Slides for public – redacted

Lead team presentation - clinical
Cabozantinib for untreated metastatic renal cell carcinoma

1st Appraisal Committee meeting; 2nd topic on agenda
Committee B, 10 May 2017

Lead team: Nicky Welton, Nigel Westwood, Stuart Williams

Company: Ipsen

Chair: Amanda Adler

Evidence review group: Southampton Health Technology Assessments Centre

NICE team: Alan Lamb, Ahmed Elsada, Elisabeth George

Preview – key clinical effectiveness issues

1. What impact, if any, will cabozantinib have on the treatment pathway for metastatic RCC?
2. Do the comparators sunitinib and pazopanib have ‘equal’ efficacy?
3. How best to measure radiographic PFS, per protocol or retrospectively?
4. Which data cut for overall survival, January 2017 or more mature July 2017?
5. Is there a reason why the curves for overall survival cross during the key trial?
6. Is there robust evidence that people live longer on cabozantinib than sunitinib?
7. Do the proportions of patients with intermediate or high risk in the key trial reflect those seen in the NHS? Does level of risk affect treatment effectiveness?

Cabozantinib (*Cabometyx*®)

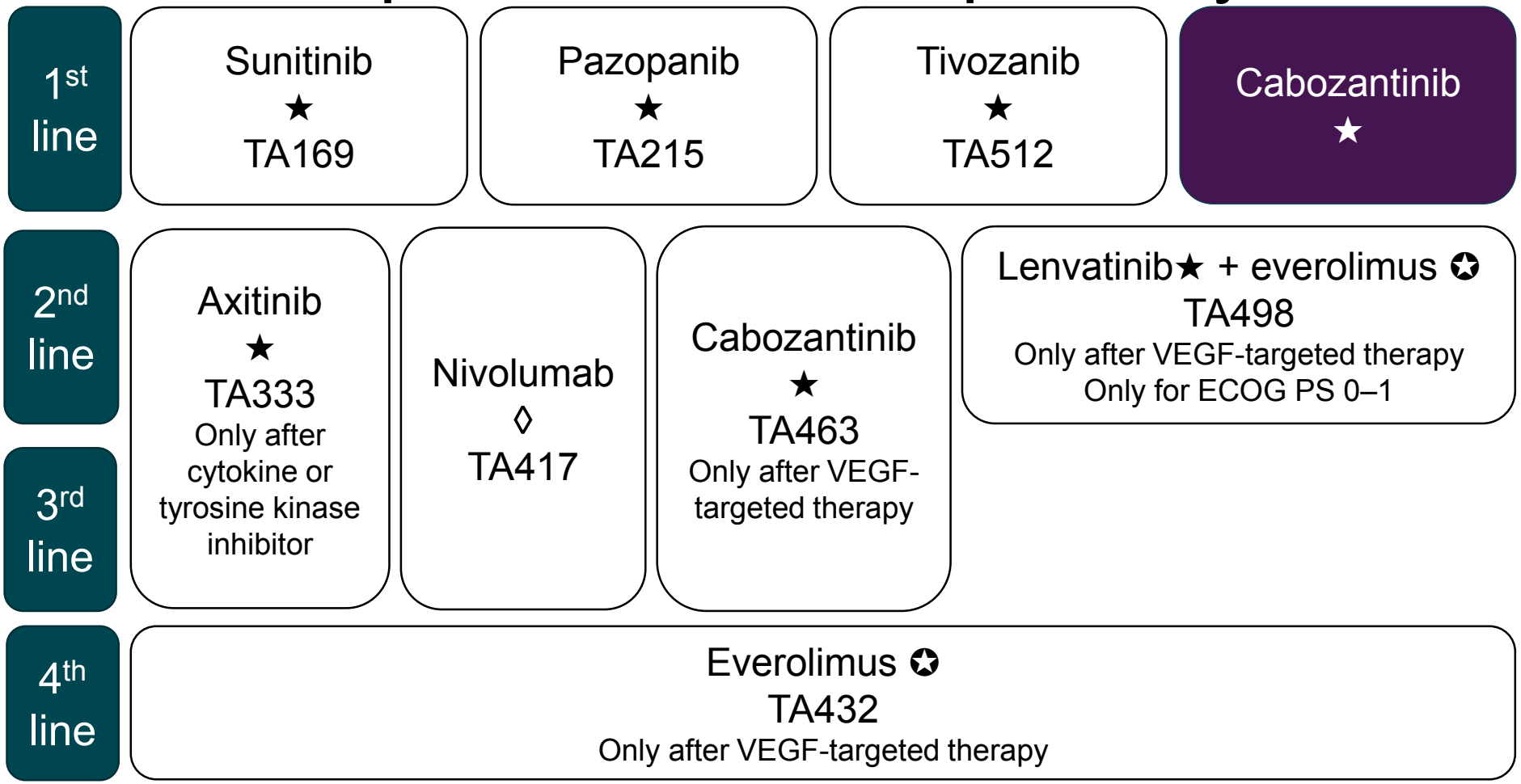
Anticipated UK marketing authorisation	Advanced renal cell carcinoma in treatment-naive adults with intermediate or poor risk per International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria (positive CHMP opinion issued Mar 2018)
Administration	Oral
Mechanism	Inhibits multiple receptor tyrosine kinases. Targets pathways implicated in tumour progression, angiogenesis, pathologic bone remodelling, and drug resistance.
Dosage	60 milligrams (1 tablet) once daily 40 and 20 milligram tablets Reduce dose as necessary
PAS	Simple PAS agreed with Department of Health as part of previous appraisal (second line)

Decision problem

	Final scope from NICE	Company's decision problem
Population	People with untreated, intermediate or poor risk, locally advanced or metastatic renal cell carcinoma	Per scope
Comparators*	1. Pazopanib 2. Sunitinib	Per scope
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

* Tivozanib not recommended at time of scoping

Proposed treatment pathway



⊙ ***What impact, if any, will cabozantinib have on the treatment pathway for metastatic RCC?***

Key; ECOG PS, Eastern Cooperative Oncology Group performance status; VEGF, vascular endothelial growth factor
★: oral tyrosine kinase inhibitors (TKI); ✪: oral mammalian target of rapamycin (mTOR) inhibitor;
◊ **:** anti-programmed death 1 (PD-1) inhibitor.

Comments from patient groups

- People may experience constant pain and psychological effects e.g. depression, loss of confidence and self-worth
- Many patients have to give up work because of debilitating effects of disease – leads to financial pressures
- Few treatment options available and adverse effects are significant, for example, extreme fatigue, hand and foot syndrome, chronic diarrhoea
- No biomarkers predict who will respond to each drug, therefore, having a range of treatment options is important
- Cabozantinib could be used to address an area of significant unmet need for an effective 1st-line treatment for people with bone metastases

Key clinical evidence

Cabozantinib vs. sunitinib
Direct comparison

CABOSUN
Phase II randomised controlled trial

ERG comments
- CABOSUN well designed and conducted
- Low risk of bias for most domains

Cabozantinib vs. pazopanib
Indirect comparison - network

COMPARZ – pazopanib vs sunitinib, phase III randomised controlled trial

CABOSUN

ERG comments
Difference in populations may bias results of indirect comparison:
- 100% intermediate/poor risk in CABOSUN vs. 75% in COMPARZ
- 36% with bone metastases in CABOSUN vs. 18% in COMPARZ

⊙ ***Committee B has previously accepted that sunitinib has the same efficacy as pazopanib. Has the committee seen evidence to change this?***

Company's clinical evidence

Cabozantinib vs sunitinib: CABOSUN trial (n=157)

Patients

- ≥18 years
- Advanced or metastatic RCC
- Treatment-naive
- Intermediate or poor risk
- ECOG performance status 0–2

Open-label phase II RCT

n=79 → Cabozantinib 60 mg oral daily

1:1 randomisation
No crossover

n=78 → Sunitinib 50 mg oral daily for 4 weeks, followed by 2 week break

Treat to progression or toxicity

Endpoints* *used in model*

1°

- Progression-free survival per investigator
- 1 data-cut: Sep 2016

2°

- Overall survival (2 data cuts)
  - Jan 2017
  - Jul 2017
- Adverse effects of treatment
- Overall response rate

- Company undertook a blinded review retrospectively – **use this in model**
- Company did not collect quality of life data (based modelling on literature)

⊙ ***How best to measure radiographic PFS, protocol or retrospectively?***
⊙ ***Which data cut for overall survival Jan 2017 or more mature Jul 2017?***

CABOSUN baseline characteristics

Characteristic	Cabozantinib n=79, n (%)	Sunitinib n=78, n (%)
Age, years		
Median (range)	63 (40-82)	64 (31-87)
Sex		
Male	66 (84)	57 (73)
Female	13 (16)	21 (27)
Risk (per IMDC)		
Intermediate	64 (81)	63 (81)
Poor	15 (19)	15 (19)
Prior nephrectomy		
Yes	57 (72)	60 (77)
No	22 (28)	18 (23)

- Clinical expert advice to ERG: baseline characteristics generally represent UK
  - One expert noted that a higher proportion of patients with prior nephrectomy

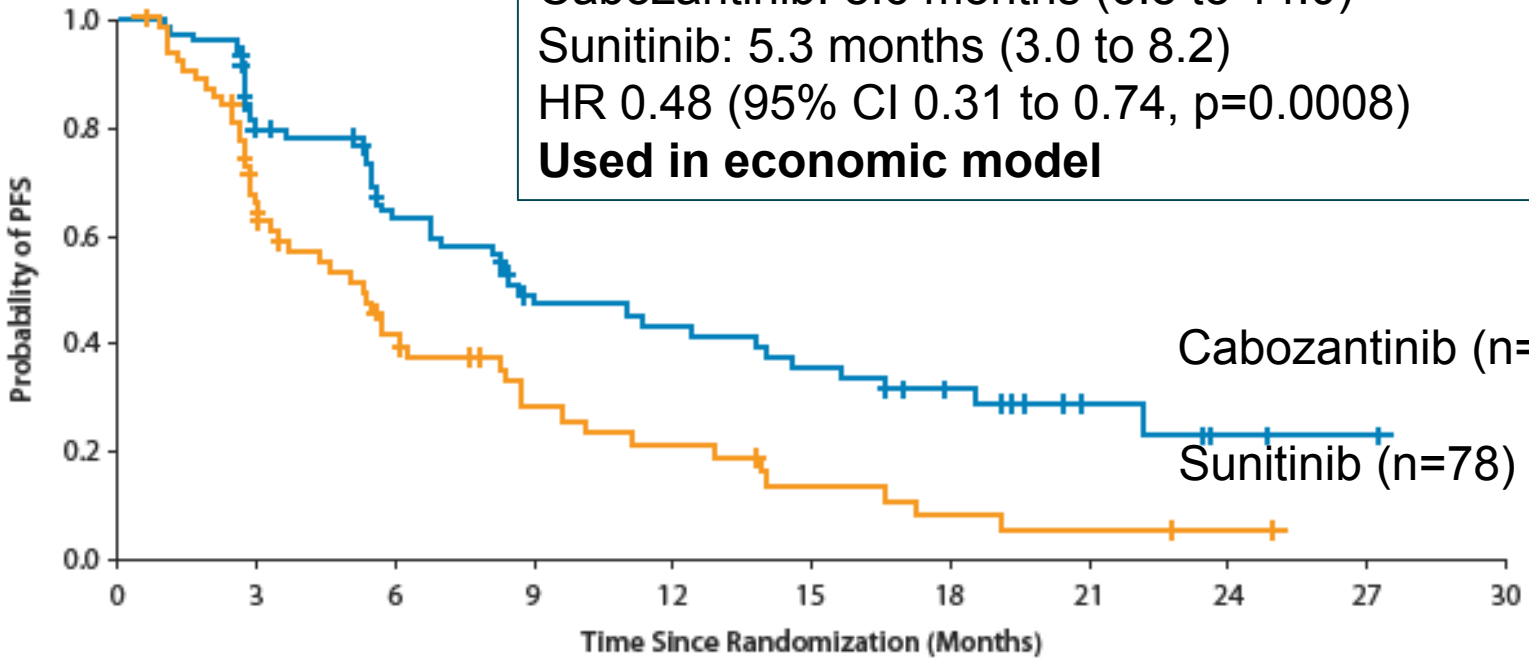
- ***Is the clinical evidence generalisable to UK clinical practice?***
- ***Do the proportions of intermediate and poor risk patients in the trial reflect UK practice?***

Progression-free survival results

Company uses more favourable retrospectively assessed analysis in model (Sep 2016 data cut)

PFS by independent review committee assessment

Median PFS (95% CI)
Cabozantinib: 8.6 months (6.8 to 14.0)
Sunitinib: 5.3 months (3.0 to 8.2)
HR 0.48 (95% CI 0.31 to 0.74, p=0.0008)
Used in economic model



No. at risk										
Cabozantinib	79	51	37	24	22	18	12	5	2	1	0
Sunitinib	78	36	21	12	9	5	3	2	1	0	0

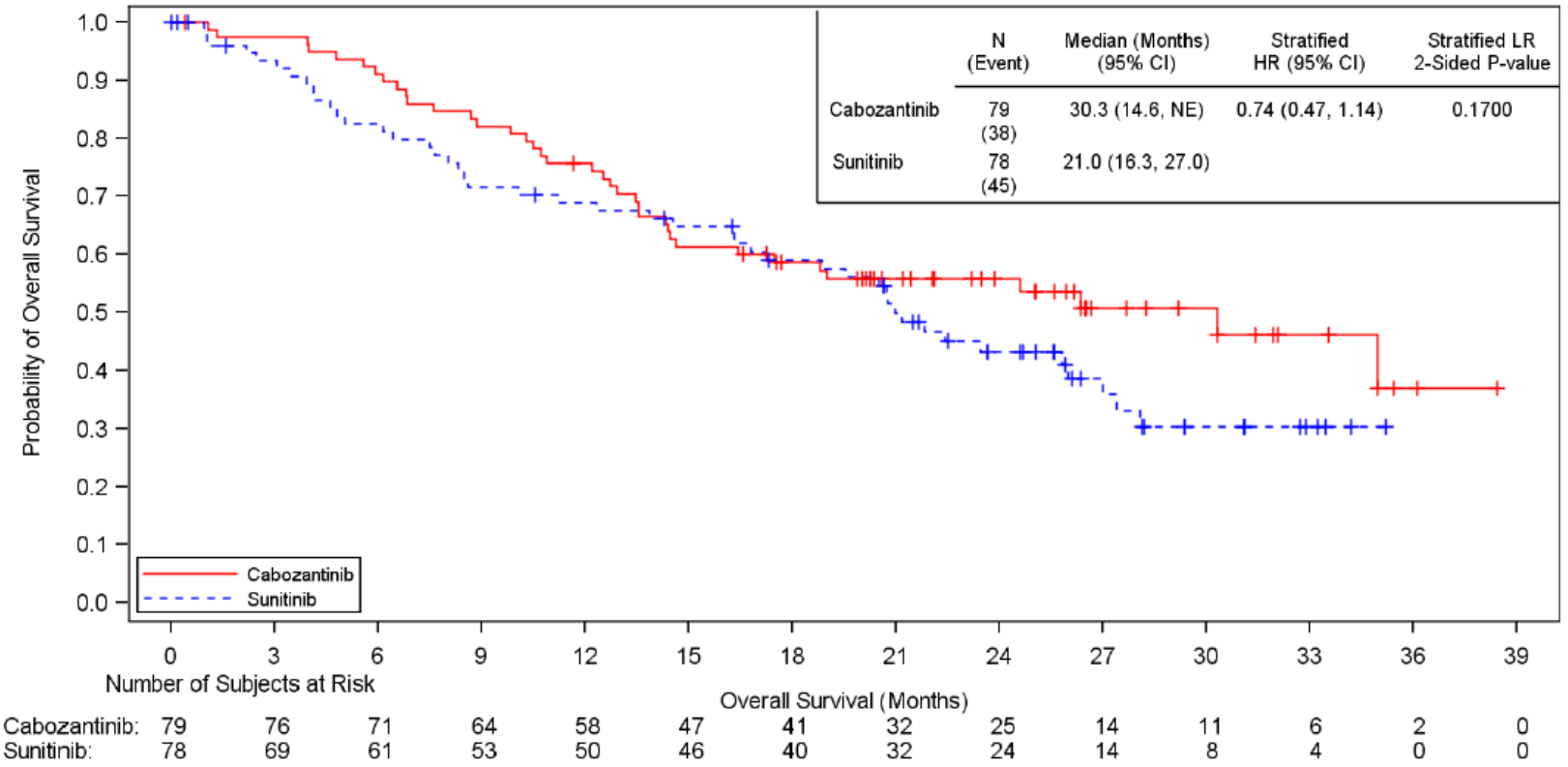
Data cut-off: September 15, 2016

- Results using per protocol investigator-assessed analysis: 8.3 vs 5.4 months, HR=0.56; 95% CI 0.37 to 0.83, p=0.0042

Overall survival results

Jan 2017 data cut

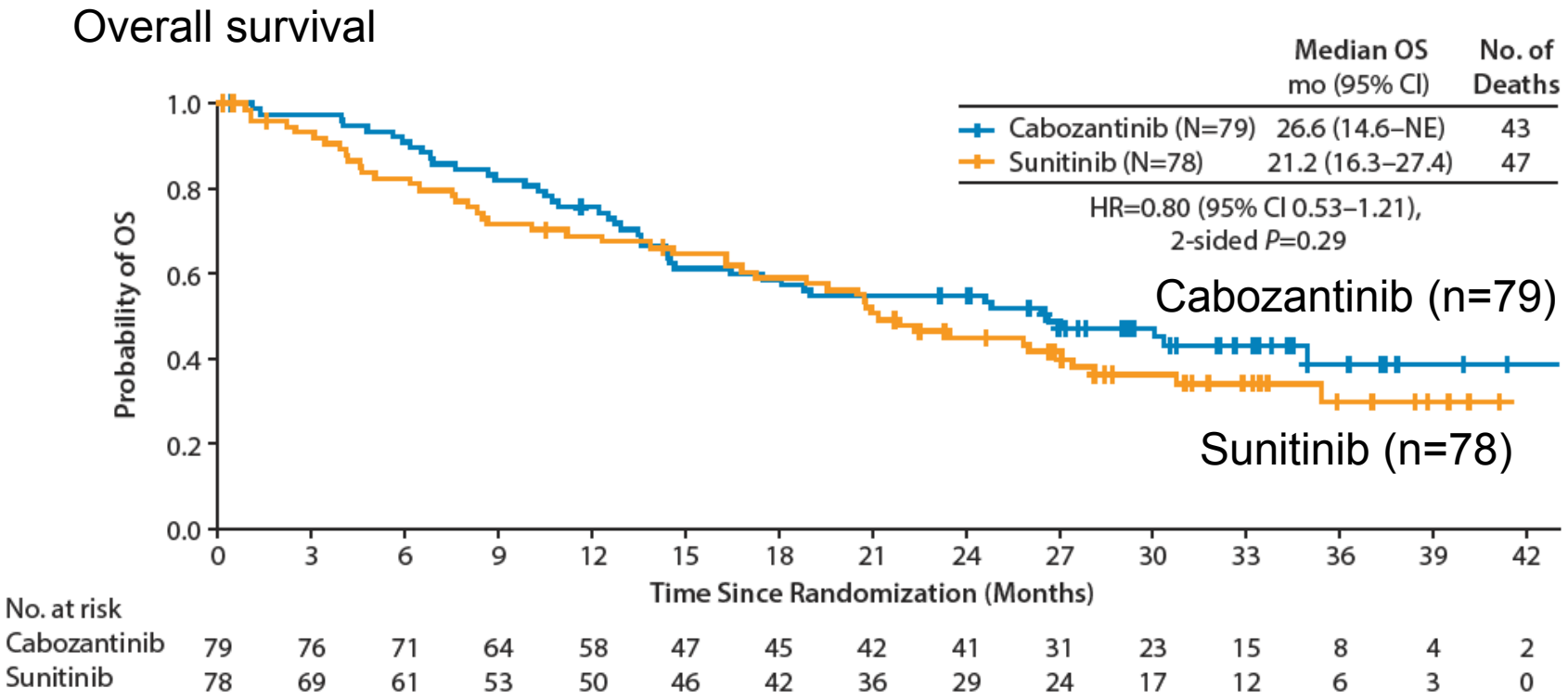
Overall survival



- Company uses more favourable Jan 2017 data-cut in economic model
- ERG: Impact of subsequent treatment on OS uncertain

⊙ ***Is there a reason why the curves for overall survival cross?***
⊙ ***Is there evidence that people live longer on cabozantinib than sunitinib?***

Overall survival results
July 2017 data cut



- ERG: not stated in the company submission why data from the earlier (January 2017) data cut were used
  - ERG used July 2017 data cut in economic model

Subgroup analysis

Survival by risk group

	Cabozantinib Median, months (95% CI)	Sunitinib Median, months (95% CI)	HR (95% CI)
Intermediate	n=64	n=63	
Radiographic PFS – measured retrospectively	11.4	6.8	0.52 (0.32 to 0.82)
Overall survival	30.3 (16.4 to NE)	23.5 (18.9 to 28.1)	0.80 (0.45 to 1.31)
Poor	n=15	n=15	
Radiographic PFS – measured retrospectively	6.8	2.7	0.31 (0.11, 0.92)
Overall survival	18.4 (6.1 to NE)	6.4 (2.2 to 22.4)	0.51 (0.20 to 1.32)

⊙ ***Is there evidence of interaction (differential effectiveness) by subgroup?***

Slides for projector – contains AIC

Lead team presentation – Economic

Cabozantinib for untreated metastatic renal cell carcinoma

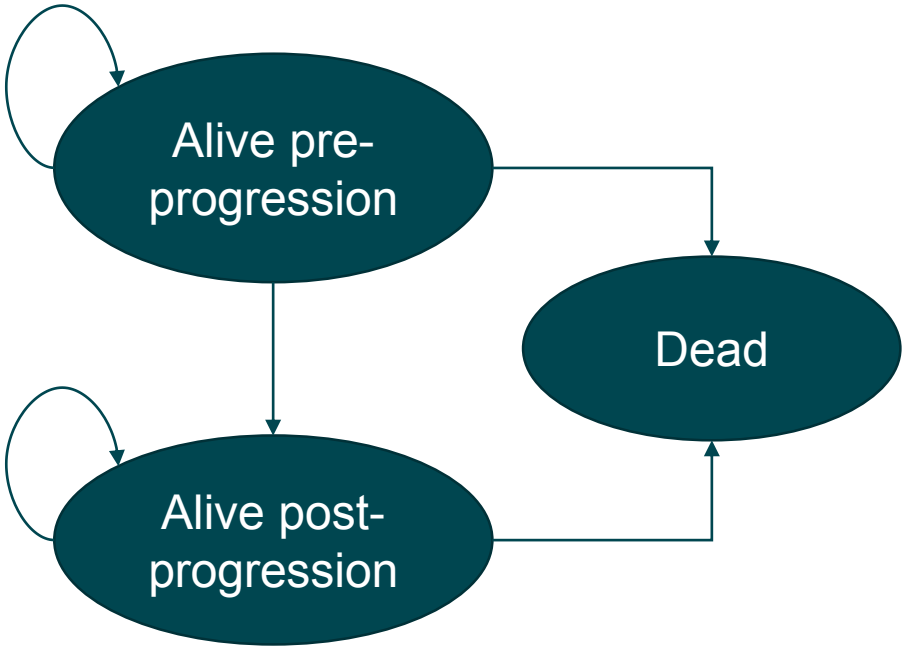
Because Patient Access Schemes (PAS) discounts exist for treatments received 2nd line and beyond, the estimates for cost-effectiveness estimates which include these will be presented in the closed part 2 of this meeting

Because estimates of life-expectancy are confidential, estimates related to 'end-of-life' will be presented in part 2

Preview of key cost effectiveness issues

1. Do proportional hazards hold for modelling overall survival? What is the most appropriate approach to modelling overall survival?
2. Is the modelling for time to stopping treatments reasonable?
3. How long should treatment benefit with cabozantinib persist?
4. How should treatment costs 2nd line and beyond be modelled?

Company's model: approach + structure



- Partitioned-survival model
- Estimated proportions in each health state based on parametric survival curves fitted to clinical trial data for PFS and OS
- Time horizon: 20 years
- Cycle length: 1 week
- Company presented 2 separate analyses (trial-based and ITC-based) – slides focus on trial-based analysis

Treatment	Dosage regimen to progression or toxicity
Cabozantinib (oral)	60 mg daily
Sunitinib (oral)	50 mg daily for 4 weeks followed by 2 weeks without treatment
Pazopanib (oral)	800 mg daily

Key data sources for company's model

- Data sources related to key issues in the appraisal highlighted in **bold**

Efficacy	**Trial-based analysis: CABOSUN (cabozantinib vs sunitinib)**
Treatment duration	**CABOSUN (cabozantinib vs sunitinib), pazopanib assumed equal to sunitinib based on COMPARZ**
Quality of life	Utility values from TA512 (tivozanib)
Adverse events	Disutility values from Amdahl 2016 (based on COMPARZ data), duration based on METEOR (cabozantinib) clinical trial
Costs – resource use	TA512 (tivozanib) and TA215 (pazopanib)
Post progression treatments	• **Those seen in clinical trials (CABOSUN for cabozantinib and sunitinib, COMPARZ for pazopanib)** • **Scenario analyses based on clinical opinion**

Company's model parameters from CABOSUN

Trial-based analysis (CABOSUN)

	Progression free survival	**Overall survival**	**Time to stopping treatment**
Assume proportional hazards	No (ERG – Yes)	No	No
Type of model	Independent curves for each treatment group		
Distribution	Log-normal	Exponential	Log-normal
ERG comments: curve choice	Log-normal, exponential and Gompertz show reasonable visual fit, **all overestimate median PFS for cabozantinib**	**Exponential gives plausible estimates** of long-term survival. **More recent OS data cut** should be used to generate curve.	**Appropriate** but no obvious reason to exclude log-logistic from scenario analysis
	Other alternatives not fully considered/tested as scenario analyses		
Assumption for pazopanib	Company: Assumes pazopanib = sunitinib for time to stopping treatment ERG: Assumes pazopanib = sunitinib for all parameters		

Proportional hazards - yes or no?

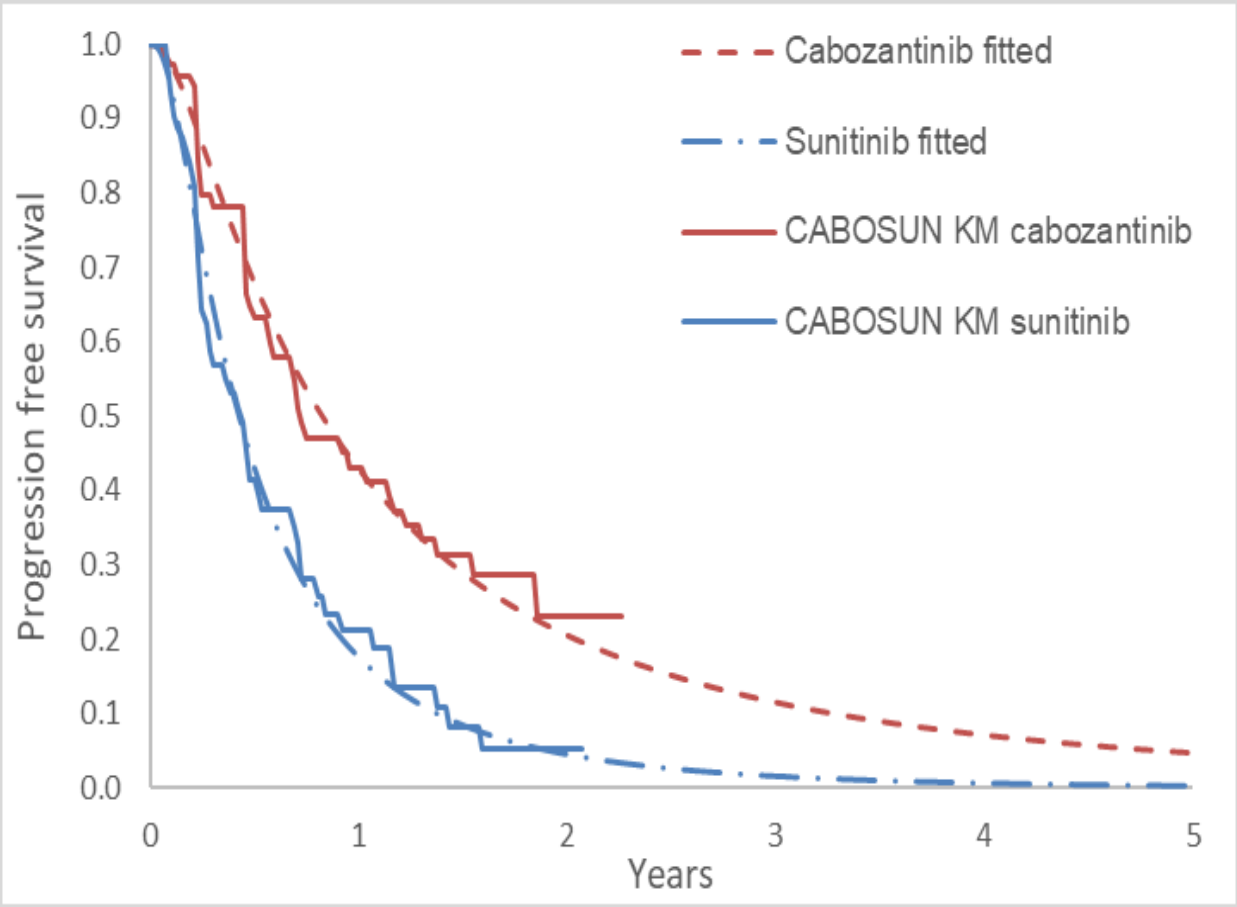
- Progression-free survival
  - Company states that proportional hazards do not hold for CABOSUN
  - ERG: company's conclusion not supported by tests for proportionality: i.e. Schoenfeld and log-cumulative hazard plots
- Overall survival
  - Company states that proportional hazards does **not** hold for CABOSUN
  - ERG: Agrees with company. Suggests that one should not 'over-interpret' shape of CABOSUN Kaplan–Meier curves because of modest sample size and no explanation for why curves cross then diverge

⊙ ***Does committee believe that proportional hazards hold for overall survival?***

Survival extrapolations

Trial-based analysis (CABOSUN) – progression-free survival

PFS – lognormal distribution



- ERG: Reasonable visual fit, although overestimates median PFS for cabozantinib – also used in ERG base case

Company's approach to overall survival

- Company fit **separate** exponential curves to cabozantinib and sunitinib
  - Did not use latest data cut from CABOSUN
- ERG's preferred modelling of overall survival:
  - Taking sunitinib curve from CABOSUN data (exponential fit)
  - Applying OS hazard ratio to generate the OS curve for cabozantinib
    - Despite proportional hazards assumption not being met
  - Using most recent OS data cut (Jul 2017)
    - Using Jan 2017 data cut and assuming no benefit (HR=1) in scenario analyses

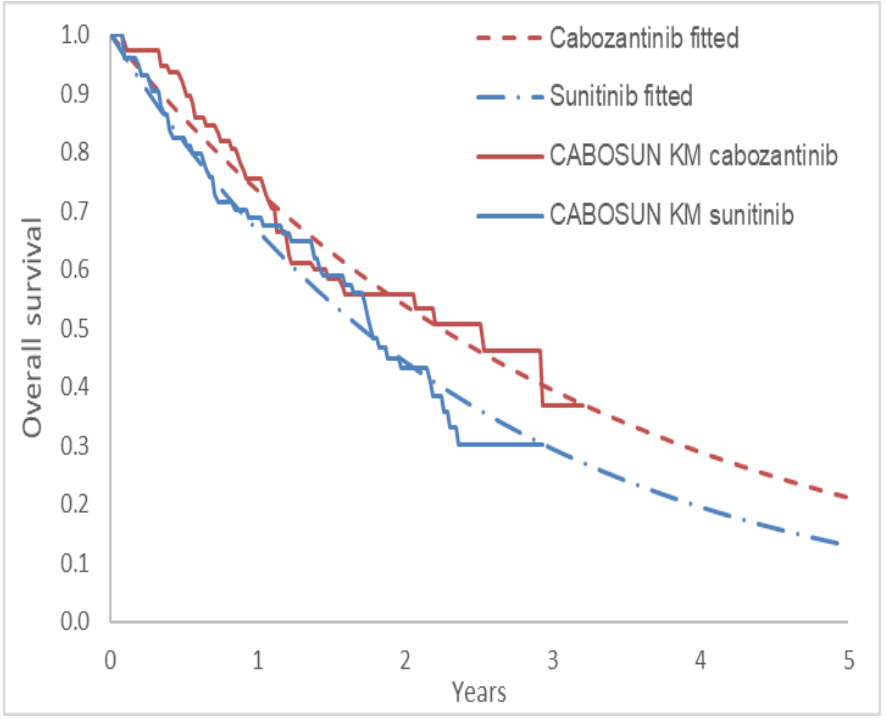
⊙ ***What is the most appropriate approach to modelling overall survival?***

Survival extrapolations company vs. ERG

*Trial-based analysis (CABOSUN) – **Overall survival***

Company base case

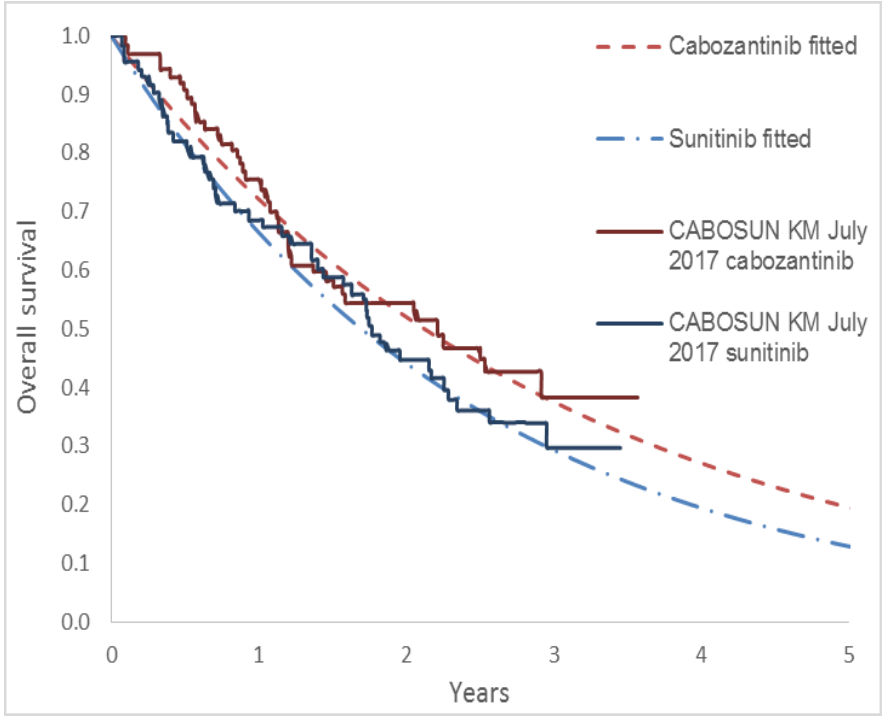
Jan 2017 data cut



Exponential curves fit separately to both arms

ERG base case

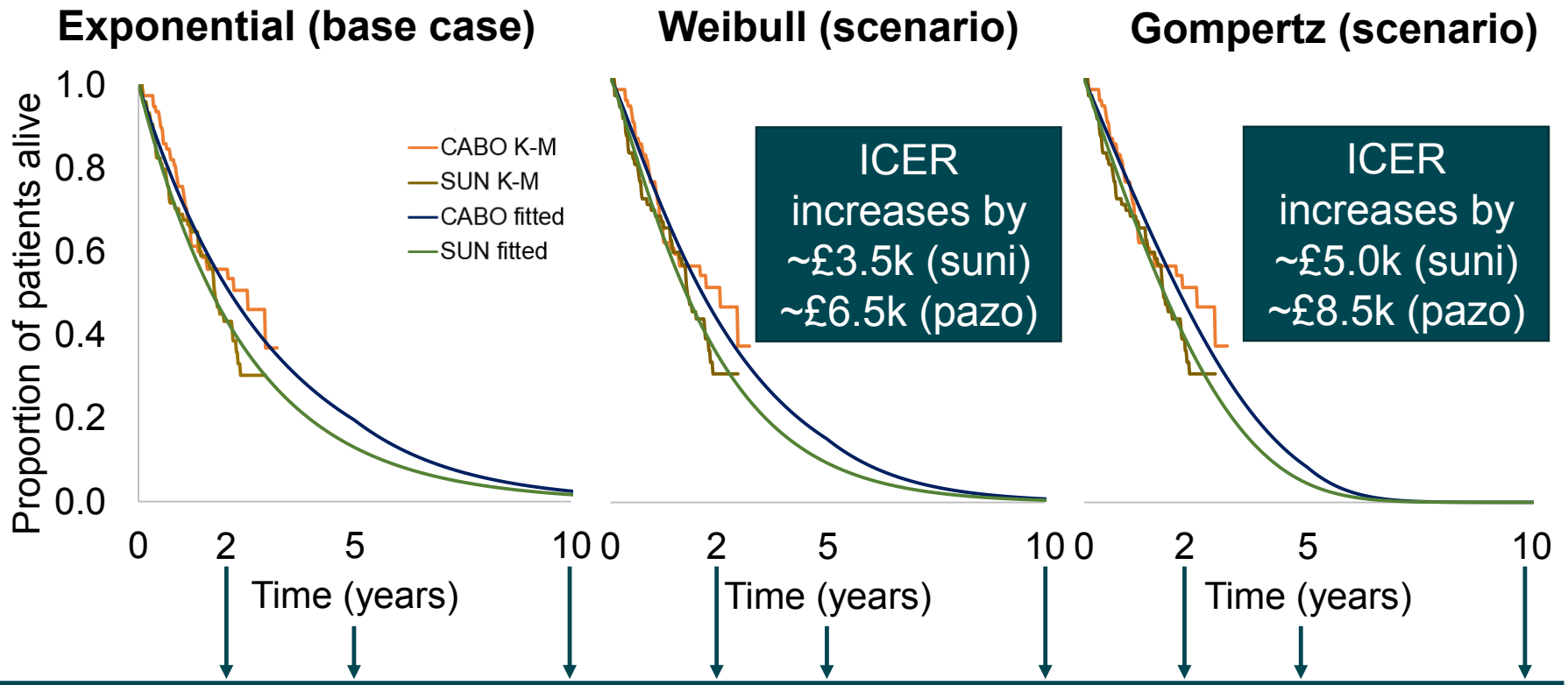
July 2017 data cut



Exponential curves fit to sunitinib then cabozantinib curve generated using HR=0.80 from July 2017 data

⊙ *Given that proportional hazards do not hold, is an exponential curve and a hazard ratio appropriate? Did the company attempt to validate projections?*

Overall survival truncated at 10 years - ERG



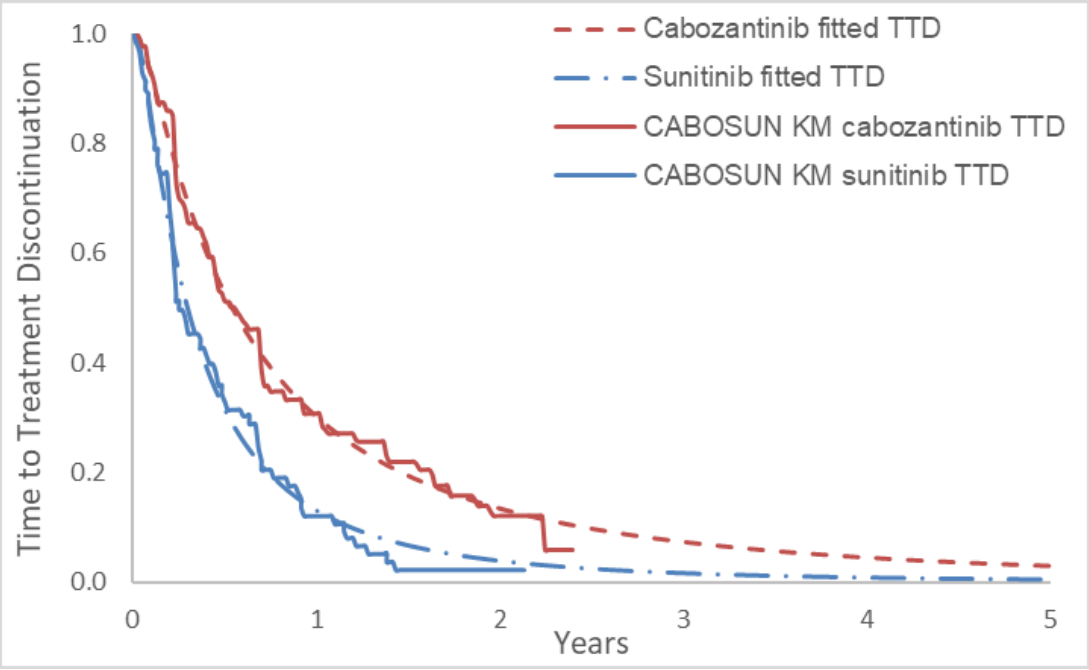
Proportion of patients alive (%)									
CABO	52%	20%	3%	52%	15%	1%	52%	8%	0%
SUN	44%	13%	2%	44%	9%	1%	45%	4%	0%

⊙ ***Are any of the OS extrapolations presented plausible?***

Time to stopping treatment

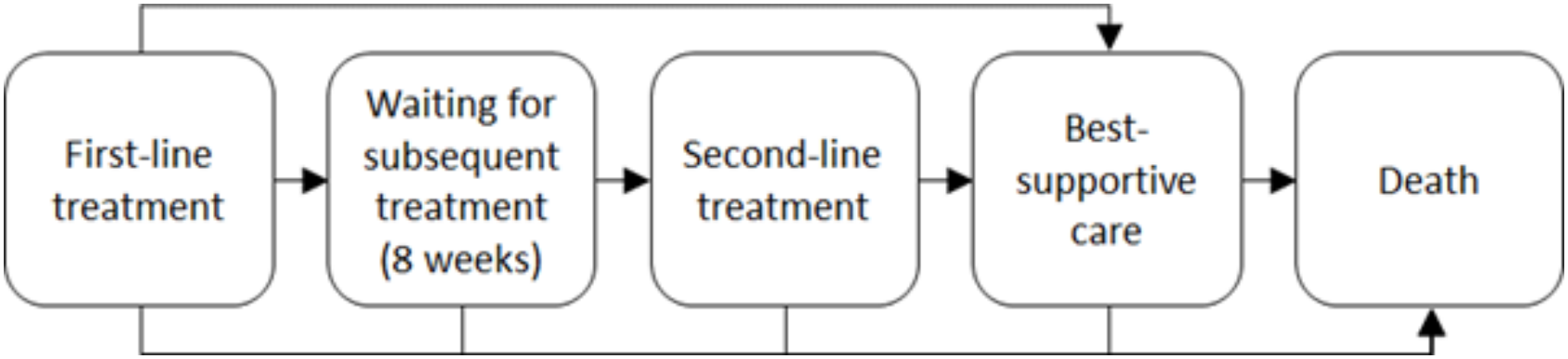
Trial-based analysis (CABOSUN)

- Company and ERG base case
  - Cabozantinib and sunitinib: CABOSUN-based and extrapolated with log-normal
  - Pazopanib = sunitinib based on COMPARZ
  - Using loglogistic has no effect on ICERs; alternatives reduce them



⊙ ***Is the modelling for time to stopping treatments reasonable?***

Source of transitions in company model

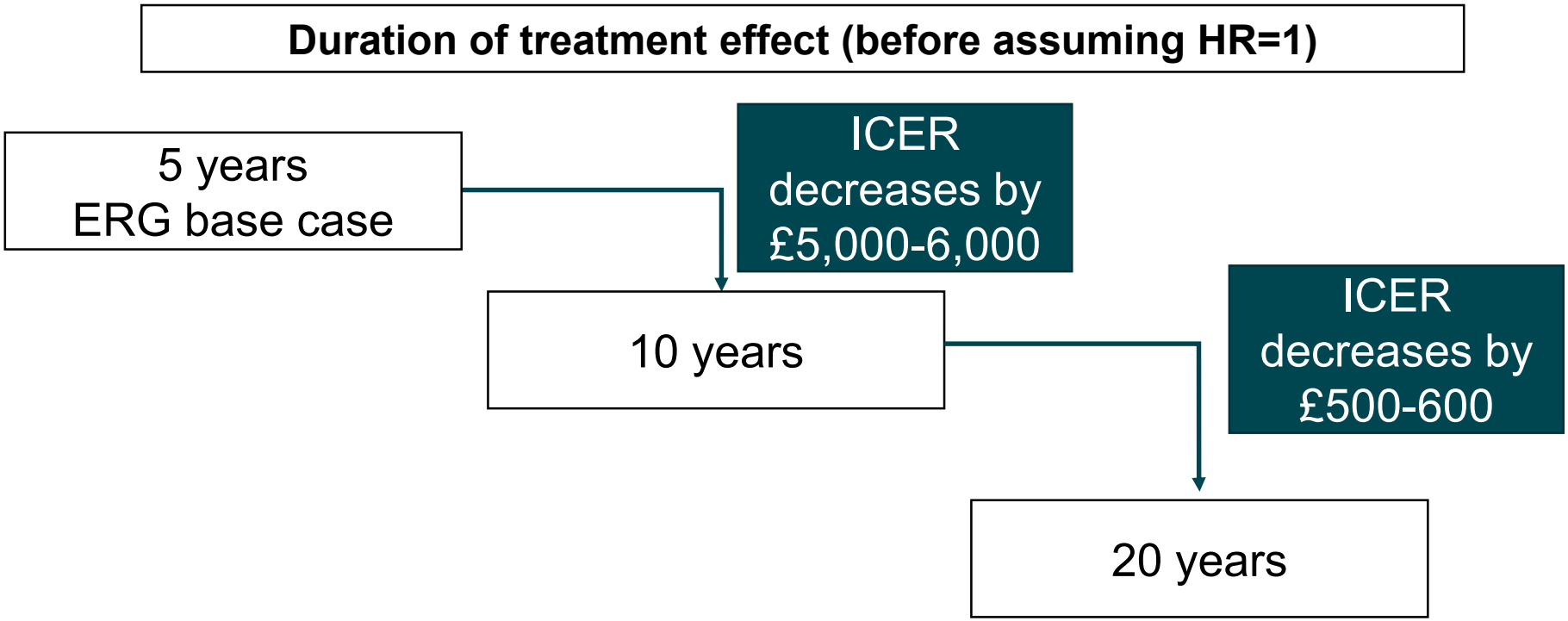


Time in state	Minimum of PFS and time to stopping treatment curves	Increases as patients accumulate over 8 weeks	From literature for specific therapies	Until death or end of time horizon

⊙ ***Does limiting treatment to 2 lines of active therapy reflect the current NHS pathway? What better reflects time on treatment, time to disease progression or time to stopping treatment?***

Duration of treatment effect

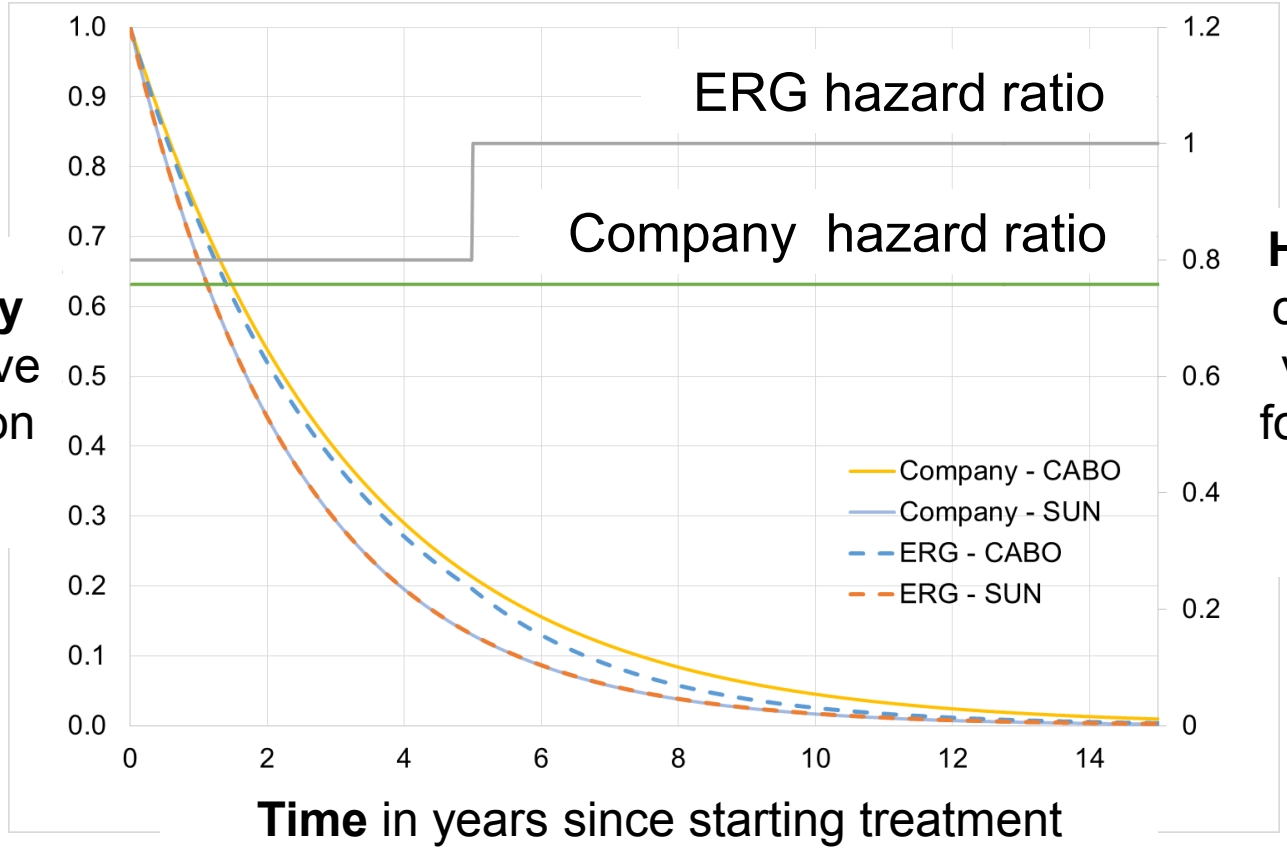
- Company base case assumed treatment benefit persists over entire time horizon – even beyond the end of treatment
- ERG preferred assuming that benefit does not persist
- ERG base case assumes equivalent efficacy for cabozantinib and sunitinib (HR=1) at 5 years; tested 10 and 20 years as scenarios



Duration of treatment effect

Survival probability and hazard ratios in company's and ERG's analysis

Probability of being alive as a function of time



Hazard ratio cabozantinib vs. sunitinib for death as a function of time

⊙ ***Has committee seen evidence that treatment benefit with cabozantinib extends beyond trial? Committee did not accept this for cabozantinib 2nd line – is this different?***

2nd line therapy by 1st line therapy trial data

Company and ERG base case both use data from CABOSUN and COMPARZ

	1st line		
2nd line	Cabozantinib CABOSUN (%)	Sunitinib CABOSUN (%)	Pazopanib COMPARZ (%)
Axitinib	23	19	6
Pazopanib	16	12	0
Sunitnib	13	13	29
Temsirolimus	9	4	6
Nivolumab	13	15	0
Everolimus	8	19	31
Sorafenib	1	3	11
Bevacizumab	0	6	7
Cabozantinib	1	6	0
Interferon	1	0	0

- ERG notes that model overestimates duration and cost of 2nd-line therapy as the company assumes the same mortality rate before and after 1st-line treatment

2nd line therapy – company + ERG scenarios

ICER sensitive to scenario

	Cabozantinib (%)			Sunitinib/Pazopanib (%)		
	Company	ERG 1	ERG 2	Company	ERG 1	ERG 2
Axitinib	50	10	0	40	10	0
Nivolumab	30	30	45	30	20	30
Everolimus	10	20	0	10	20	0
Cabozantinib	0	0	0	10	20	30
Lenvatinib + everolimus	0	30	45	0	20	30
BSC	10	10	10	10	10	10

- All analyses consider cost but not clinical effect of 2nd therapy
- Company scenario analysis based on clinical expert opinion elicited during TA512 (Tivozanib). Lenvatinib + everolimus was not a treatment option at that time
- ERG 1: only NICE recommended 2nd-line drugs, ERG 2: clinical opinion to ERG on 2nd-line treatments

⊙ ***Which scenario, if any, reflects 2nd-line (and further?) NHS treatment?***

End-of-life criteria – life expectancy

Treatment is indicated for patients with a short life expectancy, normally less than 24 months

- Committee previously considered that this criterion is **not** meet for the general RCC population (i.e. including favourable-risk group) (TA512)
- Life expectancy for intermediate-/poor risk group summarised below:

Preferred assumptions	Sunitinib median OS (95% CI) (trial data, July 2017 data cut)	Sunitinib mean OS (95% CI) (modelled)
Company	21.2 months (16.23, 27.4)	XXXX months (XXXX)
ERG		XXXX months (XXXX)
Note: committee has previously considered mean estimates from the model more relevant for life expectancy considerations (TA516)		

- Criterion on life extension will be discussed further during part 2

⊙ ***Do people with intermediate-/poor-risk RCC normally live less than 24 months?***

Equality considerations and innovation

- No equality considerations identified
- Company highlights a novel mechanism of action: cabozantinib is the first and only multi-targeted therapy for RCC which targets pathways involved in both tumour growth and drug resistance (MET, AXL), as well as tumour angiogenesis (VEGF).
- Cabozantinib granted Promising Innovative Medicine (PIM) designation under the Early Access to Medicines Scheme (EAMS) in July 2016
- Company and patient groups highlighted that cabozantinib may be more effective than other treatments in the treatment of bone metastases
- For cabozantinib 2nd-line, committee did not consider cabozantinib to reflect a 'step change' in treatment nor did it identify a benefit to utility that was not otherwise accounted for in the modelling

⊙ Is cabozantinib 1st-line innovative?