Erdafitinib for treating metastatic or unresectable FGFR-altered urothelial cancer

For Zoom – contains no CON information

Technology appraisal committee C [04 December 2024]

Chair: Steve O'Brien

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Company: Johnson & Johnson

Erdafitinib for treating metastatic or unresectable FGFR-altered urothelial cancer

- ✓ **Background**
- ❑ Clinical effectiveness and key issues
- ❑ Modelling and cost effectiveness
- ❑ Cost effectiveness results

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Background on metastatic or unresectable FGFR-altered urothelial cancer

Causes and epidemiology

- Urothelial carcinoma (UC) is cancer of the cells which form the inner lining of the bladder (most common), urethra, ureter, or renal pelvis
- ~16,500 cases of bladder cancer diagnosed in 2020, alterations of FGFR genes are observed in ≈20% of cases of metastatic UC. Incidence increases with age.
- ≈10% of patients have locally advanced or metastatic disease at diagnosis
- ≈50% of patients who undergo radical treatment for muscle-invasive disease experience relapse and are likely to develop distant metastases

Prognosis and impact

- Data from the company's RW study found that in England the median OS from diagnosis of patients with metastatic UC was 5.4 months (95% CI: 5.2, 5.6)
- Metastatic and unresectable UC is associated with pain, fatigue and problems urinating
- Current treatments options often lead to treatment related AEs that add to disease symptoms
- Patients report an increased reliance on family and friends as the disease progresses

NICE Abbreviations: fibroblast growth factor receptor; CI, confidence intervals; AE, adverse events; OS overall survival; UC, urothelial cancer

Patient perspectives

Submissions from Action Bladder Cancer UK, Fight Bladder Cancer and patient expert

Effects on patients and carers

- Psychological impact of coming to terms with poor outcomes and limited options

Current care

- Aim of treatment is generally to control cancer and maintain quality of life
  - ↳ However, patients and their families can be shocked by limited treatment options
- Patients and carers express mixed feelings about care available. Praise for quality of care as well as frustration with delays in diagnosis and treatment

Erdafitinib

- Patients would value a targeted treatments and felt longer OS from the THOR trial was of paramount importance
- Targeted treatment meets unmet need in disease that responds poorly to immunotherapies
- It being an oral drug provides significant advantages over other available treatments
- Variation in access to genetic testing, often geographic may be linked to health inequalities

"I've had 3 cycles of chemo and the side effects are unbearable, leaving me in constant pain and unable to move around as I used to."

"It was a shock to be told my cancer had gone through the [bladder] wall … I had chemotherapy and that made me really ill so they had to stop it. Then I was told they couldn't do much more. That's it."

Abbreviations: OS, overall survival

Clinical perspectives

Submissions from British Uro-oncology Group (BUG) and clinical expert

Current treatment and unmet need

- First line treatment is platinum-based chemo and/or immunotherapy (optimally delivered as chemotherapy with avelumab maintenance).
- Further chemotherapy is of limited value, the alternative is palliative care
- Clinically significant response would be extended survival and a period without progression (and hopefully symptom control)
- No other life extending treatments for this group with poor prognosis (unmet need)

Use of Erdafitinib

- People with mUC would need FGFR testing (already on NHS genomic directory)
- Available on access scheme for this indication so short period of experience
- Would be a step change in management of the condition (first targeted treatment)

"This is the first biomarker selected treatment option for urothelial carcinoma based on a somatic gene alteration. A life extending precision medicine option for this disease, rather than chemotherapy, is a welcome advance. "

"This drug has a toxicity profile that is broadly similar in frequency and severity overall compared to chemotherapy" - "However. . . a small minority of patients develop central serous retinopathy"

Abbreviations: 1L, first line; mUC, metastatic urothelial cancer; FGFR, fibroblast growth factor receptor

Equality considerations

Some potential equalities issues identified at scoping

Scoping consultation and patient organisation submissions

- People in remote or rural areas might face challenges accessing testing and treatment
- Women with disease experience worse outcomes and higher mortality than men
- The shift away from the NICE end of life criteria to the severity modifier may result in disadvantages to older people

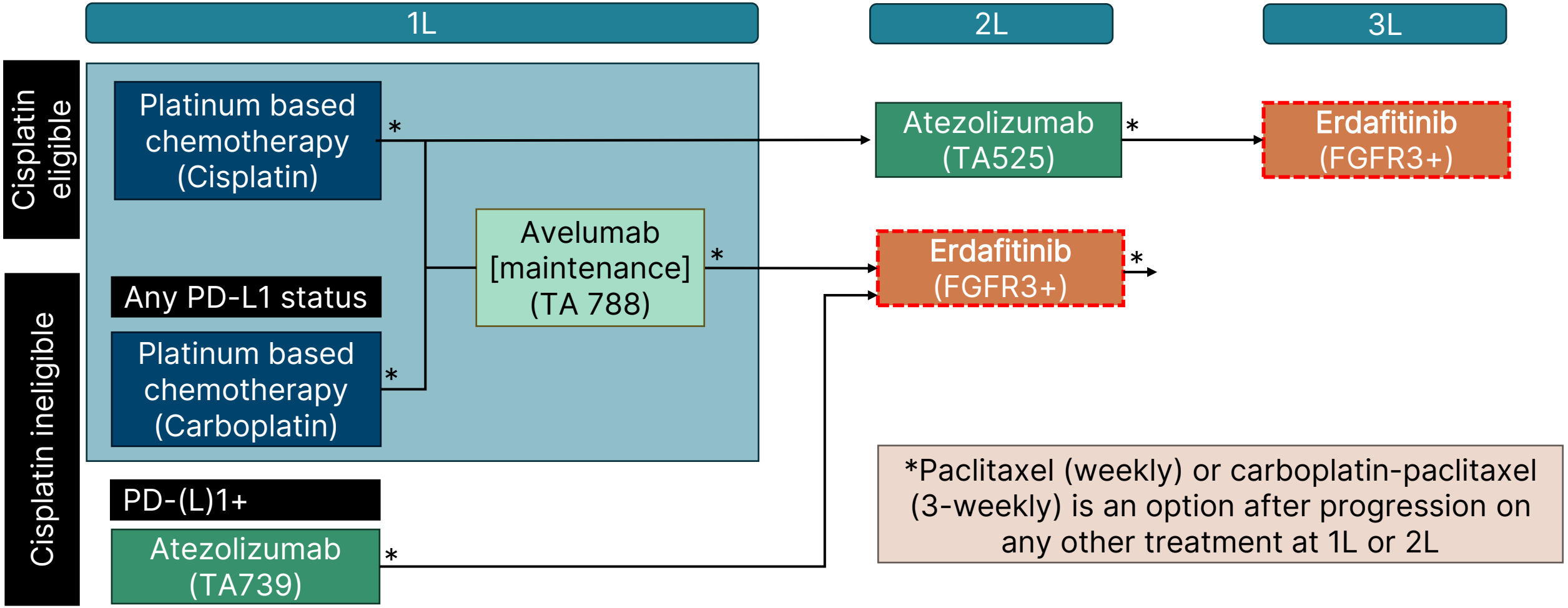
Company submission – No equality issues identified

EAG Report – No equality issues identified

Are there any equalities issues which can be addressed in this technology appraisal?

Abbreviations: EAG, external assessment group

Treatment pathway



Abbreviations: 1L/2L/3L, first/second/third line; FGFR, fibroblast growth factor receptor

PD-(L)1, programmed cell death (ligand) 1 (this is a molecule on the surface of either tumour or immune cells which when bound to its receptor blunts the immune response)

Erdafitinib (Balversa, Johnson & Johnson)

Marketing authorisation	"Erdafitinib as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting"
Mechanism of action	Erdafitinib is a pan-fibroblast growth factor receptor (FGFR) tyrosine kinase inhibitor ↳ It suppresses FGFR phosphorylation and signalling, thereby decreasing the viability of cell lines with FGFR alterations
Administration	• Oral tablets administered at a dose of 8 mg, once daily for 21 days (3 weeks) ↳ The dose may be increased to 9 mg once daily based on serum phosphate levels and tolerability • Treatment should continue until disease progression or unacceptable toxicity occurs
Price	• List price £12,750.00 per pack (28 days) • Modelled erdafitinib acquisition cost per patient (at list price): £98,897.89 ↳ A confidential patient access scheme (PAS) price has been agreed

Abbreviations: 1L/2L/3L, first/second/third line; FGFR, fibroblast growth factor receptor

PD-(L)1, programmed cell death (ligand) 1 (this is a molecule on the surface of either tumour or immune cells which when bound to its receptor blunts the immune response

Decision problem

	Final Scope	Company	EAG comments
Population	People with metastatic or unresectable fibroblast growth factor receptor (FGFR)-altered urothelial cancer	Adult patients with unresectable or metastatic UC, harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-(L)1 inhibitor in the unresectable or metastatic treatment setting.	The narrower population is in line with the MA
Intervention	Erdafitinib	As per final scope	Agree
Comparators	ECM without erdafitinib, including but not limited to: • Chemotherapy (inc. docetaxel, paclitaxel) • Atezolizumab • Best supportive care	Paclitaxel as a monotherapy, or in combination with carboplatin (including a basket of the two)	The exclusion of comparators raises concerns about the comprehensiveness of the assessment.
Outcomes	OS, PFS, RR , AE, HRQoL	As per final scope	Has concerns about limitations in the depth and quality of data provided for certain outcomes, particularly HRQoL

Abbreviations: 1L/2L/3L, first/second/third line; FGFR, fibroblast growth factor receptor; UC, urothelial cancer; PD-(L)1, programmed cell death (ligand) 1; OS, overall survival; PFS, progression free survival; RR, response rate; AE, adverse evens; HRQoL, health related quality of life; MA, marketing authorisation;

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Key issues

Issue		Resolved?	ICER impact
1	Basket of comparators - Relative effectiveness of individual comparators and the basket of comparators	No – for discussion	Large
2	Treatment effectiveness extrapolation	No – for discussion	Moderate
3	QALY weightings for severity	No – for discussion	Large

Other issues

Issue		Resolved?	ICER impact
1	Missing data	No – for discussion	Unknown
2	Plausibility of modelled results	No – for discussion	Unknown
3	Resource use and costs	No – for discussion	Moderate
4	Utility values	No – for discussion	Low
5	Additional committee preferences	Partially – to confirm	Low

Abbreviations: ICER, Incremental cost-effectiveness ratio; QALY, quality adjusted life year

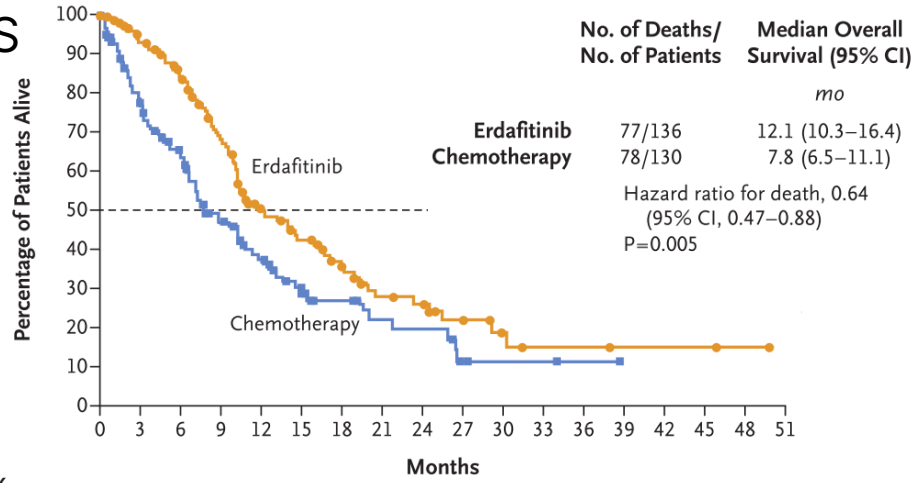
Key Clinical Trials

	THOR (n=266)	BLC2001 (n=99)	PLUTO (n=140)	UK RW mUC Study (n=72)
Design	International, Phase III, randomised, open-label	Phase II, single-arm	Phase II, randomised	Real world study
Population	FGFR-altered mUC, progressed after 1-2 treatments including an anti PD-(L)1 agent (Cohort 1)	FGFR-altered mUC, previously treated	Patients with mUC who had received prior platinum-based chemotherapy	Patients diagnosed with mUC in England between 2016-2021
Intervention	Erdafitinib	Erdafitinib	Paclitaxel	Basket of paclitaxel ± carboplatin
Comparator	Docetaxel or vinflunine	-	Pazopanib	-
Locations	121 sites in 23 countries	-	-	UK
Key outcomes	OS, PFS, ORR, HRQoL	ORR, safety	OS, PFS	OS, TTD, PFS (derived)
Role in analysis	Primary evidence source for IPD ITCs and MAICs; compared with RW data and other trials	Pooled with THOR data for more robust MAICs	MAIC *(Exploratory analysis comparing erdafitinib to paclitaxel)*	Primary comparator in IPD ITCs against erdafitinib

Abbreviations: FGFR, fibroblast growth factor receptor; mUC, metastatic urothelial cancer; OS, overall survival; TTD, time-to-discontinuation; PFS, progression free survival; ORR, objective response rate; HRQoL, health related quality of life; MAIC, matching adjusted indirect comparison; IPD, individual patient data; ITC, indirect treatment comparison;

THOR clinical trial results

OS



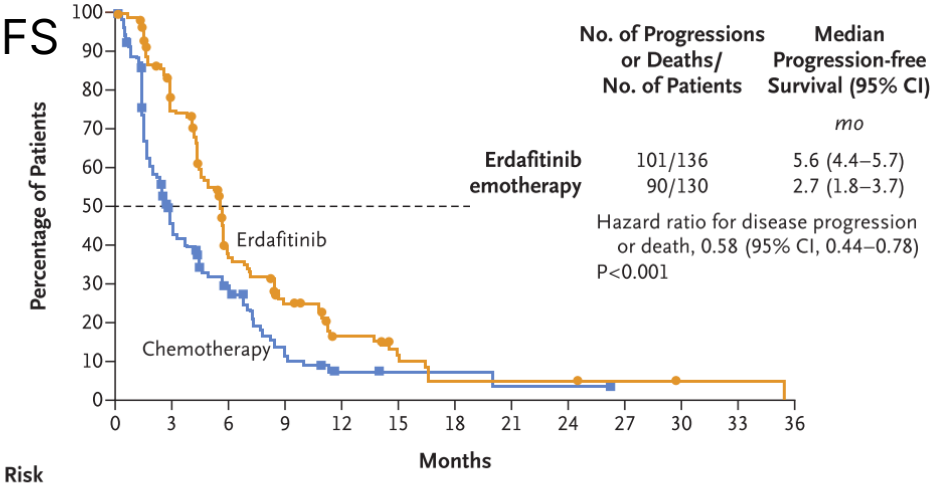
	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI) mo
Erdafitinib	77/136	12.1 (10.3–16.4)
Chemotherapy	78/130	7.8 (6.5–11.1)

Hazard ratio for death, 0.64 (95% CI, 0.47–0.88)
P=0.005

No. at Risk (no. with censored data)

Erdafitinib	136	117	97	74	46	35	25	17	15	9	5	3	3	2	2	2	1	0
	(0)	(10)	(20)	(25)	(35)	(39)	(44)	(47)	(48)	(52)	(55)	(56)	(56)	(57)	(57)	(57)	(58)	(59)
Chemotherapy	130	87	66	43	30	18	13	9	8	3	2	2	1	0	0	0	0	0
	(0)	(17)	(25)	(30)	(35)	(41)	(45)	(47)	(47)	(49)	(50)	(50)	(51)	(52)	(52)	(52)	(52)	(52)

PFS



	No. of Progressions or Deaths/ No. of Patients	Median Progression-free Survival (95% CI) mo
Erdafitinib	101/136	5.6 (4.4–5.7)
emotherapy	90/130	2.7 (1.8–3.7)

Hazard ratio for disease progression or death, 0.58 (95% CI, 0.44–0.78)
P<0.001

No. at Risk (no. with censored data)

Erdafitinib	136	90	39	24	12	7	3	3	3	2	1	1	0
	(0)	(15)	(23)	(26)	(31)	(33)	(33)	(33)	(33)	(34)	(35)	(35)	(35)
Chemotherapy	130	43	23	9	4	2	2	1	1	0	0	0	0
	(0)	(28)	(33)	(35)	(37)	(39)	(39)	(39)	(39)	(40)	(40)	(40)	(40)

	Erdafitinib (n = 136)	Chemotherapy (docetaxel or vinflunine; n = 130)
Number of events (%)	77 (56.6)	78 (60.0)
Median OS, months (95% CI)	12.06 (10.28 to 16.36)	7.79 (6.54 to 11.07)
OS HR (95% CI)	0.64 (0.47 to 0.88)	
p-value	0.005	
12-month survival (95% CI)	[redacted]	[redacted]
24-month survival (95% CI)	[redacted]	[redacted]
Median PFS, months (95% CI)	5.55 (4.40, 5.65)	2.73 (1.81, 3.68)
PFS HR (95% CI)	0.58 (0.44, 0.78)	

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Abbreviations: OS, overall survival; PFS, progression free survival; CI, confidence interval; PFS, progression free survival

ITC Networks

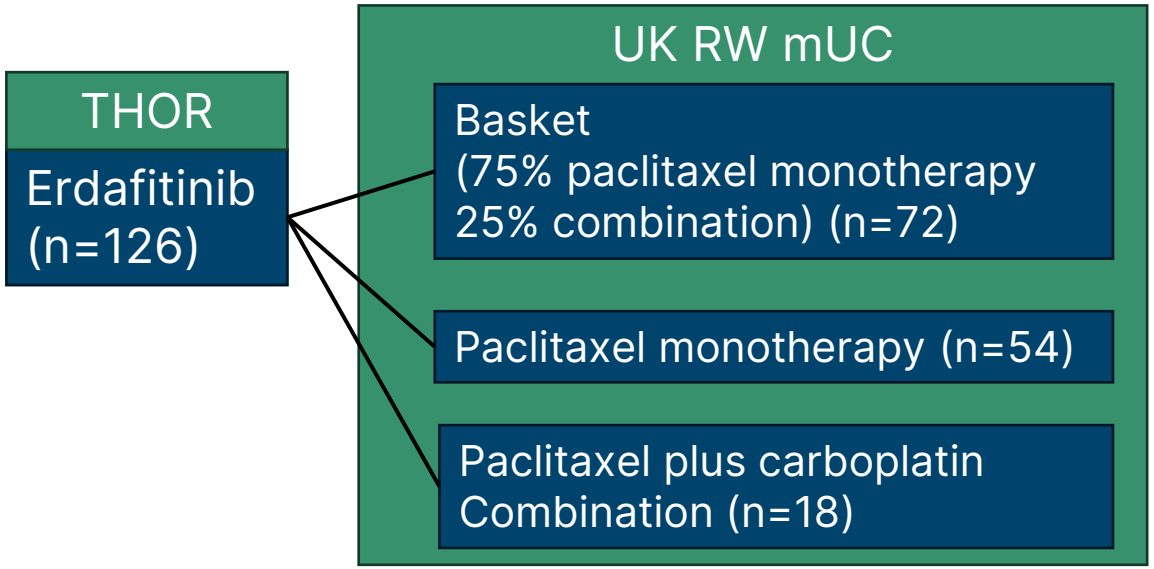
To further ITC details

- The company stated that the comparator arm of THOR consisted of treatments that are not used in the NHS
  ↳ ITC required to inform comparison with current NHS clinical practice

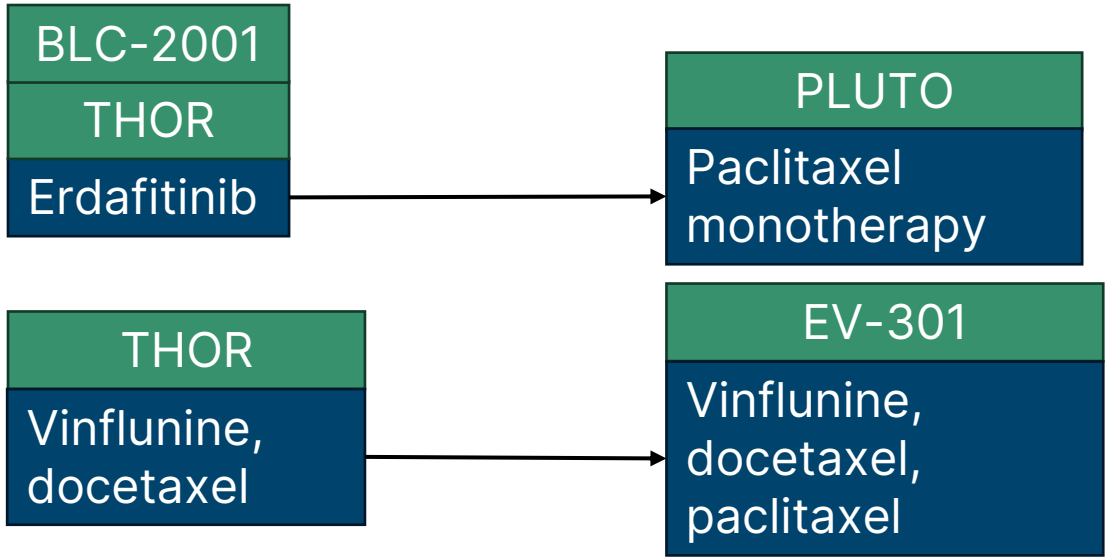
- IPD-ITC compared erdafitinib from the THOR trial to a basket of 75% paclitaxel monotherapy and 25% paclitaxel plus carboplatin (as well as the two regimens separately) from the UK RW mUC study

- Both company and EAG base cases use the average treatment effect of the comparator (ATC) propensity scoring method. This adjusts the treatment effect towards the comparator population, as a UK RWE study was considered to be more reflective of NHS clinical practice than THOR.

IPD-ITCs (IPW, ATC in base case)



Exploratory MAICs

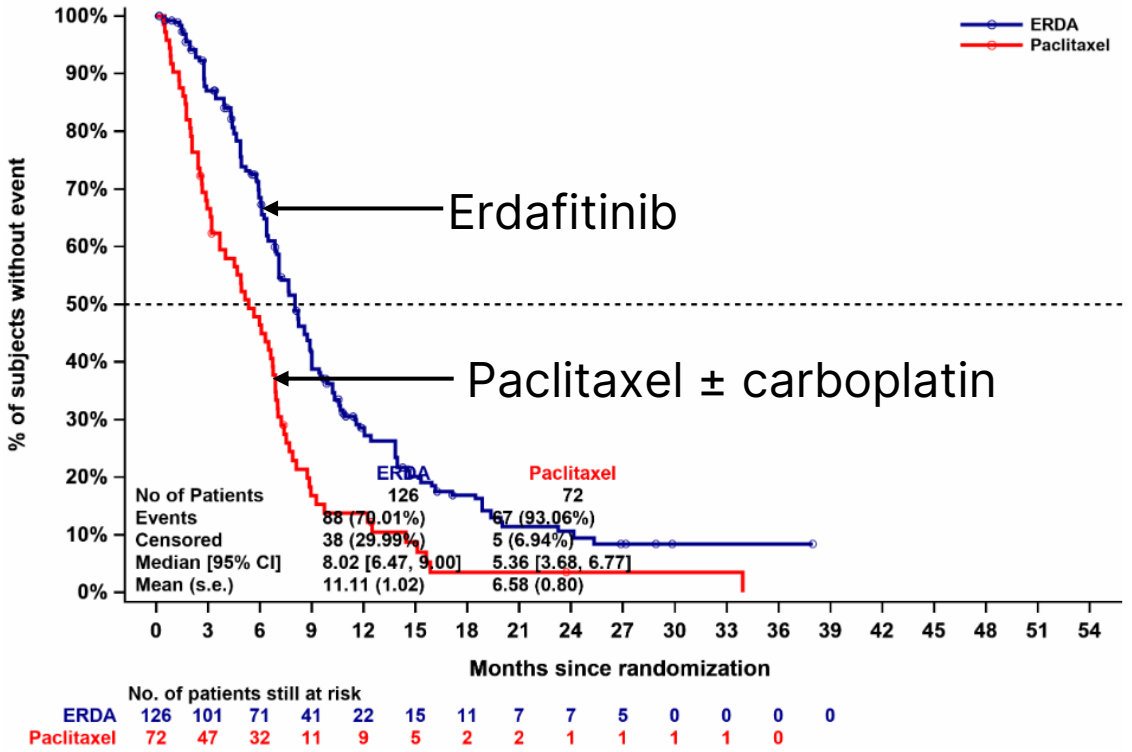


Abbreviations: IPD-ITC, individual patient data indirect treatment comparison; IPW, inverse probability weighting; RWE, real world evidence; MAIC, matching adjusted indirect comparison; mUC, metastatic urothelial cancer

Key ITC results (1/3)

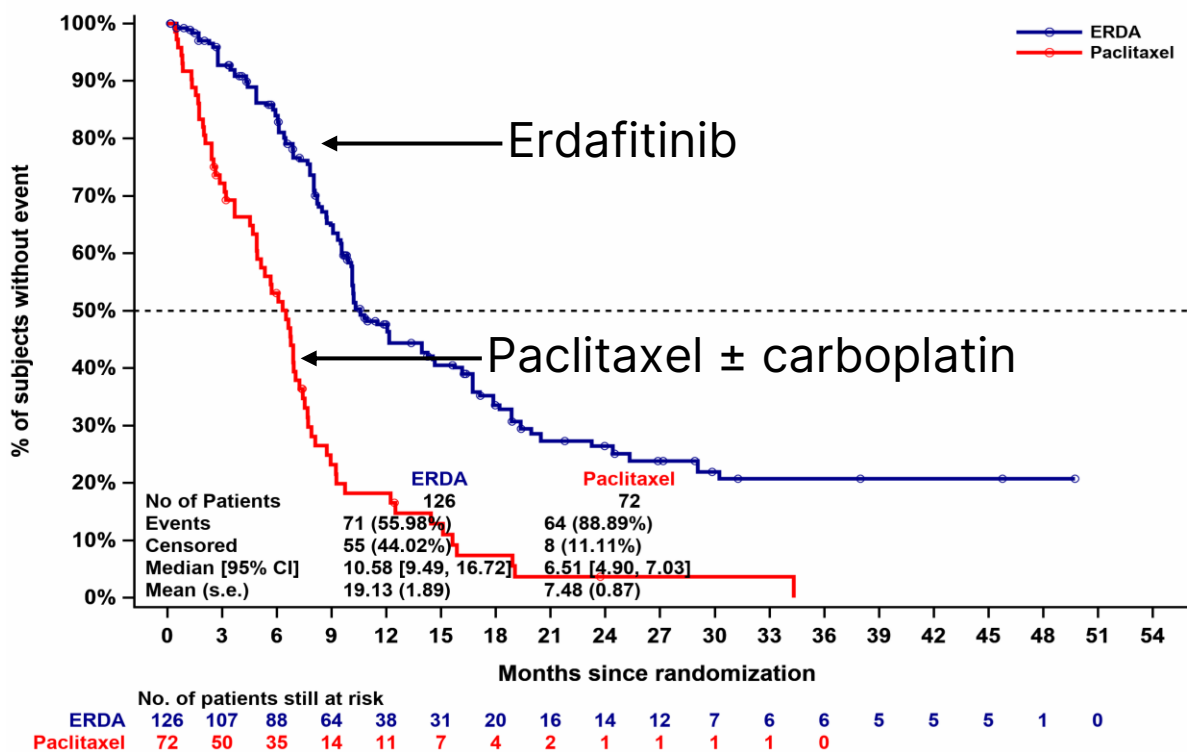
ITC results using ATC weighting (base case) - Erdafitinib improves OS and TTNT (in the absence of PFS) compared to **basket comparator**

Figure: Kaplan-Meier curve for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel ± carboplatin



HR (95% CI; p-value)	0.53 (0.37 to 0.76), p<0.0005

Figure: Kaplan-Meier curve for ATC-adjusted OS comparison for erdafitinib versus paclitaxel ± carboplatin



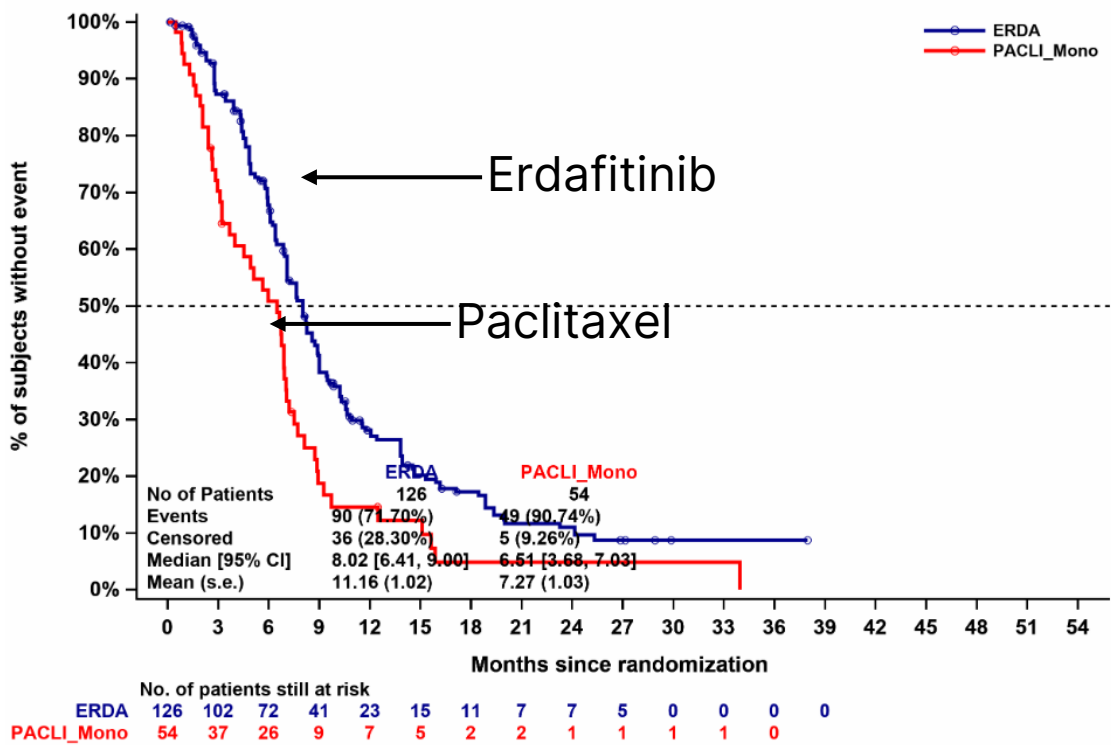
HR (95% CI; p-value),	0.35 (0.23 to 0.52), p < 0.0001

Abbreviations: ATC, Average treatment effect for the control; IPD-ITC, individual patient data indirect treatment comparison; IPW, inverse probability weighting; RWE, real world evidence; MAIC, matching adjusted indirect comparison; mUC, metastatic urothelial cancer; OS, Overall survival; TTNT, Time to next treatment;

Key ITC results (2/3)

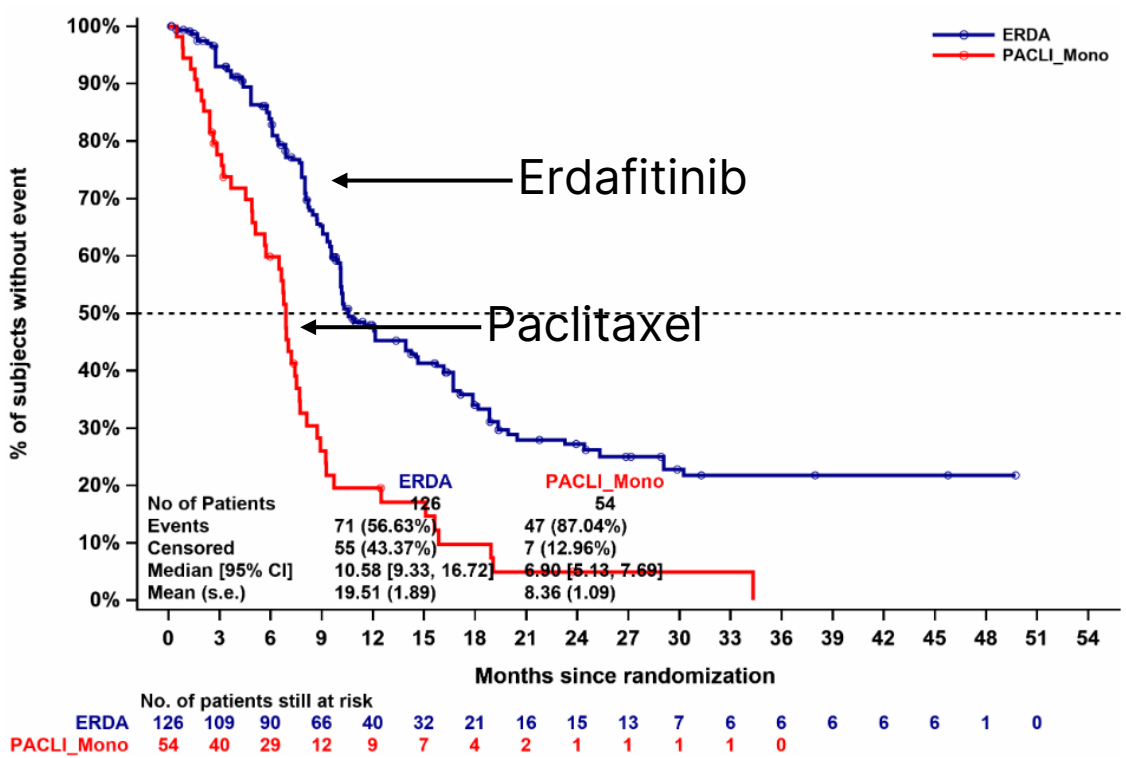
ITC results Erdafitinib improves OS and TTNT (in the absence of PFS) compared to **paclitaxel monotherapy**

Figure: Kaplan-Meier curve for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel monotherapy



HR (95% CI; p-value)	0.59 (0.39-0.87), p=0.0084

Figure: Kaplan-Meier curve for ATC-adjusted OS comparison for erdafitinib versus paclitaxel monotherapy



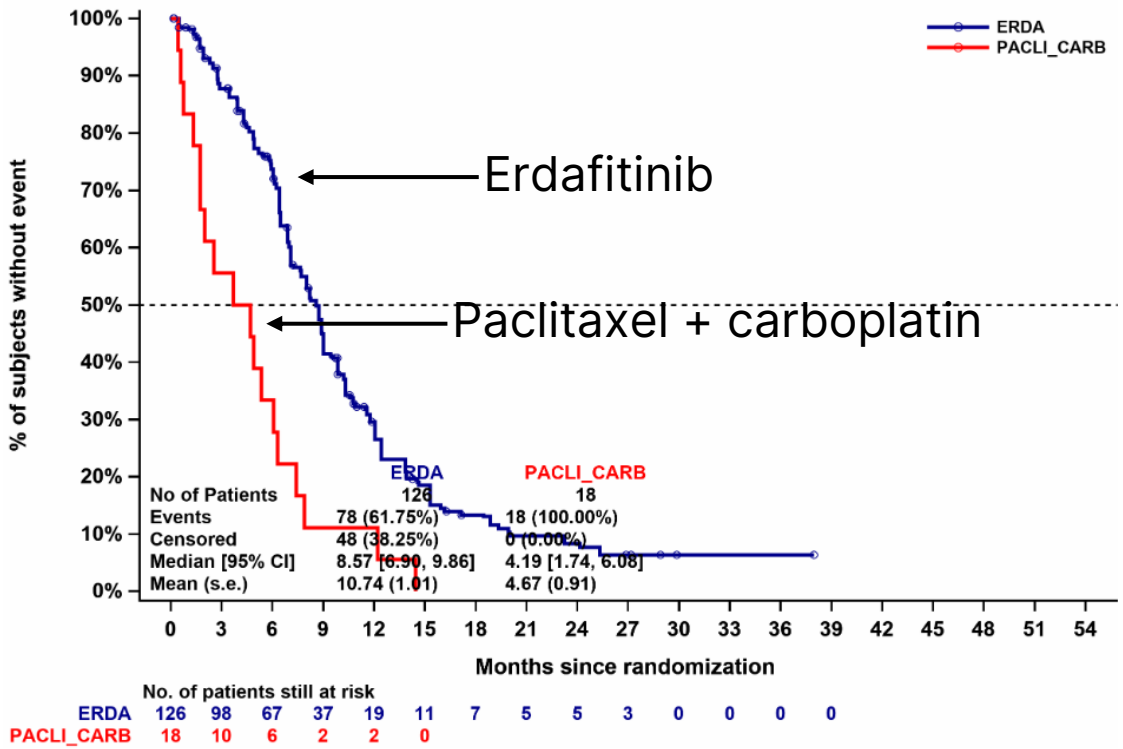
HR (95% CI; p-value)	0.38 (0.25-0.59), p<0.0001

Abbreviations: ATC, Average treatment effect for the control; CI; Confidence interval; HR, Hazard ratio; ITC, Indirect treatment comparison; OS, Overall survival; PFS, Progression-free survival; TTNT, Time to next treatment;

Key ITC results (3/3)

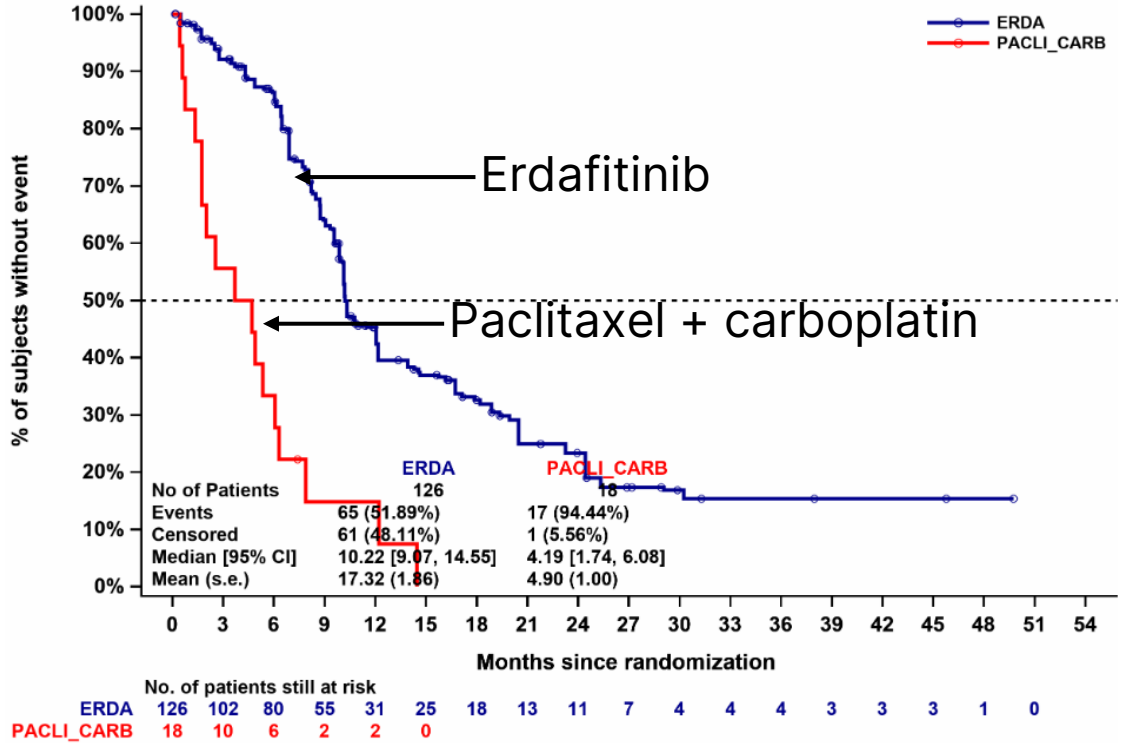
ITC results Erdafitinib improves OS and TTNT (in the absence of PFS) compared to **paclitaxel plus carboplatin combination**

Figure: Kaplan-Meier curve for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel + carboplatin



HR (95% CI; p-value)	0.34 (0.18-0.64), p=0.0008

Figure: Kaplan-Meier curve for ATC-adjusted OS comparison for erdafitinib versus paclitaxel + carboplatin



HR (95% CI; p-value)	0.22 (0.11-0.44), p<0.0001

Abbreviations: ATC, Average treatment effect for the control; CI; Confidence interval; HR, Hazard ratio; ITC, Indirect treatment comparison; OS, Overall survival; PFS, Progression-free survival; TTNT, Time to next treatment;

ICER Impact: Large

Key Issue: Basket of comparators

Company

- Comparator in the model is a basket of paclitaxel monotherapy and paclitaxel + carboplatin (weighted 3:1)
  - ↳ The 3:1 ratio was derived from the UK RW mUC study, in which 75% of patients that received paclitaxel ± carboplatin after PD-L(1) treatment received paclitaxel monotherapy and 25% received paclitaxel + carboplatin
- Ratio supported by consensus from UK based Advisory board meeting

EAG comments

- Acknowledges the limitation of lower patient numbers when modelling comparators separately
- Provides results comparing both to the basket of treatments and the individual comparators separately
- ITC and model results for each comparator separately are counterintuitive
  - ↳ Suggest paclitaxel monotherapy provides superior results than paclitaxel + carboplatin

Table: Summary of modelled QALYs and ITC results (OS, TTNT) for the basket and individual comparators

	Basket	Paclitaxel monotherapy	Paclitaxel + carboplatin
Total unmodified comparator QALYs	0.484	0.511	0.348
Median OS (months)	6.51	6.90	4.19
Median TTNT (months)	5.36	6.51	4.19

What is the most appropriate comparator to include in the modelling?

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Abbreviations: ITC, Indirect treatment comparison; mUC, Metastatic urothelial carcinoma; OS, Overall survival; PD-L1, Programmed death-ligand 1; QALY, Quality adjusted life year; RW, Real-world; TTNT, Time to next treatment;

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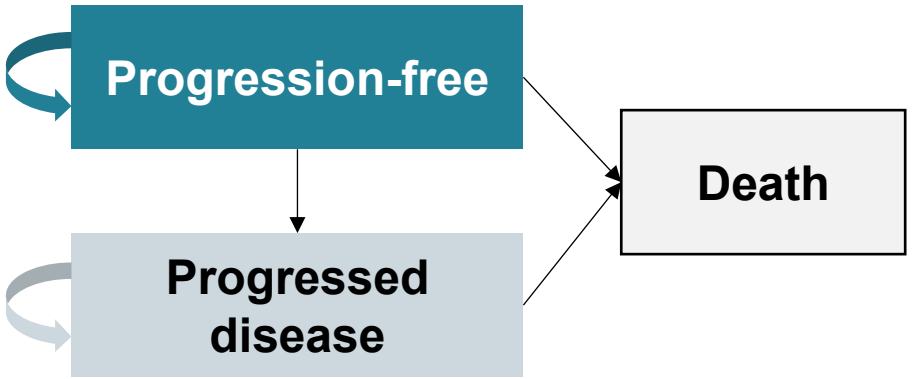
Company's model overview

Figure: Model structure



Technology affects <u>costs</u> by:

- Increased treatment costs
- Increased resource-use costs
- Reduced administration costs

Technology affects <u>QALYs</u> by:

- Increased time progression free
- Increased OS

Assumptions with <u>greatest ICER effect</u>:

- Choice of comparator
- QALY weightings for severity

Abbreviations: ICER, Incremental cost-effectiveness ratio; OS, Overall survival; QALY, Quality adjusted life year;

ICER Impact: Moderate

Key Issue: Treatment effectiveness extrapolation (1/2)

Background

- Parametric survival curves fitted to ITC results for intervention and comparators (OS, TTNT, PFS and TTD)

Company

- Assumed that the PH assumption did not hold for OS, TTNT, PFS and TTD
- Individually fitted distributions that can model PH fit poorly, including shared parameter would worsen fit
- AFT models could provide good fits but the assumption of a constant treatment effect is very strong, and even small violations can be meaningful in long-term extrapolations

EAG comments

- Fitting curves to data including few patients at risk for substantial periods introduces uncertainty
  - ↳ Seems particularly true for OS (erdafitinib OS ≈6% of patients at risk after 30 months (total 51 months of data))
- Scenario analyses showed that the ICER difference between the most pessimistic and optimistic erdafitinib OS curves is approximately £5,000 per QALY gained

Abbreviations: AFT, Accelerated failure time; ITC, Indirect treatment comparison; OS, Overall survival; PFS, Progression-free survival; PH, Proportional hazards; QALY, Quality adjusted life year; TTD, Time to treatment discontinuation; TTNT, Time to next treatment;

ICER Impact: Moderate

Key Issue: Treatment effectiveness extrapolation (2/2)

Figure: Erdafitinib long term OS extrapolations, THOR

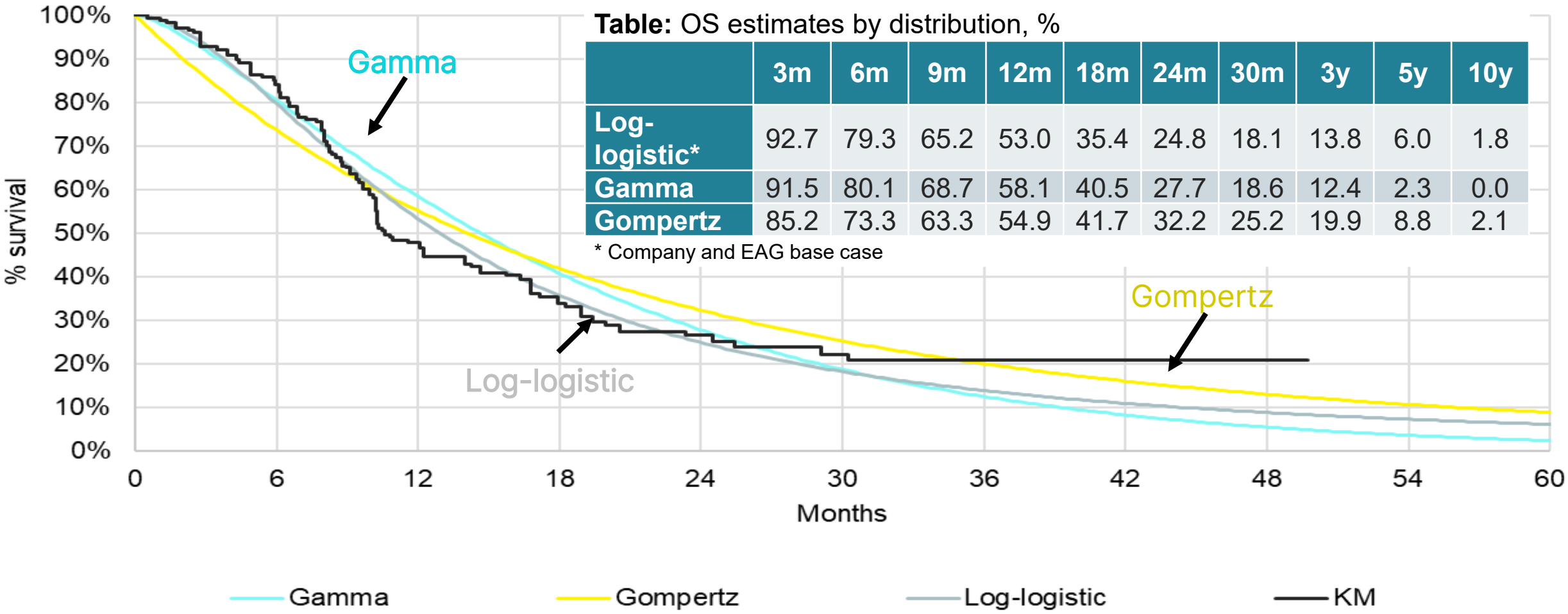


Table: OS estimates by distribution, %

	3m	6m	9m	12m	18m	24m	30m	3y	5y	10y
Log-logistic*	92.7	79.3	65.2	53.0	35.4	24.8	18.1	13.8	6.0	1.8
Gamma	91.5	80.1	68.7	58.1	40.5	27.7	18.6	12.4	2.3	0.0
Gompertz	85.2	73.3	63.3	54.9	41.7	32.2	25.2	19.9	8.8	2.1

* Company and EAG base case

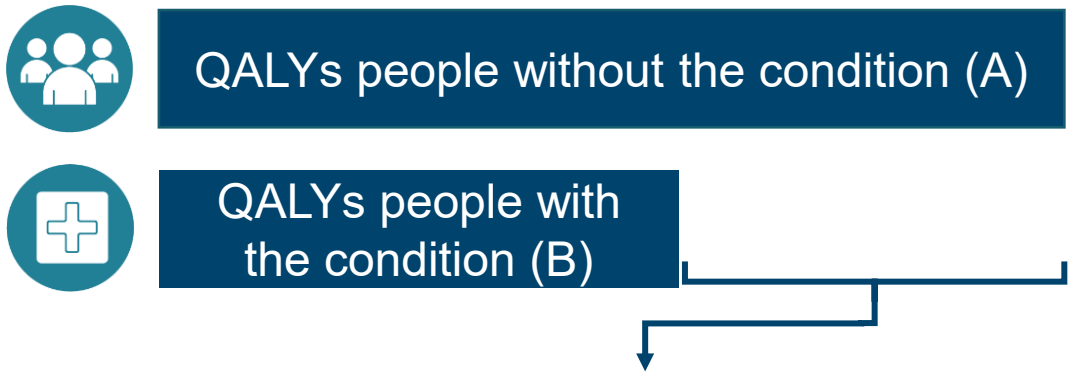
What is the most appropriate distribution to use to extrapolate OS for erdafitinib?

Abbreviations: OS, Overall survival;

ICER Impact: Large

QALY weightings for severity (1/3)

Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

QALY weight	Absolute shortfall	Proportional shortfall
1	Less than 12	Less than 0.85
X 1.2	12 to 18	0.85 to 0.95
X 1.7	At least 18	At least 0.95

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Abbreviations: QALY, quality-adjusted life year

ICER Impact: Large

Key Issue: QALY weightings for severity (2/3)

Company

- Calculated the severity weight for erdafitinib versus comparators based on adjusted THOR population characteristics (mean age 66.5 years and 26% females).
  - ↳ Mean age of population that received paclitaxel monotherapy or paclitaxel + carboplatin in the UK RW mUC study: 64.7 years
- Assessing the severity modifier using PSA methodology is not appropriate
  - ↳ Includes parameters that might not be relevant for the remaining QALYs in the population (e.g. costs)

EAG comments

- Considers it uncertain whether a x1.2 or x1.7 severity weight should be applied
  - ↳ Base-case assumptions resulted in a severity weight of x1.7 (except paclitaxel monotherapy, x1.2)
  - ↳ UK population characteristics from THOR and the clinical expert input both resulted in a weight of x1.2
- Is concerned about uncertainty in the modelled patient characteristics
  - ↳ UK population in THOR was small ([redacted]) → But, the mean age and % females were higher (i.e. [redacted]) as was the mean age (76 years) suggested during the advisory board
- Is concerned about uncertainty in the modelled treatment effectiveness of the comparators
- Considers using PSA to quantify uncertainty in selected severity weight to be informative and appropriate
  - ↳ In 51% of simulations the 1.7x modifier was met and 49% met the 1.2x modifier

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Abbreviations: PSA, Probabilistic sensitivity analysis; QALY, Quality adjusted life year;

ICER Impact: Large

Key Issue: QALY weightings for severity (3/3)

Table: Summary of QALY shortfall analysis depending on the comparator arm and population characteristics

	EAG (ITC)						Company (ITC)					
	Basket		Paclitaxel plus carboplatin		Paclitaxel monotherapy		Basket		Paclitaxel plus carboplatin		Paclitaxel monotherapy	
Population	THOR	THOR UK	THOR	THOR UK	THOR	THOR UK	THOR	THOR UK	THOR	THOR UK	THOR	THOR UK
Total expected QALYs - current treatment	0.48	0.48	0.35	0.35	0.51	0.51	0.50	0.50	0.37	0.37	0.53	0.53
Absolute QALY shortfall	9.69	7.16	9.82	7.29	9.66	7.13	9.67	7.14	9.80	7.27	9.64	7.11
Proportional QALY shortfall	95.2%	93.7%	96.6%	95.5%	94.98%	93.3%	95.1%	93.4%	96.4%	95.2%	94.8%	93.1%
QALY weight	1.7	1.2	1.7	1.7	1.2	1.2	1.7	1.2	1.7	1.7	1.2	1.2

THOR – 67 years 26% females (Remaining QALYs without disease 10.17)
THOR UK – [redacted] (Remaining QALYS without disease 7.64)

Should an x1.2 or an x1.7 QALY weighting for severity be applied?

Abbreviations: ITC, Indirect treatment comparison; QALY, Quality adjusted life year;

ICER Impact: Unknown

Key Issue: Missing data

Background

- Disease stage data was missing in 27% of patients in the THOR trial, and ECOG PS data was missing in 57% of patients in the UK RW data

Company

- Adopted worst-case approach to deal with missing data → Patients with missing ECOG PS or stage assigned less favourable characteristics → conservative as upweights less favourable erdafitinib patients
- Analyses showed no major difference in association with the outcome between the missing category and the other categories
- Chosen approach retains the available data from both studies, increasing sample size and robustness
- Sensitivity analyses showed "missing excluded" and "best case" scenarios generated comparable results
- Alternative methods (such as multiple imputation) were not feasible due to the limited number of variables available and high percentage of missing data

EAG comments

- The worst-case approach resulted in shorter erdafitinib PFS and lower ICERs than in the other scenarios
- Questions the assumption that data was not missing at random
- If available data is unsuitable for multiple imputation, then this brings into questions the reliability of the ITC
- Want to see scenario analysis using alternative methods (such as multiple imputation)

What is the most appropriate approach for dealing with missing data in THOR and UK RW studies?

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Abbreviations: ECOG, Eastern Cooperative Oncology Group; ICER, Incremental cost-effectiveness ratio; ITC, Indirect treatment comparison; PFS, Progression-free survival; PS, Performance status; RW, Real-world;

ICER Impact: Unknown

Key Issue: Plausibility of modelled results

Table: Breakdown of discounted LY & QALY gains in observed (up to 3 yrs) vs extrapolated period (beyond 3 yrs)

	Observed period (0-3 yrs)		Extrapolated period (3+ yrs)		Total	
	LYs	QALYs	LYs	QALYs	LYs	QALYs
Erdafitinib	1.298	[redacted]	0.362	[redacted]	1.660	[redacted]
Progression-free	0.562	[redacted]	0.022	[redacted]	0.584	[redacted]
Progressed	0.736	[redacted]	0.339	[redacted]	1.076	[redacted]
Paclitaxel ± carboplatin	0.656	0.454	0.078	0.052	0.732	0.506
Progression-free	0.546	0.385	0.060	0.041	0.605	0.426
Progressed	0.110	0.069	0.018	0.011	0.127	0.080

EAG comments

- In the company's revised base-case the majority of the LYs (65%) and QALYs (62%) for erdafitinib were modelled to occur in the PD health state → The same was not seen for paclitaxel ± carboplatin
- Expected most benefits to occur in the PF health state, as erdafitinib was given until progression
- Potential explanation could be uncertainty in the long term OS extrapolations
  - ↳ However, a similar trend was observed in the trial data with the majority of LYs and QALYs occurring in the PD health state (58% of total LYs and 54% of total QALYs)
- Requests an explanation of the mechanism by which the economic model generated these results

Do committee consider that the model generates plausible (externally valid) results?

Abbreviations: LY, Life years; PD, Progressed disease; PF, Progression free; QALY, Quality adjusted life year;

ICER Impact: Moderate

Key Issue: Resource use and costs

Background

- Health care resource use costs associated with disease management, monitoring and patient follow-up were included in the model → Pre- and post-progression costs were calculated separately

Company

- Base case included higher pre-progression treatment cycle costs for paclitaxel ± carboplatin
  - ↳ Difference could be due to a lower number of outpatient visits for patients receiving erdafitinib
  - ↳ Based on a single clinical expert comment during the advisory board stating that [redacted]
- Base case included equivalent post-progression cycle costs for erdafitinib and paclitaxel ± carboplatin
  - ↳ A conservative assumption as compared to patients not receiving erdafitinib patients receiving erdafitinib are expected to live longer and experience improvements in overall health

EAG comments

- Base case included equivalent pre and post progression costs for erdafitinib and paclitaxel ± carboplatin
- Evidence from a single clinical expert is insufficient to justify modelling different resource use.

Is it appropriate to assume different HCRU between erdafitinib and paclitaxel ± carboplatin?

Abbreviations: HCRU, Health care resource use;

ICER Impact: Low

Key Issue: Utility values (1/2)

Background

- Utility values estimated for the PF and PD states were based on EQ-5D data from THOR

Company

- Base case utility estimates were derived separately for the PF and PD health states using linear mixed models for repeated measures (MMRMs) without including any additional covariates
- MMRM approach produced utilities values that were close to those estimated in TA522
- Provided scenario analysis using multivariable regression modelling with additional covariates for the estimation of the PF and PD health state utilities
  - ↳ Multivariable models including baseline characteristics may not be valid unless the distribution of those characteristics is tracked over time, given that baseline characteristics may change over time and may bias the results
  - ↳ Fitting a joint MMRM for the PF and PD health states would mean that PF HRQoL would influence estimated PD HRQoL. This is undesirable as patients spent much more time PF than with PD

EAG comments

- Base case used the company's best fitting multivariable regression model
  - ↳ Prefers estimating the PF and PD utilities in a single model, including additional relevant covariates

Abbreviations: HRQoL, Health-related quality of life; PD, Progressed disease; PF, Progression free; TA, Technology appraisal; MMRM, Mixed models for repeated measures; EQ-5D, EuroQol 5-Dimensions;

ICER Impact: Low

Key Issue: Utility values (1/2)

EAG comments

- Reasonable to assume that there is a relationship between HRQoL in the PF and PD health states so it is reasonable to estimate PF and PD utility values within a single model
- Acknowledged the potential limitation that baseline characteristics may not be valid unless the distribution of those characteristics is tracked over time
  - ↳ However, the company's best fitting multivariable regression model included progression status and AEs (covariates that were tracked over time)
- Agrees MMRM utilities were close to those in TA522, but the PF utility from the multivariable regression model was even closer to the PF utility estimated in TA522
- Using MMRMs without including additional covariates may miss potential confounding effects resulting in potentially biased HSUVs.

Health state	MMRM approach (SE)	Multivariable regression model approach	TA522 (TA692) (pembrolizumab vs chemotherapy – pooled)
Progression free	[redacted]	[redacted]	0.678
Progressed disease	[redacted]	[redacted]	0.614
*Weighted average of ECOG 1–2 coefficients applied to the intercept.			

Which is the most appropriate method to derive utilities for the model?

Abbreviations: AE, Adverse event; ECOG, Eastern Cooperative Oncology Group; HRQoL, Health-related quality of life; HSUV, Health state utility values; MMRM, Mixed models for repeated measures; PD, Progressed disease; PF, Progression free; SE, Standard error; TA, Technology

ICER Impact: Low

Key Issue: Additional committee preferences

Background

- Company base case does not include a stopping rule for paclitaxel and paclitaxel + carboplatin
- PFS data for paclitaxel ± carboplatin was not collected in the UK mUC RW study
- The majority of patients in the THOR trial were from outside the UK

Company

- At clarification, agreed a hard stop at 24 weeks could improve alignment with UK practice and would be in line with assumptions in TA530 and TA692
- Base case uses PFS data from Vaishampayan et al. 2005 extrapolated using a log-logistic curve
- Company clinical experts noted that the trial population are younger than the NHS population

EAG comments

- Base case assumes patient receiving paclitaxel ± carboplatin are treated up to a maximum of 6 cycles
  - ↳ Stopping rule of 6 cycles (i.e. 24 weeks) supported by EAG clinical experts and existing guidelines
- Base case uses paclitaxel ± carboplatin TTNT data from the UK mUC RW study as to inform PFS
- There are likely differences in race and ECOG score between the trial population and NHS clinical practice
- Subgroup analysis not powered to detect significant differences

1) Should a stopping rule be modelled for paclitaxel ± carboplatin?
2) Is the THOR trial generalisable to NHS clinical practice?
3) How should PFS for paclitaxel ± carboplatin be modelled?

Abbreviations: ECOG, Eastern Cooperative Oncology Group; mUC, Metastatic urothelial carcinoma; PFS, Progression-free survival; RW, Real-world; TA, Technology appraisal; TTNT, Time to next treatment;

Summary of company and EAG base case assumptions (1/2)

Table: Assumptions in company and EAG base case (Part 1)

Assumption	Company	EAG	
	Base case	Base case	Requested additional analysis
Missing data	A worst-case scenario approach to deal with missing data		• Alternative data imputation methods • Best-case scenario analysis for dealing with missing data
Basket of comparators	Basket of paclitaxel monotherapy and paclitaxel in combination with carboplatin, weighted 3:1, respectively* *Results also provided against individual comparators		• A fully incremental analysis including all relevant comparators
Paclitaxel ± carboplatin stopping rule	**No stopping rule**	**Stopping rule of 6 cycles (i.e. 24 weeks)**	-
Lack of data in the UK mUC RW study	**Data from Vaishampayan et al. 2005 to inform paclitaxel ± carboplatin PFS**	**TTNT data from the UK mUC RW study as a proxy for paclitaxel ± carboplatin PFS**	• Using the PFS of taxanes in TA525 and TA692 as a proxy for paclitaxel ± carboplatin PFS.

Summary of company and EAG base case assumptions (2/2)

Table: Assumptions in company and EAG base case (Part 2)

Assumption	Company	EAG	
	Base case	Base case	Requested additional analysis
Treatment effectiveness extrapolation	-	-	• Jointly fitted parametric models.
Utility values	**Derived separately for the PF and PD health states using linear MMRMs**	**Derived using a joint multivariable regression model**	-
Resource use and costs	**Higher pre-progression treatment cycle costs for paclitaxel ± carboplatin**	**Equivalent pre and post progression costs for erdafitinib and paclitaxel ± carboplatin**	-
QALY weightings for severity	x1.7	x1.7 **(Considers it uncertain whether a x1.2 or x1.7 severity weight should be applied)**	-

Committee preferences (1/3)

Parameter	Key Question	Scenarios	Committee preference
Comparators	What are the appropriate comparators for this appraisal?	-	?
Generalisability of THOR trial population	Is the THOR trial generalisable to NHS clinical practice?	-	?
FGFR status in RW UK study	• Is the presence of FGFR alteration an effect modifier for chemotherapy? • Is the UK RW study suitable to inform efficacy of paclitaxel +/- carboplatin in the model?	-	?
Plausibility of modelled results	Do committee consider that the model generates plausible (externally valid) results?	-	?

Committee preferences (2/3)

Parameter	Key Question	Scenarios	Committee preference
Missing data	What is the most appropriate approach for dealing with missing data in the THOR and UK RW studies?	• Worst-case approach • Patients with missing ECOG PS PF and/or stage omitted • Alternative methods (such as multiple imputation)	?
QALY weightings for severity	What QALY weighting for severity should be applied?	• x1.7 • x1.2	?
Treatment effectiveness extrapolation	What are the most appropriate distributions to use to extrapolate OS, TTNT, PFS and TTD?	• Choice of standard parametric models • Jointly fitted survival model (PH, AFT)	?
Stopping rule	Should a stopping rule be modelled for paclitaxel ± carboplatin?	• No stopping rule • Stopping rule of 6 cycles (i.e. 24 weeks)	?

Committee preferences (3/3)

Parameter	Key Question	Scenarios	Committee preference
Resource use and costs	Is it appropriate to assume different HCRU between erdafitinib and paclitaxel ± carboplatin?	• Higher pre-progression treatment cycle costs for paclitaxel ± carboplatin • Equivalent pre and post progression costs	?
Basket of comparators	What is the most appropriate way to represent the paclitaxel +/- carboplatin comparator?	• Paclitaxel • Paclitaxel + carboplatin • Paclitaxel ± carboplatin, 3:1 ratio	?
Utility values	Which is the most appropriate method to derive utilities for the model?	• Linear MMRMs without including any additional covariates • Multivariable regression model	?
Modelling PFS	How should PFS for paclitaxel ± carboplatin be modelled?	• Vaishampayan et al. 2005 • Paclitaxel ± carboplatin TTNT data from the UK mUC RW study • PLUTO	?

Erdafitinib for treating metastatic or unresectable FGFR-altered urothelial cancer

- ❑ Background
- ❑ Clinical effectiveness and key issues
- ❑ Modelling and cost effectiveness
- ✓ **Cost effectiveness results**

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Company base case results

Table: Company probabilistic base case results **vs basket of paclitaxel ± carboplatin**, 1.7x modifier applied

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Erdafitinib	[redacted]	1.671	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.743	0.865	[redacted]	0.928	[redacted]	21,406

Table: Company probabilistic base case results **vs paclitaxel monotherapy** , 1.2x modifier applied

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Erdafitinib	[redacted]	1.694	[redacted]				
Paclitaxel	[redacted]	0.786	0.643	[redacted]	0.908	[redacted]	28,876

Table: Company probabilistic base case results **vs paclitaxel + carboplatin**, 1.7x modifier applied

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Erdafitinib	[redacted]	1.547	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.570	0.666	[redacted]	0.976	[redacted]	25,177

NICE Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, Life years; QALY, Quality adjusted life year;

EAG base case results

Table: EAG probabilistic base case results **vs basket of paclitaxel ± carboplatin**, 1.7x severity modifier applied

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Erdafitinib	[redacted]	1.671	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.743	0.833	[redacted]	0.928	[redacted]	£30,386

Table: EAG probabilistic base case results **vs paclitaxel monotherapy** , 1.2x severity modifier applied

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Erdafitinib	[redacted]	1.694	[redacted]				
Paclitaxel	[redacted]	0.786	0.624	[redacted]	0.908	[redacted]	42,061

Table: EAG probabilistic base case results **vs paclitaxel + carboplatin**, 1.7x severity modifier applied

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Erdafitinib	[redacted]	1.547	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.570	0.630	[redacted]	0.976	[redacted]	32,233

Abbreviations: ICER, Incremental cost-effectiveness ratio; LY, Life years; QALY, Quality adjusted life year;

Company base case deterministic scenario analysis
Erdafitinib vs paclitaxel ± carboplatin basket (1.7x severity)

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
0. CS base-case					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.856	[redacted]	[redacted]	£21,052
1. CS + Stopping rule of 6 cycles (i.e. 24 weeks) to paclitaxel monotherapy and paclitaxel + carboplatin					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.856	[redacted]	[redacted]	£25,222
2. CS + TTNT of paclitaxel +carboplatin RW data for modelling of paclitaxel +carboplatin PFS					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.851	[redacted]	[redacted]	£21,745
3. CS + Multivariable regression model for estimation of health state utilities					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.829	[redacted]	[redacted]	£22,798
4. CS + Assuming equal HCRU between erdafitinib and comparators					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.856	[redacted]	[redacted]	£23,820
5. EAG base case (1 to 4 combined)					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.822	[redacted]	[redacted]	£30,194

Abbreviations: CS, Company submission; HCRU, Health care resource use; ICER, Incremental cost-effectiveness ratio; QALY, Quality adjusted life year; TTNT, Time to next treatment;

Note: Scenarios are presented separately with EAG base case combining all EAG preferred assumptions Deterministic results presented for basked comparator weighted 75% paclitaxel monotherapy with 25% paclitaxel plus carboplatin

Company base case deterministic scenario analysis Erdafitinib vs paclitaxel monotherapy (1.2x severity)

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
0. CS base-case					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.634	[redacted]	[redacted]	£28,214
1. CS + Stopping rule of 6 cycles (i.e. 24 weeks) to paclitaxel monotherapy and paclitaxel + carboplatin					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.634	[redacted]	[redacted]	£35,150
2. CS + TTNT of paclitaxel +carboplatin RW data for modelling of paclitaxel +carboplatin PFS					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.634	[redacted]	[redacted]	£28,085
3. CS + Multivariable regression model for estimation of health state utilities					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.613	[redacted]	[redacted]	£30,560
4. CS + Assuming equal HCRU between erdafitinib and comparators					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.634	[redacted]	[redacted]	£32,197
5. EAG base case (1 to 4 combined)					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.613	[redacted]	[redacted]	£41,740

Abbreviations: CS, Company submission; HCRU, Health care resource use; ICER, Incremental cost-effectiveness ratio; QALY, Quality adjusted life year; TTNT, Time to next treatment;
Note: Scenarios are presented separately with EAG base case combining all EAG preferred assumptions
Deterministic results presented for paclitaxel monotherapy with clinical effectiveness from the NCRAS dataset

Company base case deterministic scenario analysis
Erdafitinib vs paclitaxel plus carboplatin (1.7x severity)

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
0. CS base-case					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.625	[redacted]	[redacted]	£24,367
1. CS + Stopping rule of 6 cycles (i.e. 24 weeks) to paclitaxel monotherapy and paclitaxel + carboplatin					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.625	[redacted]	[redacted]	£26,367
2. CS + TTNT of paclitaxel +carboplatin RW data for modelling of paclitaxel +carboplatin PFS					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.611	[redacted]	[redacted]	£25,841
3. CS + Multivariable regression model for estimation of health state utilities					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.611	[redacted]	[redacted]	£26,238
4. CS + Assuming equal HCRU between erdafitinib and comparators					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.625	[redacted]	[redacted]	£26,924
5. EAG base case (1 to 4 combined)					
Erdafitinib	[redacted]	[redacted]			
Paclitaxel ± carboplatin	[redacted]	0.591	[redacted]	[redacted]	£31,398

Abbreviations: CS, Company submission; HCRU, Health care resource use; ICER, Incremental cost-effectiveness ratio; QALY, Quality adjusted life year; TTNT, Time to next treatment;
Note: Scenarios are presented separately with EAG base case combining all EAG preferred assumptions
Deterministic results presented for paclitaxel plus carboplatin with clinical effectiveness informed from the NCRAS dataset

EAG scenario analysis (Applied individually to EAG base case) vs paclitaxel ± carboplatin basket (1.7x severity modifier applied)

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
EAG base-case							
Erdafitinib	[redacted]	1.671	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.743	0.833	[redacted]	0.928	[redacted]	£30,386
EAG BC + Adjusted population where patients with missing ECOG PS PF and/or stage were omitted							
Erdafitinib	[redacted]	1.482	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.677	0.754	[redacted]	0.805	[redacted]	43,032
EAG BC + PFS of paclitaxel monotherapy from PLUTO to inform comparator PFS							
Erdafitinib	[redacted]	1.671	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.743	0.830	[redacted]	0.928	[redacted]	30,099
EAG BC + TTD of paclitaxel + carboplatin modelled using TTD of taxanes from TA525							
Erdafitinib	[redacted]	1.671	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.743	0.833	[redacted]	0.928	[redacted]	31,581

Abbreviations: BC, Base case; ECOG, Eastern Cooperative Oncology Group; ICER, Incremental cost-effectiveness ratio; LY, Life years; PF, Progression free; PS, Performance status; QALY, Quality adjusted life year; TA, Technology appraisal; TTD, Time to treatment discontinuation;

EAG scenario analysis (Applied individually to EAG base case) vs paclitaxel (1.2x severity modifier applied)

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
EAG base-case							
Erdafitinib	[redacted]	1.694	[redacted]				
Paclitaxel	[redacted]	0.786	0.624	[redacted]	0.908	[redacted]	42,061
EAG BC + Adjusted population where patients with missing ECOG PS PF and/or stage were omitted							
Erdafitinib	[redacted]	1.490	[redacted]				
Paclitaxel	[redacted]	0.754	0.594	[redacted]	0.736	[redacted]	61,024
EAG BC + PFS of paclitaxel monotherapy from PLUTO to inform comparator PFS							
Erdafitinib	[redacted]	1.694	[redacted]				
Paclitaxel	[redacted]	0.786	0.875	[redacted]	0.908	[redacted]	29,551
EAG BC + TTD of paclitaxel + carboplatin modelled using TTD of taxanes from TA525							
Erdafitinib	[redacted]	1.694	[redacted]				
Paclitaxel	[redacted]	0.786	0.624	[redacted]	0.908	[redacted]	44,570

Abbreviations: BC, Base case; ECOG, Eastern Cooperative Oncology Group; ICER, Incremental cost-effectiveness ratio; LY, Life years; PF, Progression free; PS, Performance status; QALY, Quality adjusted life year; TA, Technology appraisal; TTD, Time to treatment discontinuation;

EAG scenario analysis (Applied individually to EAG base case) vs paclitaxel + carboplatin (1.7x severity modifier applied)

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
EAG base-case							
Erdafitinib	[redacted]	1.547	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.570	0.630	[redacted]	0.976	[redacted]	32,233
EAG BC + Adjusted population where patients with missing ECOG PS PF and/or stage were omitted							
Erdafitinib	-	-	-	-	-	-	-
Paclitaxel + carboplatin	-	-	-	-	-	-	-
EAG BC + PFS of paclitaxel monotherapy from PLUTO to inform comparator PFS							
Erdafitinib	[redacted]	1.547	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.570	0.640	[redacted]	0.976	[redacted]	31,696
EAG BC + TTD of paclitaxel + carboplatin modelled using TTD of taxanes from TA525							
Erdafitinib	[redacted]	1.547	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.570	0.630	[redacted]	0.976	[redacted]	32,384

Abbreviations: BC, Base case; ECOG, Eastern Cooperative Oncology Group; ICER, Incremental cost-effectiveness ratio; LY, Life years; PF, Progression free; PS, Performance status; QALY, Quality adjusted life year; TA, Technology appraisal; TTD, Time to treatment discontinuation;

Optimistic and pessimistic OS extrapolations for erdafitinib conditional upon company and EAG base cases – (Basket comparator)

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER (£/QALY)
CS base-case					
Erdafitinib	[redacted]	[redacted]			
Basket	[redacted]	0.856	[redacted]	[redacted]	£21,052
CS + Alternative OS for erdafitinib (Gamma)					
Erdafitinib	[redacted]	[redacted]			
Basket	[redacted]	0.856	[redacted]	[redacted]	£23,806
CS + Alternative OS for erdafitinib (Gompertz)					
Erdafitinib	[redacted]	[redacted]			
Basket	[redacted]	0.856	[redacted]	[redacted]	£18,469
EAG base-case					
Erdafitinib	[redacted]	[redacted]			
Basket	[redacted]	0.822	[redacted]	[redacted]	£30,194
EAG + Alternative OS for erdafitinib (Gamma)					
Erdafitinib	[redacted]	[redacted]			
Basket	[redacted]	0.822	[redacted]	[redacted]	£34,731
EAG + Alternative OS for erdafitinib (Gompertz)					
Erdafitinib	[redacted]	[redacted]			
Basket	[redacted]	0.822	[redacted]	[redacted]	£26,100

Abbreviations: CS, Company submission; ICER, Incremental cost-effectiveness ratio; OS, Overall survival; QALY, Quality adjusted life year;

Erdafitinib for treating metastatic or unresectable FGFR-altered urothelial cancer

Supplementary appendix

NICE National Institute for Health and Care Excellence

Supplementary slide: Comparators

Table: Patients in the RW UK mUC study, treatments after PD-(L)1 treatment (not specific to FGFR+ population)

Treatment	Patients (n)	Patients (%)	Included	Comments
Paclitaxel ± carboplatin	72	36.4%	Yes	Base-case; the most appropriate comparator in the submission. N=54 is monotherapy, N=18 is combination.
PD-(L)1 retreatment	47	23.7%	No	PD-(L)1 retreatment, combined atezolizumab and pembrolizumab (16/31 atezolizumab/pembrolizumab split).
Platinum (cisplatin or carboplatin) + gemcitabine after PD-(L)1 in front line	54	27.3%	No	Platinum (cisplatin or carboplatin) + gemcitabine use after PD-(L)1 1L treatment, not clinical practice after COVID-19 pandemic, not included. N=47 is carboplatin based, N=7 is cisplatin based.
Potential platinum (cisplatin + carboplatin) based rechallenge in 3L	7	3.5%	No	Potential platinum (cisplatin or carboplatin) + gemcitabine rechallenge; patient number too low to make a comparison. N=6 is carboplatin based, N=1 is cisplatin based.
Docetaxel	4	2.0%	No	Docetaxel use is very limited and is not considered a relevant comparator.
12 different treatment options*	14	7.1%	No	Unable to make a comparison. A blend of the rest of treatments being used

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Abbreviations: FGFR, Fibroblast growth factor receptor; mUC, Metastatic urothelial carcinoma; PD-L1, Programmed death-ligand 1; RW, Real-world;

Link to – Comparators (1/2)

Supplementary slide: Baseline characteristics

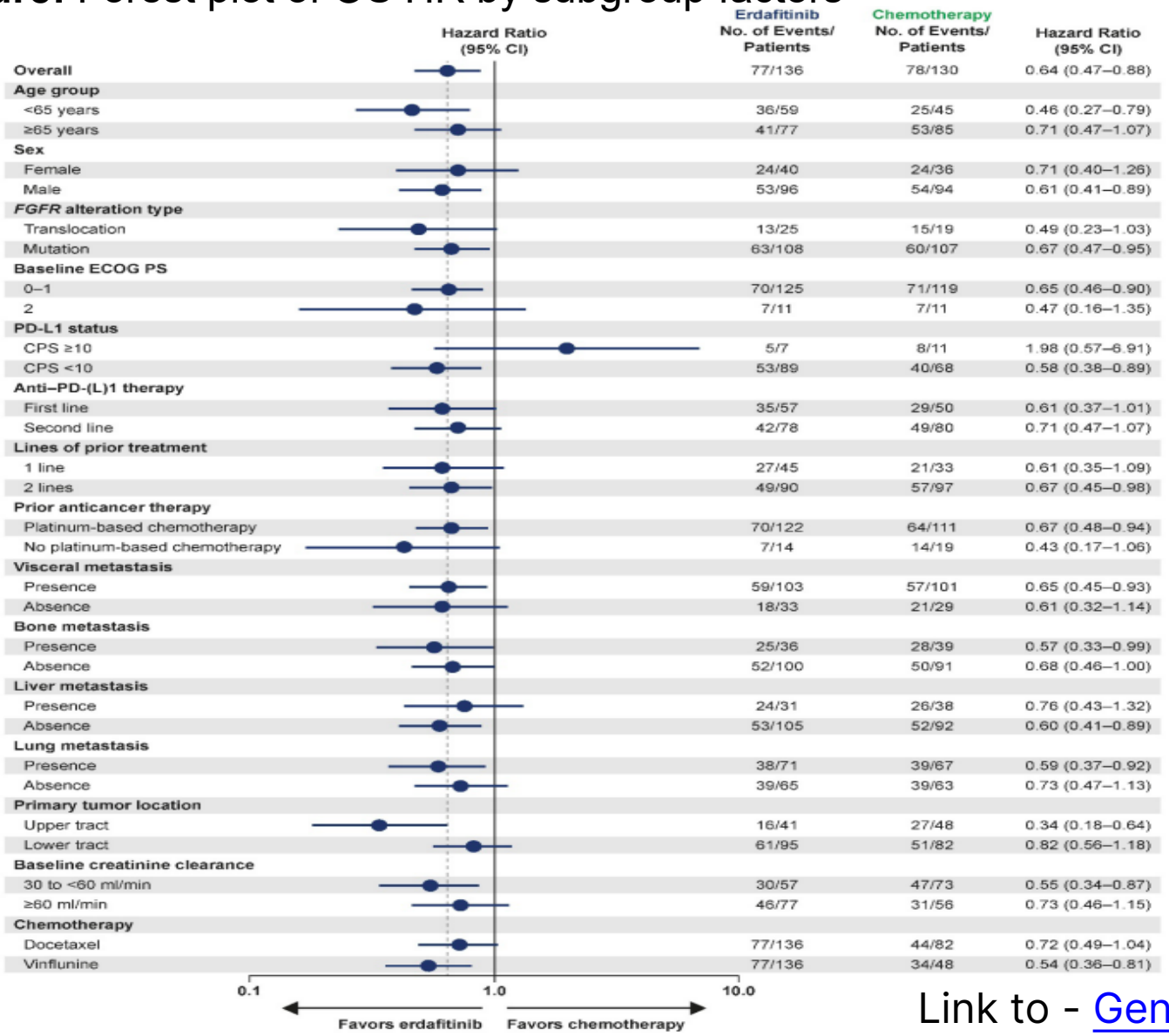
Characteristic	Erdafitinib (n = 136)	Chemotherapy (n = 130)
Median (range)	66.0 (32-85)	69.0 (35-86)
Male	96 (70.6)	94 (72.3)
Female	40 (29.4)	36 (27.7)
Asian	37 (27.2)	40 (30.8)
Black or African American	0	1 (0.8)
White	81 (59.6)	63 (48.5)
Multiple	0	1 (0.8)
Not reported	18 (13.2)	25 (19.2)
North America	8 (5.9)	5 (3.8)
Europe	82 (60.3)	80 (61.5)
Rest of the world	46 (33.8)	45 (34.6)
ECOG 0	63 (46.3)	51 (39.2)
ECOG 1	61 (44.9)	66 (50.8)
ECOG 2	12 (8.8)	13 (10.0)

Link to - Generalisability of THOR trial population

Abbreviations: Eastern Cooperative Oncology Group;

Supplementary slide: THOR trial forest plot

Figure: Forest plot of OS HR by subgroup factors



Abbreviations:

Link to - Generalisability of THOR trial population

Indirect treatment comparison methodology

ITC	Sub-method	Purpose	Notes
IPD-ITC	1. Regression adjustment	Regression model to adjust for confounders	
	2. IPW (ATC in base case)*	Reweighting to match RW UK population	Used in base cases
	3. Doubly robust (1 & 2)	Combines regression and IPW	
MAIC	1. “PLUTO MAIC”	Compare erdafitinib (THOR and BLC2001) to paclitaxel (PLUTO) as “upper bounds” of effectiveness	
	2. “FGFR MAIC”	THOR matched to EV-301 to see if FGFR status effect modifier for chemotherapy.	No evidence it is effect modifier

*Average treatment effect for comparator (ATC) means the treatment effect was adjusted to match the comparator (RW UK) average which was assumed to better represent the target population. ATT (adjusted to treated population from THOR and ATE (adjusted to whole population) were also explored.

ITC Results

Comparison	OS HR (95% CI)	TTNT HR (95% CI)
Unadjusted comparison	0.33 (0.24–0.47)	-
Covariate adjustment	0.37 (0.26–0.54)	-
IPW ATT	0.32 (0.21–0.48)	-
IPW (ATC base case)	0.35 (0.23–0.52)	0.53 (0.37 to 0.76)
IPW (ATO)	0.36 (0.24–0.52)	-
IPW (ATE)	0.33 (0.22-0.48)	-
Doubly robust estimator	0.377 (0.250 – 0.567)	-

Abbreviations: ATC, Average treatment effect for the control; ATE, Average treatment effect; ATO, Average treatment effect for overlap; ATT, Average treatment effect for the treated; HR, Hazard ratio; IPD, Individual patient-level data; IPW, Inverse probability weighting; ITC, Indirect treatment comparison; MAICs, Matched-adjusted indirect comparison OS, Overall survival; RW, Real-world;

Back to ITC networks

Supplementary slide: Key ITC results

Table: Analysis of OS and PFS HRs from ITCs (vs individual comparators), MAIC and THOR

	OS HR (95% CI; p-value)	PFS / TTNT (95% CI; p-value)
Erdafitinib vs paclitaxel + carboplatin (ITC)	0.22 (0.11-0.44), <0.0001	0.34 (0.18-0.64), 0.0008
Erdafitinib vs paclitaxel (ITC)	0.38 (0.25-0.59), <0.0001	0.59 (0.39-0.87), 0.0084
Erdafitinib vs paclitaxel (MAIC PLUTO)*	0.59 (0.42-0.85), NR	0.81 (0.59, 1.11), NR
Erdafitinib vs chemotherapy (THOR)	0.64 (0.47,0.88), 0.005	0.58 (0.44. 0.78), 0.0002

**matching of the important characteristics: ECOG score, liver metastases, primary site bladder, and time since last platinum therapy*

Company

- ITCs looking at paclitaxel ± carboplatin individually result in relatively small sample sizes
- MAIC vs paclitaxel is an exploratory analysis that represents the upper bounds of relative efficacy
  - ↳ PLUTO patients had only recently been diagnosed and had received less intensive treatment
- Chemotherapy regimens in THOR (i.e docetaxel & vinflunine) are not relevant comparators

EAG comments

- All things being equal the ITC should be more accurate than the MAIC
  - ↳ But the ITC was associated with notable limitations (i.e missing data and lack of PFS data)
- MAIC results inform the ITC key issue
  - ↳ Evidence suggests the matching was successful
  - ↳ PFS HR does not align with the idea that the results represent the upper bounds of relative efficacy

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Abbreviations: CI; Confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, Hazard ratio; ITC, Indirect treatment comparison; NR, Not reported; OS, Overall survival; PFS, Progression-free survival; TTNT, Time to next treatment;

Comparators (1/2)*

Background

- NICE final scope included several comparators – Chemotherapy (including docetaxel, paclitaxel), atezolizumab and BSC

Company

- The main comparator was paclitaxel ± carboplatin, implemented as a basket of paclitaxel monotherapy and paclitaxel with carboplatin, weighted 3:1, respectively
- Company clinical experts and RWE confirms paclitaxel ± carboplatin are the relevant comparators
- Rational for excluding potential comparators
  - ↳ Docetaxel: RWE and company clinical expert opinion suggests very limited use in clinical practice
  - ↳ Atezolizumab: Clinical experts do not consider it to be part of ECM due to a lack of evidence of the efficacy of retreating with an anti PD-(L)1 inhibitor
  - ↳ BSC: No evidence is available in patients after exposure to PD-(L)1 inhibitors, so a comparative analysis is not feasible
  - ↳ Carboplatin + gemcitabine: It is not recommended at second line in NICE guidance and there is limited evidence for rechallenging with platinum-based chemotherapy.

*See appendix - Comparators

Abbreviations: BSC, Best supportive care; ECM, Established clinical management; PD-L1, Programmed death-ligand 1; RWE, Real-world evidence;

Comparators (2/2)

EAG comments

- Believes exclusion of potential comparators could limit the comprehensiveness of the analysis and a fully incremental analysis could relieve some uncertainty
- Inclusion of other potential comparators would provide a more complete understanding of erdafitinib's relative treatment effect in different clinical scenarios and for different subgroups
- RWE used to support the exclusion of potential comparators is not specific to the population with FGFR genetic alternations so may not be generalisable to that population
- EAG clinical experts
  - ↳ Support the decision to focus on paclitaxel ± carboplatin → But 3:1 ratio would differ between centres
  - ↳ Agree with excluding atezolizumab as a comparator due to the decreasing immunotherapy naïve population
  - ↳ Agree with excluding BSC as a comparator due to it being primarily used in patients who cannot receive active treatment
  - ↳ Agree platinum rechallenge would only be relevant after a long platinum-free interval

What are the appropriate comparators for this appraisal?

Abbreviations: BSC, Best supportive care; FGFR, Fibroblast growth factor receptor; RWE, Real-world evidence;

Generalisability of THOR trial population

Company

- Company clinical experts noted that the population in the clinical trial are younger than in the NHS clinical practice population, but ages in THOR and the RW study were similar (Mean 66.5 and 68.8, respectively)
- Previous appraisals in mUC used data from trials with similar median ages (TA525: 67 and TA692: 66)

EAG comments

- Company clinical expert stated [redacted]
- Expect changing the starting age alone would have limited impact on the ICER
- [redacted] THOR participants from UK and [redacted]
- There are likely differences in race between the trial population and NHS clinical practice
  - ↳ In the trial 54% were white, >1% were black or african american and 29% were asian
- Participants in THOR predominantly had and ECOG PS of 0-1 indicating a healthier population
- Concerns remain despite company's reweighting approach
- Subgroup analysis not powered to detect significant differences, so it is possible differences in treatment effect were not detected due to the small sample size
- Forest plot of OS HR by subgroup factors suggests effect modification based on age, prior treatment, baseline PS and FGFR alternation type which could have significant implication in clinical practice

Is the THOR trial generalisable to NHS clinical practice?

*See appendix - THOR trial forest plot

*See appendix - Baseline characteristics

Abbreviations: ECOG, Eastern Cooperative Oncology Group; FGFR, Fibroblast growth factor receptor; HR, Hazard ratio; ICER, Incremental cost-effectiveness ratio; mUC, Metastatic urothelial carcinoma; OS, Overall survival; PS, Performance status; RW, Real-world; TA, Technology appraisal;

FGFR status in RW UK study

Background

- ITC used in company base case used data from the RW mUC study that lacked information on FGFR alternation status

Company

- Explored if chemotherapy efficacy differed depending on FGFR alteration status → Performed a MAIC of chemotherapy regimens in THOR (with FGFR alternations) and EV-301 (all-comers)
  - ↳ MAIC showed no significant difference between two trials in OS and PFS (no effect modification)

EAG comments

- The findings from the company's exploratory MAIC should be interpreted with caution due to the substantial reduction in sample size, reliance on retrospective data and limitations in the matching process
  - ↳ Little difference does not imply no difference
  - ↳ Lack of FGFR status data does not imply lack of FGFR alterations
  - ↳ Little difference between chemotherapy regimens in THOR and EV-301 does not imply generalisability to paclitaxel ± carboplatin

Is the presence of FGFR alteration an effect modifier for chemotherapy?
Is the UK RW study suitable to inform efficacy of paclitaxel +/- carboplatin in the model?

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Abbreviations: FGFR, Fibroblast growth factor receptor; ITC, Indirect treatment comparison; mUC, Metastatic urothelial carcinoma; OS, Overall survival; PFS, Progression-free survival; RW, Real-world;

Paclitaxel ± carboplatin stopping rule

Company

- Base case did not include a stopping rule for paclitaxel and paclitaxel + carboplatin
- Base case assumed that TTD for paclitaxel ± carboplatin would be equivalent to the generated PFS
  - ↳ Because TTD data for paclitaxel ± carboplatin was not collected in the UK RW mUC study
- Provided scenario where TTD of paclitaxel + carboplatin was modelled using TTD of taxanes from TA525

EAG comments

- Base case assumes patient receiving paclitaxel ± carboplatin are treated up to a maximum of 6 cycles
- Stopping rule of 6 cycles (i.e. 24 weeks) supported by EAG clinical experts and existing guidelines
- In response to clarification the company:
  - ↳ Agreed that a hard stop at 24 weeks could improve alignment with UK clinical practice
  - ↳ Would be in line with assumptions in TA530 and TA692
- A stopping rule of 6 cycles would mean that TTD for paclitaxel ± carboplatin in the economic model is zero from week 25 onwards
- Assuming TTD is equivalent to PFS may overestimate TTD → Due to the stopping rule and people stopping treatment due to toxicity and reasons other than progression
  - ↳ Scenario using TTD of taxanes from TA525 also relies on assuming TTD is equal to PFS

Should a stopping rule be modelled for paclitaxel ± carboplatin?

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Abbreviations: mUC, Metastatic urothelial carcinoma; PFS, Progression-free survival; RW, Real-world; TA, Technology appraisal; TTD, Time to treatment discontinuation;

Modelling PFS for paclitaxel ± carboplatin

Background

- PFS data for paclitaxel ± carboplatin was not collected in the UK mUC RW study

Company

- Uses PFS data from Vaishampayan et al. 2005 extrapolated using a log-logistic curve as a proxy
- Using TTNT as a proxy for PFS would be inappropriate as the curve was close to the OS curve

EAG comments

- Prefers to use paclitaxel ± carboplatin TTNT data from the UK mUC RW study as a proxy to inform PFS
  - ↳ Company's base case assumes a relatively low number of modelled LYs gained in the PD health state for paclitaxel ± carboplatin indicates PFS being close to OS is plausible
  - ↳ Using TTNT data from the UK RW mUC study uses data from patients in the UK
- Acknowledges that using TTNT may overestimate PFS for patients that progress before the paclitaxel stopping rule of 24 weeks, and may underestimate PFS for patients progressing after
- Vaishampayan et al. 2005 was conducted a relatively long time ago and has a relatively small sample size (0 patients were from the UK) → Choice of log-logistic curve was not justified
- Scenario analysis presented using PFS data for paclitaxel monotherapy from PLUTO
  - ↳ Additional scenario using the PFS of taxanes in TA525 and TA692 as a proxy would be informative

How should PFS for paclitaxel ± carboplatin be modelled?

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Abbreviations: LY, Life years; mUC, Metastatic urothelial carcinoma; OS, Overall survival; PD, Progressed disease; PFS, Progression-free survival; RW, Real-world; TTNT, Time to next treatment;