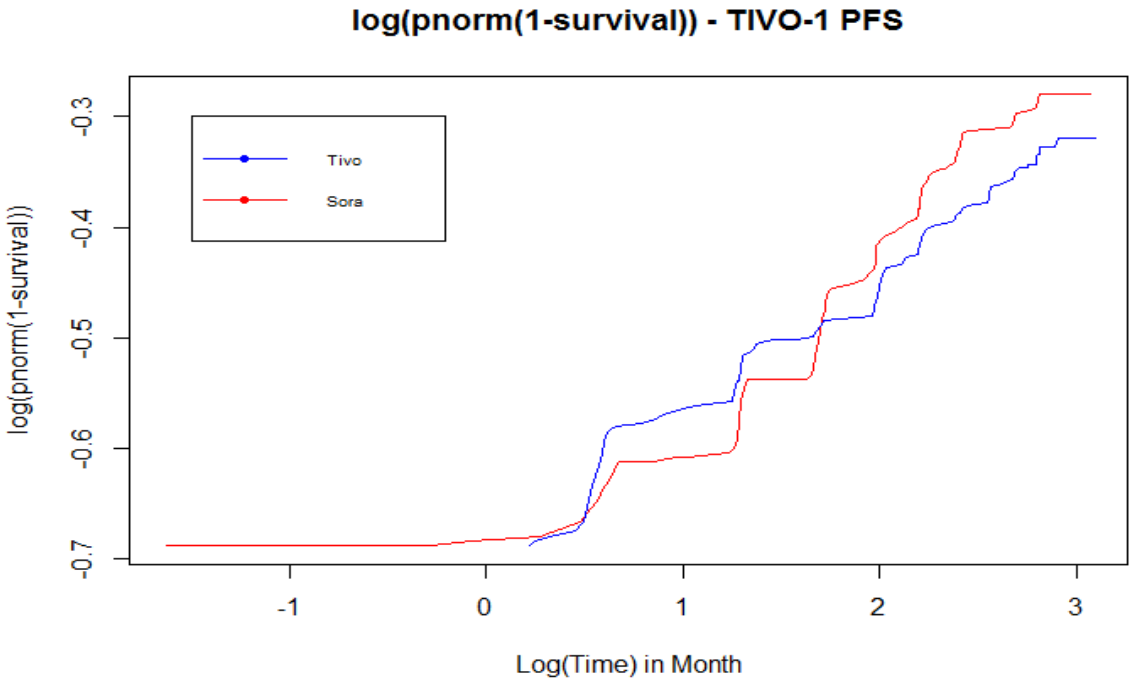


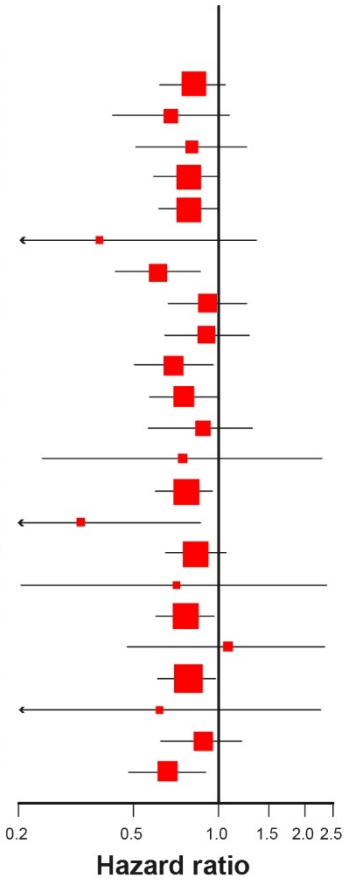
Figure 43. Log (inverse standard normal distribution function (1-survival Function)) plots versus Log (time) for PFS in the TIVO-1 treatment-naive population (from the company's clarification responses)



9.5 TIVO-1 subgroup analyses for PFS

Figure 44. Forest plot subgroup HR (95% CI) for PFS (reproduced from CS, Figure 10, pg. 75)

Subgroup	Tivozanib Event/N	Sorafenib Event/N	HR
<65 years	119/195	131/193	0.818
≥65 years	34/65	37/64	0.686
Female	40/75	42/68	0.805
Male	113/185	126/189	0.782
White	146/249	161/249	0.791
Non-white	7/11	7/8	0.384
ECOG status 0	57/116	92/139	0.617
ECOG status 1	96/144	76/118	0.92
<1 year since diagnosis	71/109	71/105	0.911
≥1 year since diagnosis	73/137	84/137	0.698
No prior systemic therapy for met disease	104/181	118/181	0.756
1 prior systemic therapy for met disease	48/78	50/76	0.877
1 metastatic site	5/16	8/17	0.753
≥2 metastatic sites	148/244	160/240	0.772
North America/Western Europe	8/22	11/18	0.335
Central/Eastern Europe	140/229	149/228	0.836
Rest of World	5/9	8/11	0.706
SBP at Baseline ≤140	143/243	151/233	0.772
SBP at Baseline >140	10/17	17/24	1.067
DBP at Baseline ≤90	150/254	157/238	0.785
DBP at Baseline >90	3/6	11/19	0.627
MSKCC Intermediate	79/118	70/101	0.879
MSKCC Favourable	72/140	98/155	0.67



9.6 Goodness of fit statistics for TIVO-1 trial

Table 93 and Table 94 present the Akaike's information criterion (AIC) statistics for both the tivozanib arm and sorafenib arm of the TIVO-1 trial obtained from the company's response to clarification questions. Highlighted cells indicate the distributions with the lowest AIC for each outcome.

Table 93. AIC statistics for tivozanib arm of TIVO-1 trial (table 29, company's response to clarification questions)

Distributions	AIC - PFS	AIC - OS
Exponential	837.65	916.74
Weibull	839.6	915.07
Gompertz	836.18	918.6
Log-logistic	832.1	909.23
Log-normal	824.75	904.46

Abbreviations in table:AIC, Akaike's information criterion; PFS, progression-free survival; OS, overall survival.

Table 94. AIC statistics for sorafenib arm of TIVO-1 trial (table 30, company's response to clarification questions)

Distributions	AIC - PFS	AIC - OS
Exponential	891.78	860.46
Weibull	890.14	857.2847
Gompertz	893.7	859.19
Log-logistic	877.7	857.2883
Log-normal	877.43	864.49

Abbreviations in table:AIC, Akaike's information criterion; PFS, progression-free survival; OS, overall survival.

Tivozanib for treating renal cell carcinoma [ID591]

STA REPORT ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 16/56/14

BMJ Technology Assessment Group

This document contains errata for the ERG report in response to the company's factual inaccuracy check.

The table below lists the pages to be replaced in the original document and the nature of the changes.

Page number	Change
1	Wording added to clarify why comparative estimates of quality of life could not be presented in the company submission.
30	Acquisition cost and average cost of a course of treatment updated in Table 6.
34	Sorafenib changed to tivozanib.
65	Safety paragraph amended to distinguish between contraindications and cautions, as per the final summary of product characteristics.
105	Edited sentence on Excel calculations in ERG critique paragraph.
151	Table 79 amended.
156 - 157	Table 82 and 83 amended.
162	Table 86 and 87 amended.

1 SUMMARY

1.1 Critique of the decision problem in the company's submission

The company (Fotivda®; EUSA Pharma Ltd) submitted to the National Institute for Health and Care Excellence (NICE) clinical and economic evidence in support of the effectiveness of tivozanib in the treatment of renal cell carcinoma (RCC).

At the time of writing this report, marketing authorisation had not been granted for the use of tivozanib in RCC and the Committee for Medicinal Products for Human Use (CHMP) had not yet issued a positive opinion.

The clinical evidence presented in the company submission (CS) was based on the randomised controlled trial (RCT), TIVO-1, and its extension study (AV-951-09-902). The study recruited 517 patients with metastatic or recurrent RCC with a clear cell component, good performance status, and prior nephrectomy; 70% were treatment naïve and 30% had received one prior systemic therapy for metastatic RCC. The Evidence Review Group (ERG) agrees with the company's proposed positioning of tivozanib as a first-line treatment for people with recurrent or metastatic RCC, and considers those who were treatment-naïve in TIVO-1 relevant to the population outlined in the NICE final scope.

The final scope issued by NICE also indicated that people who had received prior treatment for metastatic RCC are of interest to the decision problem, but the scope did not specify type of prior therapy. In TIVO-1, those who were not treatment naive had received predominantly cytokines before being treated with tivozanib; this is in line with the proposed marketing authorisation of tivozanib, which outlines an eligible population for tivozanib as those who failed prior treatment with interferon-alpha (IFN-α) or interleukin-2 (IL-2). The ERG believes no relevant evidence was submitted for a pretreated population because cytokines, the most common prior treatment in TIVO-1, have been replaced as first-line treatment in UK clinical practice by pazopanib and sunitinib.

The ERG considers only pazopanib and sunitinib to be relevant comparators for the treatment-naïve population; the ERG's clinical experts confirm that cytokines are no longer a relevant comparator for those who are treatment naive and thus are not relevant for this decision problem.

All clinically relevant outcomes were reported in the CS, except for comparative effect estimates for health-related quality of life (HRQoL) due to a lack of comparable data in the included studies.

1.2 Summary of clinical effectiveness evidence submitted by the company

the treatment of adults with advanced RCC who are VEGFR and mTOR pathway inhibitor-naïve and are either untreated or who have failed prior therapy with IFN- or IL-2.[54]

Tivozanib is taken in four-week cycles once a day as a 1,340µg hard capsule. A four- week cycle comprises three weeks on treatment and a one week rest period. Tivozanib is also available in 840µg hard capsules for patients who require a dose reduction due to adverse effects. The draft SmPC states that this treatment schedule should be maintained if clinical benefit is observed or until unacceptable toxicity occurs. Prescribing information for tivozanib is summarised in Table 6, reproduced from the CS (Table 7, pg. 33).

The daily dose of 1.5mg (1,500µg) described in TIVO-1 is different to the dose of 1,340µg stated in the CS draft SmPC. The company states that the dose given in the TIVO-1 was the same as the proposed licensed dose, and that the discrepancy is a result of CHMP guidelines to state only the amount of active substance in the SmPC, with the difference of 160µg made up by excipients (CS footnote, page 34). The four-week cycle used in TIVO-1 is the same as that described in the draft SmPC. Protocols for dose reduction, interruption and study drug discontinuation due to adverse events in TIVO-1, and how these compare to other studies in the NMA, are discussed in Section 4.2.4.6.

Table 6. Tivozanib prescribing information and costs (adapted from CS, Table 7, pg. 33)

	Cost	**Source**
Pharmaceutical formulation	Hard capsule	Draft SmPC
Acquisition cost (excluding VAT)	[redacted]	EUSA Pharma Please note that the cost of tivozanib has not yet been confirmed and is confidential
Method of administration	Oral	Draft SmPC
Doses	1,340µg; 890µg in patients requiring dose reduction	Draft SmPC
Dosing frequency	Once daily	Draft SmPC
Average length of a course of treatment	Until disease progression or unacceptable toxicity	Draft SmPC
Average cost of a course of treatment	[redacted]	Based on cost per month x median PFS in TIVO-1(11.9 months)[41] Calculated as 13 x price
Anticipated average interval between courses of treatment	Given for 3 weeks in a 4-week cycle	Draft SmPC
Anticipated number of repeat courses of treatments	N/A	Draft SmPC
Dose adjustments	Dose adjustments may be required to manage side effects or in patients with hepatic impairment.	Draft SmPC

on tivozanib. A full description of the extension study crossover design can be found in Section 4.2.1, and the impact on the OS results is discussed in Section 4.2.4.1

PFS in the ITT population was the primary endpoint of TIVO-1, defined as the time between date of randomisation and the date of disease progression or death. Local investigators assessed magnetic resonance imagining or computed tomography scans at baseline and every 8 weeks thereafter to identify progressive disease (PD), which was then confirmed within 48 hours by a blinded independent radiology review (IRR) panel. The protocol for assigning PFS, and how this may have affected the clinical effectiveness results, is discussed in more detail in Section 4.2.4.2.

All the outcomes listed above were captured in TIVO-1 and are presented in the CS for tivozanib versus sorafenib. NMAs were conducted for all outcomes except HRQoL. TIVO-1 captured HRQoL using a kidney cancer-specific measure (Functional Assessment of Cancer Therapy Kidney Symptom Index – Disease-Related Symptoms [FKSI-DRS]), a general cancer measure (the Functional Assessment of Cancer Therapy-General [FACT-G]), and a generic measure of health status (EuroQol five Dimensions questionnaire [EQ-5D]). The FKSI-DRS is likely to give a more sensitive representation of the problems experienced by patients with RCC, whereas the generic measures allow HRQoL to be mapped for the cost-effectiveness analyses (see Section 5.4.7).

Data on response rate were captured using RECIST criteria in TIVO-1 (CS, Table 20, pg. 71), and the CS presents supplementary RECIST response data from the discontinuation study AV-951-07-201 (CS, Table 37) and the biomarker study AV-951-07-202 (CS, Section 4.11.3.2). RECIST is a set of published rules that define when the status of cancer improves, remains stable, or progresses during treatments, and can be used to reduce measurement bias in open-label studies. TIVO-1 response data include complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), and overall response rate (ORR; complete response plus partial response).

The CS describes the acronym ORR as ‘overall response rate’ in some places (CS, Table 10, pg. 52; CS, Table 20, pg. 71; CS Tables 37, 38 and 39), and as ‘objective response rate’ in others (CS, Table of abbreviations, pg. 10; CS, pg. 58; CS, Table 25, pg. 86; and CS, pg. 103). The ERG understands the ORR, despite the variation in the use of ‘overall’ or ‘objective’, to mean the sum of patients demonstrating partial and complete response (CS, Table 10, pg. 52 and the primary reference for TIVO-1[41]). In some cases, including the primary ORR data presented for TIVO-1 (CS, Table 20, pg. 70), response was confirmed by an independent radiology review panel (discussed in more detail in Section 0).

The company presents multiple analyses for treatment-emergent AEs comprising: AEs “of particular interest based on clinical opinion” (diarrhoea, nausea/vomiting, fatigue/asthenia, hypertension and

AV-951-09-301 TIVO-1	A Phase 3, Randomized, Controlled, Multi-Center, Open-Label Study to Compare Tivozanib (AV-951) to Sorafenib in Subjects with Advanced Renal Cell Carcinoma	259 (257 sorafenib)
AV-951-09-902 Extension study	An Extension Treatment Protocol for Subjects who have Participated in a Phase 3 Study of Tivozanib vs. Sorafenib in Renal Cell Carcinoma (Protocol AV-951- 09-301) – cross-over patients	161*
Total number of patients exposed to tivozanib across the studies		**835**
*Only includes patients who received sorafenib in Study AV-951- 09-301 and then crossed over into the extension study AV-951-09-902 to receive tivozanib. Patients who rolled over from Study AV-951- 09-301 and continued their study treatment (sorafenib or tivozanib) are already counted with Study AV-951-09-301. Abbreviations: RCC, renal cell carcinoma		

Contraindications outlined in the SmPC are summarised in Section 3.2. Briefly, tivozanib is contraindicated for coadministration with St John's Wort and in patients with hypersensitivity to the active substance, and should not be used in pregnancy. Tivozanib should be used with caution for patients undergoing dialysis, and those with histories of arterial thrombotic events, bleeding, QT interval prolongation or gastrointestinal perforation/fistula.[54] Tivozanib is not recommended for patients with severe hepatic impairment and for those with mild to moderate hepatic impairment, the dose should be reduced to alternate days and patients should be monitored closely.[54]

The SmPC lists the following AEs that may require dose reduction, interruption or discontinuation of tivozanib: hypertension, cardiac failure, proteinuria, bleeding, hand-foot syndrome, QT interval prolongation, gastrointestinal perforation and fistula, wound healing complications, and hypothyroidism. The ERG's clinical experts consider the safety considerations listed in the draft SmPC for tivozanib to be broadly comparable with those of other VEGFR-TKIs.

Safety data in the submission are mostly from the TIVO-1 data cut in June 2012 (data cut used for the published paper),[41] with some longer-term follow-up from a cut in October 2012, and from the final safety analysis in January 2015 (see Figure 34). Table 23 shows data compiled from the CS and final CSR[46] for TIVO-1, alongside data from the discontinuation[47, 49] and biomarker[48, 50] Phase II studies. In TIVO-1, nearly all patients in both groups experienced at least one treatment-emergent AE of any severity, and slightly fewer patients in the tivozanib group (64.1%) than the sorafenib group (70.4) experienced AEs of Grade 3 or above.[46] No effect estimates are listed for the January 2015 data cut in the final CSR, but are available for the earlier timepoint (June 2012) in the CS (Table 40). At the June 2012 data cut, patients had received tivozanib for 12 months and sorafenib for 9.5 months; these data showed that tivozanib was associated with higher rates of hypertension and dysphonia, and lower rates of diarrhoea, hand-foot syndrome, alopecia, increased AST, increased amylase, increased lipase and hypophosphataemia compared with sorafenib. Fewer patients in the tivozanib group had dose reductions and interruptions due to AEs than the sorafenib group, but more patients in the tivozanib group had fatal AEs than the sorafenib group (10.8% vs 5.8%).

The company used a life time horizon of 10 years for the model based on the parametric extrapolation of OS in the TIVO-1 study which estimated that greater than 98% of patients would be dead after 10 years.

5.4.4.1 ERG critique

The ERG considers the company's model to have an appropriate structure, capturing all relevant health states and clinically plausible transitions between health states that are largely similar to other published oncology models. The one-week cycle length used in the model is suitable to capture changes in the health state of patients, allowing for robust estimates of costs and benefits to be calculated for each treatment. The 10-year time horizon of the model was verified with the ERG's clinical expert who agreed that patients in this stage of their disease would not live longer than 10 years. Errors were found in the Excel calculations used in the model and are outlined in Section 6.1. A critique of the methods used to estimate proportions of patients within each health state is given in Section 5.4.5.

5.4.5 Treatment effectiveness

5.4.5.1 Overview of method selection

From the time of the initial CS, there have been several iterations of relative treatment effectiveness for tivozanib, sunitinib and pazopanib estimated by the company. The CS presented relative treatment effectiveness estimated using hazard ratios for the treatment naïve population applied to baseline PFS and OS extrapolated curves for tivozanib. The tivozanib curves were estimated using Kaplan-Meier (KM) data for the overall ITT population from the TIVO-1 trial and extrapolated using a Weibull distribution. Treatment naïve hazard ratios were obtained using a NMA of relevant studies (see Section 4.3 for more detail). The ERG found that there were several issues with the data being used in the model compared to what was reported by the company, most notably that the tivozanib KM data for PFS and OS related to the overall ITT population, despite the company's focus for the analysis on the treatment naïve population. This was raised during the clarification stage and the company subsequently amended the KM data to reflect the treatment naïve population in the first economic model submitted with the clarification response.

Another issue the ERG found with the analysis was that the company did not provide any assessment for assuming the proportional hazards (PHs) assumption holds for the trials included in the network or for the TIVO-1 trial. At clarification stage the ERG requested the company to provide a thorough assessment of PHs. The company provided log cumulative, log(survival function/ (1-survival function)) and log(inverse standard normal distribution function(1-survival function)) plots for the TIVO-1 trial data for PFS and OS. Based on visual inspection of the plots, the company determined that the PH assumption was violated for PFS and only held for OS after 2-3 months. During the clarification stage, the ERG suggested two methods that can be employed if there is a violation of the PH assumption,

Sunitinib	£84,199	2.876	1.983	£24,615	0.120	0.120	£205,840	£205,840
Pazopanib	£85,094	2.997	2.063	£25,509	0.241	0.199	£128,228	£11,272
Tivozanib	£86,176	3.028	2.085	£26,591	0.272	0.221	£120,303	£48,955
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; IFN: Interferon; LYG, Life years gained; QALY, Quality-adjusted life year.								

Table 78. Fully incremental cost-effectiveness results of parametric NMA (Company's updated clarification responses, Table 15)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Tivozanib	£72,592	2.692	1.893	-	-	-	-
Pazopanib	£83,541	2.930	2.006	£10,949	0.238	0.113	£97,138
Sunitinib	£92,965	3.172	2.180	£20,373	0.479	0.287	£38,942
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

Table 79. Fully incremental cost-effectiveness results of revised base case – Second order FP-based NMA (P1= -2, P2= -1) (obtained from company's economic model)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Pazopanib	£58,537	2.076	1.432		-	-	-
Tivozanib	£70,476	2.543	1.757	£11,938	0.467	0.325	£36,757
Sunitinib	£105,566	3.586	2.425	£35,091	1.51	0.668	£52,533
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

5.5.2 Sensitivity analysis

The company carried out deterministic (scenario analysis and one-way sensitivity analyses), and probabilistic sensitivity analyses to assess the uncertainty surrounding the results of the revised base case second-order FP (P1= -2, P2= -1) model. However, it did not report the results of the one-way sensitivity analysis to the ERG. The ERG notes that since there were major errors in the company's revised base case model as reported throughout this report with corrections by the ERG described in Section 6.1, the results of the company's scenario analysis and probabilistic sensitivity analysis are of limited value in terms of assessing the uncertainty surrounding the cost-effectiveness results.

5.5.2.1 Scenario analysis

The company carried out scenario analyses, testing assumptions in the revised base case second-order FP (P1= -2, P2= -1) model surrounding the following parameters:

- Effectiveness estimates: using a first-order FP (p1=-2) instead of a second-order FP;
- Discounting of costs and outcomes: removing discounting for costs and outcomes from the model;
- HSUVs: using alternative values for HSUVs from previous technology appraisals;

6 ADDITIONAL WORK UNDERTAKEN BY THE ERG

6.1 Model corrections

As reported in Section 5.4.5.3, the ERG corrected the fundamental flaw in the calculation of treatment effectiveness based on the parameters generated in the FP analysis. In addition to this, the weekly costs (per cycle) for disease management during pre-progression and post-progression were estimated incorrectly. Monthly costs were converted to weekly costs by dividing by 4, instead of 4.35 (365 days/12 months/7 days) which is the correct estimate of number of weeks per month. The ERG corrected this accordingly. Lastly, the company did not discount costs for subsequent therapy disease management and this has been rectified by the ERG.

The company's corrected base case ICERs for the revised base case second order FP-based NMA (P1= -2, P2= -1) analyses are reported in Table 82. The ERG also reran the scenario analyses carried out by the company except for the scenario related to subsequent treatment as this is included in the exploratory analyses reported in Section 6.3, using an alternative approach. The results of the scenario analysis are reported in Table 83. The result for the first order FP scenario should be treated with caution, as mentioned previously, the ERG does not believe the parameter estimates generated by the company are correct as they could not be validated.

Table 82. Company's corrected base case ICERs for the revised base case – Second order FP-based NMA (P1= -2, P2= -1) analysis

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (pairwise)	ICER (incremental)
Tivozanib	£71,281	1.839	-	-	-	
Pazopanib	£71,369	1.783	-£88	0.056	Dominant	Dominated
Sunitinib	£99,073	2.415	-£27,792	-0.576	£48,222 (SW Quadrant)	£48,222

Abbreviations in table: ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; SW, south-west.

Table 83. Scenario analysis results based on company's corrected base case ICERs for the revised base case – Second order FP-based NMA (P1= -2, P2= -1) analysis

Base case assumption	Scenario	Tivozanib vs Sunitinib ICER(£)	Tivozanib vs Pazopanib ICER(£)
Base case ICER	-	**£48,222 (SW Quadrant))**	**Dominant**
Second-order fractional polynomial	First-order fractional polynomial	£56,176 (SW Quadrant)	£74,693
Discount rate of 3.5% for costs and outcomes	No discounting applied to costs and outcomes	£47,623 (SW Quadrant)	£10,751
Pre-progression utility of 0.73 Post-progression utility of 0.65	Pre-progression utility of 0.78, Post-progression utility of 0.70 based on values used in TA169[23]	£44,678 (SW Quadrant)	Dominant

	Pre-progression utility of 0.70, Post-progression utility of 0.59 based on values used in TA215[25]	£53,700 (SW Quadrant)	Dominant

6.2 ERG scenario analysis

Throughout Section 5 the ERG have raised several issues with the economic model produced by the company and have described scenarios that warrant further exploration. The scenarios that the ERG have produced are applied to the corrected revised company base case and are as follows:

1) Implementation of the alternative second order fractional polynomial (FP) (P1= -2, P2= -1.5) for overall survival (OS);

2) Implementation of the following alternative second order FP-based NMAs for progression-free survival (PFS);

    a) Second order FP-based NMA (P1= -3, P2= -3);

    b) Second order FP-based NMA (P1= -3, P2= -2.5);

3) Scenario 1 + scenario 2a;

4) Scenario 1 + scenario 2b;

5) Equal efficacy for OS and PFS based on the ERG's estimates of the company preferred second order FP-based NMA (P1= -2, P2= -1) using the ERG estimates;

6) Use of treatment naïve adverse event (AE) incidence for tivozanib (from the TIVO-1 trial) based on Table 52;

7) ERG estimates of AE odds ratios (ORs) based on the simplified network meta-analysis (NMA) based on Table 53;

8) ERG clinical expert resource use assumptions for AEs, based on Table 66;

9) Removal of AE health state utility value (HSUV) decrements. HSUVs for PFS are based on the TIVO-1 trial which did not distinguish patients who were experiencing AEs and therefore inclusion of AE utility decrements is potentially double counting the impact of these on quality of life;

10) Scenarios 6 to 9;

11) Equal incidence of AEs based on the tivozanib incidence;

ICER	**£5,162 (SW quadrant)**	**£32,570**
ICER with all changes incorporated	**£1,624 (SW quadrant)**	**Dominated**
ERG's preferred base case ICER	**£1,624 (SW quadrant)**	**Dominated**
Abbreviations in table: QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio; FP, fractional polynomial; PFS, progression-free survival; OS, overall survival; SW, south-west; AE, adverse event.		

Table 86. Results of the ERG preferred base case (incremental)

Therapy	Total costs	Total LYs	Total QALYs	Incremental costs	Incremental LYs	Incremental QALYs	ICER
Pazopanib	£43,644	3.49	2.35	-	-	-	-
Tivozanib	£43,742	2.89	1.97	£98	-0.59	-0.38	Dominated
Sunitinib	£44,174	3.31	2.24	£530	-0.17	-0.11	Dominated
Abbreviations in table: ICER, incremental cost-effectiveness ratio; LYs, life-years; QALYs, quality-adjusted life-years.							

6.3.1 Scenario analysis (ERG preferred base case ICER)

The ERG found there were two potential second order FP curve choices for PFS that were assessed to be a good fit to the underlying data. The second order FP-based NMA (P1= -3, P2= -2.5) was implemented in the ERG preferred base case as it produced conservative estimates for PFS. The ERG explored a scenario using the alternative second order FP-based NMA (P1= -3, P2= -3), which was also found to be an equally good fit to the underlying data. Table 87 presents the results of this scenario.

Table 87. Results of alternative PFS scenario (incremental analysis)

Therapy	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (tivo vs. comp)	ICER (incremental)
Sunitinib	£42,228	2.23	-	-	-	
Pazopanib	£43,019	2.35	£791	0.12	Dominated	£6,714
Tivozanib	£44,111	1.97	£1,093	-0.37	Dominated	Dominated
Abbreviations in table: ICER, Incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; tivo, tivozanib; comp, comparator.						

As mentioned previously, there is a substantial amount of uncertainty around the survival data and thus the ERG explored a second scenario assuming equal efficacy for PFS and OS for all treatments (cost minimisation scenario). No ICERs were produced for this scenario as the ERG base case removes AE utility decrements, resulting in no differences in QALYs. Results of this scenario are presented in Table 88.

Table 88. Results of alternative equal efficacy scenario (cost minimisation)

Therapy	Total costs	Incremental costs
Tivozanib	£43,742	-
Sunitinib	£43,736	£6
Pazopanib	£42,656	£1,087

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Tivozanib for treating renal cell carcinoma [ID591]

You are asked to check the ERG report from BMJ Evidence to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies you must inform NICE by **5pm on 4 July** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Clarification of why comparative HRQoL outcomes not included in the CS

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
All clinically relevant outcomes were reported in the CS, except for comparative effect estimates for health-related quality of life (HRQoL). Page 16 (Folio 1)	All clinically relevant outcomes were reported in the CS, except for comparative effect estimates for health-related quality of life (HRQoL), *since comparative data on HRQoL was unavailable from all the included clinical studies.*	We believe that it is important to explain why comparative data on HRQoL was not reported in the CS. It is stated later in Table 4, but we feel important to clarify at this point too Impact: minor	The ERG has amended the text to read, "All clinically relevant outcomes were reported in the CS, except for comparative effect estimates for health-related quality of life (HRQoL) due to a lack of comparable data in the included studies."

Issue 2 Edit for sense

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Time on treatment was modelled using parametric survival distributions for PFS, as specified by the marketing authorisations for the treatments modelled (Table 67, page 150 of the CS) and published papers for sunitinib and pazopanib to estimate acquisition costs of active treatment. Page 19 (Folio 4)	Time on treatment was modelled using parametric survival distributions for PFS, as specified by the published papers for sunitinib and pazopanib and marketing authorisations for the treatments modelled (Table 67, page 150 of the CS) to estimate acquisition costs of active treatment.	Amend for sense Impact: minor	Not a factual error. No change required

Issue 3 Edit data on the exclusion of the preference study for transparency

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
a randomised preference study of tivozanib versus sunitinib was omitted, despite being listed as contributing to the safety data on which the summary	versus sunitinib was omitted, despite being listed as contributing to the safety data on which the summary of product characteristics (SmPC) is	We believe that it is important to explain why data on AV-951-12-205 was not reported. The current copy infers that it was excluded to benefit	No change made. The ERG considers it is important to acknowledge the existence of the study and that there is no

of product characteristics (SmPC) is based. Page 21 (Folio 6) Page 83 (Folio 68)	based. *However, the preference study (AV-951-12-205) enrolled only 79 patients and was never completed, therefore, would have added limited additional value to the evidence-base.*	our submission, which is not the case. Impact: to reassure readers that we were open and transparent in our selection of the evidence.	mention of it in the company submission.

Issue 4 Correction of cost minimisation results

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Assuming equal efficacy for PFS and OS using the company's preferred second order FP-based NMA option (P1= -2, P2= -1) but using the ERG's estimates. This scenario was a cost minimisation exercise and found that tivozanib dominates sunitinib and pazopanib, respectively. These results are primarily driven by statistically non-significant differences in AEs; and Page 25 (Folio 10)	Assuming equal efficacy for PFS and OS using the company's preferred second order FP-based NMA option (P1= -2, P2= -1) but using the ERG's estimates. This scenario was a cost minimisation exercise *and estimates that when treatment effectiveness is equal for all treatments, tivozanib is more expensive than sunitinib (£6) and pazopanib (£1,087).* These results are primarily driven by statistically non-significant differences in AEs; and	The original copy states that tivozanib dominates, however, this is incorrect. The suggested revised copy (in italics) makes clear that tivozanib is slightly more expensive than sunitinib and pazopanib in this scenario. Given that tivozanib is [redacted] than the other comparators, it seems odd that in a cost minimisation approach where treatment effectiveness is equal for all agents, it should be the most expensive approach. Indeed, when we explored the ERG's model in more detail we found that tivozanib was cheaper than the comparators in almost all of the other cost minimisation scenarios. Impact: to correct the copy and clarify that tivozanib is slightly more expensive than sunitinib and pazopanib in this scenario.	The scenario identified in Issue 4 relates to results presented in Table 84 of the ERG report, which is a scenario analysis based on the company's preferred base case. However, the company's proposed amendment relates to Table 88, which is a scenario analysis on the ERG preferred base case. No amendment is required.

Issue 5 Edit for clarity treatment in the tivozanib arm in the extension study

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
There was no provision of subsequent therapy for patients who progressed on tivozanib. Table 5	There was no provision of subsequent *funded* therapy for patients who progressed on tivozanib *and patients received treatment as recommended by their physician.*	We believe that the addition of *and patients received treatment as recommended by their physician* clarifies the statement. Without the additional copy, the reader may think that patients who progressed on tivozanib did not receive **any** additional therapy. Impact: for clarity for readers unfamiliar with the TIVO-1 study	No change made to Table 5 (page 26) or page 46. The ERG believe 'provision' is clear in this context and that the issue is discussed sufficiently in the rest of the report.
but did not provide subsequent therapy for people who progressed on sorafenib. Page 49 (folio 34)	but did not provide subsequent *funded* therapy for people who progressed on sorafenib *and patients received treatment as recommended by their physician*.		Page 34 has been amended to read, "but did not provide subsequent therapy for people who progressed on tivozanib."
no provision of second-line therapy was made for patients who progressed on tivozanib Page 61 (folio 46)	no provision of second-line *funded* therapy was made for patients who progressed on tivozanib *and patients received treatment as recommended by their physician.*		Not a factual error. No change required.

Issue 6 Edit to update post EMA decision

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The CS states that tivozanib was submitted to the Committee for Human Medicinal Products (CHMP) in March 2016 and a decision is anticipated in May 2017 Page 44 (Folio 29)	The CS states that tivozanib was submitted to the Committee for Human Medicinal Products (CHMP) in March 2016 and a *positive decision was reached on 22 June 2017.*	Since the ERG report was drafted the EMA have adopted a positive opinion for tivozanib. Impact: to ensure that the document is as up to date as possible.	Not a factual error. No change required – this was correct at the time of writing.

Issue 7 Price of tivozanib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Acquisition cost (excluding VAT): List price: [redacted] for 21 hard capsules Average cost of a course of treatment: List price: [redacted] Table 6	Acquisition cost (excluding VAT): List price: [redacted] for 21 hard capsules Average cost of a course of treatment: List price [redacted]	The price stated in Table 6 is the original price. The revised price is shown in the proposed amendment.	Table 6 has been amended to reflect the company's proposed change.

Issue 8 Contraindications for tivozanib

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Contraindications outlined in the SmPC are summarised in Section 3.2. Briefly, tivozanib is contraindicated for coadministration with St John's Wort, pregnancy, dialysis, and those with histories of arterial thrombotic events, bleeding, QT interval prolongation or gastrointestinal perforation/fistula).54 Tivozanib is not recommended for patients with severe hepatic impairment and for those with mild to moderate hepatic impairment, the dose should be reduced to alternate days and patients should be monitored closely. Page 80 (Folio 65)	Contraindications outlined in the SmPC are summarised in Section 3.2. Briefly, *tivozanib is contraindicated for coadministration with St John's Wort and in patients with hypersensitivity to the active substance or to any of the excipients.* *Tivozanib should be used with caution in patients at risk of or with a history of arterial thrombotic events, bleeding, QT interval prolongation, gastrointestinal perforation/fistula. Caution is advised in patients with severe renal impairment due to limited experience and in patients undergoing dialysis as there is no experience of tivozanib in this patient population* Tivozanib is not recommended in	According to the latest SmPC, tivozanib is only contraindicated for Hypersensitivity and St John's wort. All others fall under special precautions for use and we suggest rewording as proposed	Page 65 has been amended to read, "Briefly, tivozanib is contraindicated for coadministration with St John's Wort and in patients with hypersensitivity to the active substance, and should not be used in pregnancy. Tivozanib should be used with caution for patients undergoing dialysis, and those with histories of arterial thrombotic events, bleeding, QT interval prolongation or gastrointestinal perforation/fistula.[54] Tivozanib is not recommended for patients with severe hepatic impairment and for those with mild to moderate hepatic impairment, the dose should be reduced to alternate days and patients

	patients with severe hepatic impairment, and for those with mild to moderate hepatic impairment, the dose should be reduced to alternate days and patients should be monitored closely. *Tivozanib should not be used in pregnancy*.		should be monitored closely.[54]"

Issue 9 Post progression therapy assumptions

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
The company assumed that once a patient progressed and started 2nd line treatment with axitinib, they would continue treatment until death (Table 67 of the CS). Page 119 (Folio 104)	The company assumed, *on advice from their clinical advisor,* that once a patient progressed and started 2nd line treatment with axitinib, they would continue treatment until death (Table 67 of the CS).	We believe that the addition of *on advice from their clinical advisor,* clarifies the statement	Not a factual error. No change required.

Issue 10 Final indication for tivozanib has slightly different wording, actual indication remains the same

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Post EMA decision the wording of the indication has changed slightly, although this does not alter the indication The final indication is first line treatment of adult patients with advanced renal cell carcinoma (RCC) and for adult patients who are VEGFR	You may wish to note that the wording of the indication has changed.	To ensure document is as up to date as possible	Not a factual error. No change required – this was correct at the time of writing.

and mTOR pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced RCC			