Erdafitinib for treating metastatic or unresectable FGFR-altered urothelial cancer

For public – confidential information redacted [redacted]

Second committee meeting

Technology appraisal committee C [11 March 2025]

Chair: Steve O'Brien

External assessment group: Kleijnen Systematic Reviews

Technical team: Owen Swales, Samuel Slayen, Lorna Dunning

Company: Johnson & Johnson

Erdafitinib for treating metastatic or unresectable FGFR-altered urothelial cancer

- ✓ **Background and ACM1 recap**
- ❑ Consultation responses and key issues
- ❑ Cost effectiveness results

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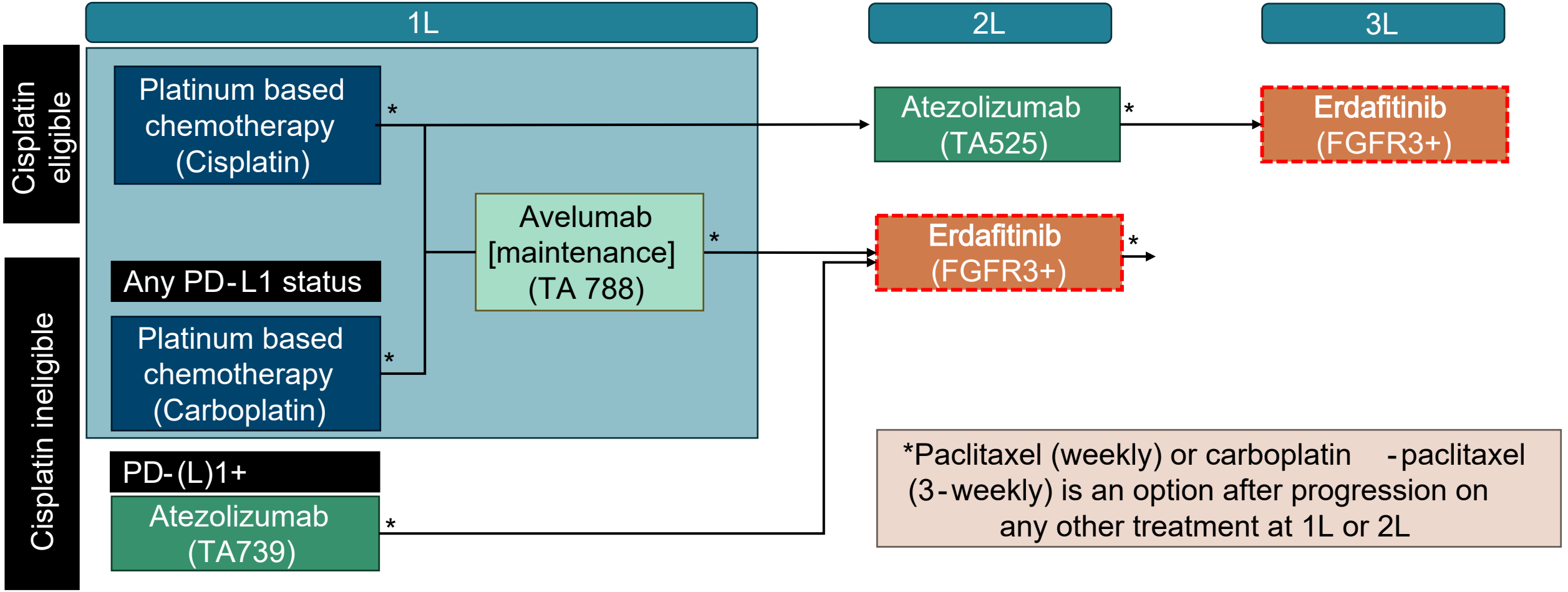
Treatment pathway



MA: "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"

Abbreviations: 1L/2L/3L, first/second/third line; FGFR, fibroblast growth factor receptor; MA, marketing authorisation PD-(L)1, programmed cell death (ligand) 1 – these are immunosuppressive molecules on the surface of either tumour or immune cells)

Committee conclusions at 1st committee meeting (ACM1)

Committee recommendation

"The committee concluded that because a relevant comparator had not been included in the basket, it was unable to establish a most plausible ICER for erdafitinib. So, erdafitinib is not recommended…"

Committee preferred assumptions

- Appropriate comparator is a basket with paclitaxel + carboplatin, paclitaxel monotherapy and BSC
- 3:1 ratio of paclitaxel monotherapy to paclitaxel + carboplatin for people having chemotherapy
- Company's 3 state partitioned-survival model
- 6 cycle stopping rule for paclitaxel ± carboplatin
- Real world TTNT data as a proxy for paclitaxel ± carboplatin PFS
- EAG's regression model to estimate utility values
- Company's lower progression-free per-cycle costs for erdafitinib

Committee identified uncertainties

- No ICERs for comparison with BSC
- Cost of diagnostic testing
- THOR trial generalisability to NHS
- Approach to account for substantial missing data in the ITC and results
- Assuming TTD is equal to PFS for paclitaxel ± carboplatin might overestimate TTD
- Time spent in PFS health state

Committee requested analyses

- BSC as a comparator in the basket
- Alternative ITC imputation methods (multiple imputation or assume best possible value for missing data)
- THOR results used directly to inform the model
- Relative treatment effect from THOR applied to the baseline risk of OS and TTNT from real world study

Abbreviations: ACM1, appraisal committee meeting 1; BSC, best supportive care; ITC, indirect treatment comparison; PFS, progression free survival; TTD, time to treatment discontinuation; TTNT, time to next treatment

Key issues

Key issue for discussion	Resolved?	ICER impact
Testing costs	No – for discussion	Large
QALY weightings for severity	No – for discussion	Large

Other issues	Resolved?	ICER impact
Inclusion of BSC as a comparator	See appendix	Moderate
Trial generalisability of THOR	See appendix	Unknown
Treatment effectiveness	See appendix	Moderate
Plausibility of modelled results	See appendix	Unknown

Abbreviations: BSC, best supportive care; QALY, quality adjusted life year

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Consultation responses – patient organisation

Action Bladder Cancer UK:

- Draft recommendation is inappropriate due to positive clinical trial evidence and strong evidence from patient groups on the unmet need for treatments that offer better quality of life and survival outcomes
- Inappropriate to include genetic testing costs:
  - Imposes barrier to wider use
  - Understand that testing costs would be covered by NHSE and not included in per-patient costs
  - Means that all precision medicine will be unaffordable, stopping progress and denying access
  - Ongoing testing costs would be low as previous test results could be used for necessary information
- Best supportive care is not an appropriate comparator:
  - No data is available for a robust, direct comparison
  - Poorer quality of life and survival, and higher costs with BSC have not been taken into consideration
  - Severity of potential negative impact of BSC on patients and carers should be considered

Abbreviations: BSC, best supportive care

Consultation responses – online web comments

Person 1:

- The recommendations is not sound or suitable guidance
- Has implemented FGFR3 testing in their clinic, easy to implement and important direction of travel for NHS
- First hand experience of very good responses and quality of life benefits for people receiving erdafitinib who otherwise have very limited systemic therapy treatment options
- THOR results show the clear overall survival benefit

Person 2 (Fight Bladder Cancer):

- BSC is not a treatment but is a lack of one, inappropriate to compare erdafitinib to a lack of treatment
- Analysis does not consider the emotional toll on patients and their families of having no treatments to prevent disease progression and make their last days as fulfilling and as long as possible
- Urge NICE to consider the NHS costs of caring for someone with rapid disease progression and the cost to the patients themselves and families and carers
- Including genetic testing costs is unfair and harms innovation, will set a precedent preventing many small patient groups from accessing innovative treatments, noting targeted therapy use will increase

Abbreviations: FGFR, fibroblast growth factor receptor

Consultation responses – company

Responses not covered in key issue slides

- Provides scenario analyses requested by the committee:
  - BSC as a comparator in the basket
  - Alternative ITC imputation methods (multiple imputation or assume best value for missing data)
- Uncaptured benefits of erdafitinib: the value of hope in dire end-of-life circumstances, the ease of use of treatment for the patient, the alleviation of carer burden and the value derived from innovation
- 6-cycle stopping rule for paclitaxel ± carboplatin limits PFS overestimation as TTNT is used as PFS proxy
- Acceptable ICER should be £30,000 per QALY because:
  - mUC is extremely rare and aggressive, has very limited survival and practically no treatment options
  - Low decision risk due to additional analyses provided showing robust cost-effectiveness, small population, the significant improvement erdafitinib delivers, and the severity of the disease

Abbreviations: BSC, best supportive care; ITC, indirect treatment comparison; mUC, metastatic urothelial cancer; PFS, progression free survival; QALY, quality adjusted life year; TTNT, time to next treatment

Key issue: Testing costs (1/2)

Company disputes the testing costs preferred by committee and NHSE

Draft Guidance/Background

- FGFR3 testing costs should be modelled, [redacted] cost (from GMS), expected FGFR3 prevalence of 16.6%

Company DG response

- [redacted] cost is for new NGS genomics testing strategy, but this is not needed as PCR testing can be used
- GLHs say that labs already have technology for FGFR3 detection, so can be included in existing testing
- TA722: £34 testing cost (FGFR test not routine), equates to £74.65 (£37 inflation adjusted for DNA/RNA)
- [redacted] equals [redacted] per eligible patient, so testing costs rise from [redacted] to [redacted] of drug costs, is excessive

NHS England (Genomic Medicine Service)

- TA722: people already tested for other treatments, so £34 cost is for adding FGFR2 target to existing panel
- NGTD currently includes two panels (DNA and RNA) for FGFR3 testing each attracting a tariff
- [redacted] is (2023/4) tariff for RNA / DNA panels when not routine (includes preparation, test, reporting)
- Preferred approach is large panels, but testing to inform treatment or surgery is low (limited targets are routinely tested in this pathway) so use medium panels for costing at marginal [redacted] tariff ([redacted] per person)
- This is aligned with the approach taken in TA1036

EAG comments

- Align base-case with company (£74.65 for 2 tests, RNA and DNA), note uncertainty and share scenarios

Abbreviations: CDF, cancer drugs fund; FGFR, fibroblast growth factor receptor; GLH, genomic laboratory hubs; mUC, metastatic urothelial cancer; NGS, next generation sequencing; PCR, polymerase chain reaction; GMS, genomic medicines service

Key issue: Testing costs (2/2)

FGFR3 testing costs and key questions for committee

Table: FGFR3 testing cost considered at different appraisal timepoints

Timepoint	Full testing cost	Cost for decision-making	Cost per eligible patient (16.6% FGFR3 prevalence)
ACM 1	[redacted] (2 large panels)	[redacted] (100% tariff)	[redacted]
GMS submission 1 (post ACM 1)	[redacted] (2 large panels, 2024/5 tariff)	[redacted] ([redacted] tariff)	[redacted]
GMS submission 2 (for ACM 2)	[redacted] (2 medium panels)	[redacted] ([redacted] tariff)	[redacted]

1) **Should the costs of introducing FGFR3 genetic testing be apportioned?**
2) **How should the costs of testing for FGFR3 genetic alterations be modelled?**
3) **Is an adjusted FGFR3 genetic testing cost of [redacted] reasonable?**

Abbreviations: ACM, appraisal committee meeting; FGFR, fibroblast growth factor receptor; GMS, genomic medicines service

Key issue: Severity modifier

Company say committee conclusion for x1.7 weighting at ACM1 still stands

Draft Guidance

- Committee concluded that although uncertain, the severity weight of 1.7 was likely to be appropriate
- Would reconsider the severity weighting once the additional comparator of BSC had been explored

Company DG response

- Basket of paclitaxel ± carboplatin and BSC gives a x1.7 severity weight so used in updated base case

EAG comments

- Company have not given detailed analysis of severity modifier given inclusion of BSC in basket
- Severity weighting calculations removed from company's model
- EAG base case assumes 1.7 weighting but would like to see updated severity threshold analysis

NICE technical team – calculated severity shortfalls

Basket comparator	QALYs w/out disease (from ACM1)	Expected QALYs – current treatment	Absolute shortfall	Proportional shortfall	QALY weight
THOR	10.17	0.415	9.755	0.96	1.7
THOR UK	7.64	0.415	7.225	0.95	1.7

Which severity weighting should be applied?

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Abbreviations: ACM1, appraisal committee meeting 1; BSC, best supportive care; QALY, quality adjusted life year

Company and EAG base cases and scenarios

Assumption	Company and EAG base cases
Missing data	A worst-case scenario approach to deal with missing data
Basket of comparators	Basket of paclitaxel monotherapy and paclitaxel in combination with carboplatin (weighted 3:1) and best supportive care
Stopping rule	Stopping rule of 6 cycles (i.e. 24 weeks) for paclitaxel ± carboplatin
Lack of data in the UK mUC real world study	TTNT data from the UK mUC real world study as a proxy for paclitaxel ± carboplatin PFS
Utility values	Derived using a joint multivariable regression model
Resource use and costs	Lower progression-free per-cycle costs in the erdafitinib arm
QALY weightings for severity	x1.7

Company scenario analyses	EAG scenario analyses
Multiple imputation for ITC	Full cost of implementing a genomic testing panel for FGFR3
Relative effect of THOR for OS & TTNT	Assume BSC resource costs equal paclitaxel ± carboplatin
THOR ITT population	70% of comparator basket receiving BSC

Abbreviations: BSC, best supportive care; FGFR, fibroblast growth factor receptor; ITC, indirect treatment comparison; ITT, intention to treat; mUC, metastatic urothelial cancer; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year; TTNT, time to next treatment

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Company and EAG base case results

Table: Company/EAG deterministic base case results, 1.7x modifier, PAS price

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Erdafitinib	[redacted]	1.660	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.822	[redacted]	0.927	[redacted]	27,465
BSC	[redacted]	0.527	0.588	[redacted]	1.133	[redacted]	28,753
Basket comparator	[redacted]	0.630	0.705	[redacted]	1.030	[redacted]	28,182

Table: Company/EAG probabilistic base case results, 1.7x modifier, PAS price

Technology	Total costs (£)	Total LYs	Total QALYs	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Erdafitinib	[redacted]	1.682	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.744	0.832	[redacted]	0.938	[redacted]	27,448
BSC	[redacted]	0.573	0.628	[redacted]	1.108	[redacted]	28,933
Basket comparator	[redacted]	0.659	0.730	[redacted]	1.023	[redacted]	28,265

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

Company scenario analysis

Table: Company deterministic scenario analysis results, 1.7x modifier, PAS price

Scenario	Technology	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Base case	Paclitaxel ± carboplatin	[redacted]	0.927	[redacted]	27,465
	BSC	[redacted]	1.133	[redacted]	28,753
	Basket comparator	[redacted]	1.030	[redacted]	28,182
Multiple imputation for ITC	Paclitaxel ± carboplatin	[redacted]	1.018	[redacted]	30,981
	BSC	[redacted]	1.223	[redacted]	31,490
	Basket comparator	[redacted]	1.121	[redacted]	31,261
Relative effect of THOR for OS & TTNT	Paclitaxel ± carboplatin	[redacted]	0.691	[redacted]	33,691
	BSC	[redacted]	0.896	[redacted]	33,699
	Basket comparator	[redacted]	0.793	[redacted]	33,695
THOR ITT population	Chemotherapy (docetaxel, vinflunine)	[redacted]	0.591	[redacted]	36,977

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

EAG scenario analysis

Table: EAG deterministic scenario analysis results, 1.7x modifier, PAS price

Scenario	Technology	Incremental costs (£)	Incremental LYs	Incremental QALYs	ICER (£/QALY)
Base case	Paclitaxel ± carboplatin	[redacted]	0.927	[redacted]	27,465
	BSC	[redacted]	1.133	[redacted]	28,753
	Basket comparator	[redacted]	1.030	[redacted]	28,182
Full cost ([redacted]) of genomic testing panel for FGFR3	Paclitaxel ± carboplatin	[redacted]	0.927	[redacted]	35,411
	BSC	[redacted]	1.133	[redacted]	35,077
	Basket comparator	[redacted]	1.030	[redacted]	35,225
Assume BSC resource costs equal paclitaxel ± carboplatin	Paclitaxel ± carboplatin	[redacted]	0.927	[redacted]	27,465
	BSC	[redacted]	1.133	[redacted]	30,415
	Basket comparator	[redacted]	1.030	[redacted]	29,108
70% of comparator basket receiving BSC	Paclitaxel ± carboplatin	[redacted]	0.927	[redacted]	27,465
	BSC	[redacted]	1.133	[redacted]	28,753
	Basket comparator	[redacted]	1.071	[redacted]	28,425
GMS marginal cost ([redacted]) of genomic testing panel for FGFR3	Paclitaxel ± carboplatin	[redacted]	0.927	[redacted]	[redacted]
	BSC	[redacted]	1.133	[redacted]	[redacted]
	Basket comparator	[redacted]	1.030	[redacted]	[redacted]

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

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Supplementary appendix

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Key issue: BSC in the basket comparator

Company have included BSC as a basket comparator at committee request

Draft Guidance

- Clinical experts: 70% of people offered chemotherapy, 30% to 50% would have it, with the rest having BSC
- Committee would like to see comparison with a basket comparator containing BSC

Company DG response

- Not aware of any study that has evaluated BSC in people who choose or are recommended to receive BSC following immunotherapy and are eligible for active treatment (the erdafitinib indicated population)
- So, use clinical outcomes from UK real world study for people having paclitaxel and carboplatin as a proxy for BSC, likely to overestimate BSC effect, and healthcare resource utilisation taken from TA272
- Basket comparator with 50% chemotherapy (3:1 paclitaxel to carboplatin with paclitaxel) and 50% BSC
- No subsequent treatments for BSC patients after they progressed were modelled
- Confirmative analysis using NMA with RCT (Study 302) in a slightly different population to generate BSC outcomes suggests it is appropriate to use carboplatin and paclitaxel as proxy for BSC

EAG comments

- Agrees that using paclitaxel and carboplatin as proxy for BSC likely to be conservative
- Scenario explores 30% chemotherapy and 70% BSC in line with range of expert opinion from ACM1
- Company approach for BSC outcomes and resource use reasonable. But per cycle radiotherapy cost in BSC arm may overestimate costs. Explores scenario with BSC costs equal to paclitaxel and carboplatin.

Is the modelled basket comparator appropriate for decision making?

Abbreviations: BSC, best supportive care; RCT, randomised controlled trial

Key issue: Generalisability of THOR trial data

Committee highlighted THOR generalisability concerns at ACM1

Draft Guidance

- **EAG**: most people in THOR had ECOG score of 0 to 1, population might be healthier than practice
- **Clinical experts**: erdafitinib patients in NHS likely older than in THOR, suggested age of 70 years
- **Committee**: age could be a treatment-effect modifier, there are generalisability concerns around THOR

Company DG response

- Use worst case imputation for ECOG in base case, more severe patients upweighted to align with UK
- Real world study median age was 65.5 years, comparable to mean age in THOR of 66 years
- Erdafitinib population is younger than whole mUC population as they are deemed fit for systemic treatment
- Mahmoudpour et al. (2024) shows mean ages for people with treated and untreated mUC in England (67.5 and 75.7 years respectively), so 70 years cited by experts relates to entire mUC population
- Consistent efficacy in all age groups, caution against other conclusions due to lack of power in subgroups
- Adults <65 years: median overall survival 14.0 months (HR: 0.46 (95% CI: 0.27, 0.79)
- Adults 65+ years: median overall survival 10.9 months (HR: 0.71 (95% CI: 0.47, 1.07)

EAG comments

- Acknowledge company response but still have concerns about age of people in THOR and NHS practice
- Agree with caution on results by age, agree with committee that age is possible treatment effect modifier

Are the THOR trial results used in the model generalisable to NHS practice?

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Abbreviations: ACM1, appraisal committee meeting 1; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; mUC, metastatic urothelial cancer

Key issue: Missing data and treatment effectiveness

Company provide alternative approaches, but EAG notes best case is missing

Draft Guidance

- Alternative ITC imputation methods needed for missing ECOG scores and tumour stage data
- Requested exploration of relative treatment effect from THOR applied to the baseline risk of OS and TTNT from real world study and direct use of THOR results to drive model

Company DG response

- Multiple imputation (MI) adjusted OS for erdafitinib is superior to results from THOR
- Median survival: multiple imputation (14.7 months [10.2 to 19.4]); THOR (12.1 months [10.3 to 16.4])
- Multiple imputation informative but not suitable for decision-making, improbable that adjusting THOR data to UK data would improve OS compared to RCT results
- So, base case uses worst case adjustment where more severe patients are upweighted to align with UK clinical practice, likely to be more realistic (median survival of 10.6 months [9.5 to 16.7])
- Provided scenario applying THOR relative treatment effect to baseline OS and TTNT. Lack of TTD data in UK requires further assumptions on the erdafitinib TTD curve, introducing a further layer of uncertainty
- Explored using results of THOR to directly inform model - no evidence to suggest this is appropriate

EAG comments

- Agree with company that multiple imputation results informative but improbable, consider these exploratory
- Appreciate worst case adjustment but note best case adjustment requested by committee not provided

How should treatment effectiveness be modelled?

Abbreviations: ITC, indirect treatment comparison; MAIC, matching adjusted indirect comparison; OS, overall survival; RCT, randomised controlled trial; TTD, time to treatment discontinuation; TTNT, time to next treatment

Key issue: Plausibility of modelled results

Company say plausibility of results is an inherent limitation for a rare disease

Draft Guidance

- Implausible that time spent in progression-free health state is similar for erdafitinib and basket comparator

Company DG response

- Lack of PFS data from UK real world study is inherent limitation for a rare condition with high unmet need
- MAIC indicates that the PFS for paclitaxel monotherapy is comparable to that of erdafitinib
- TTNT for erdafitinib and paclitaxel is more aligned with OS, so PFS could be overestimated

EAG comments

- No compelling new arguments or evidence were provided by the company to address this issue

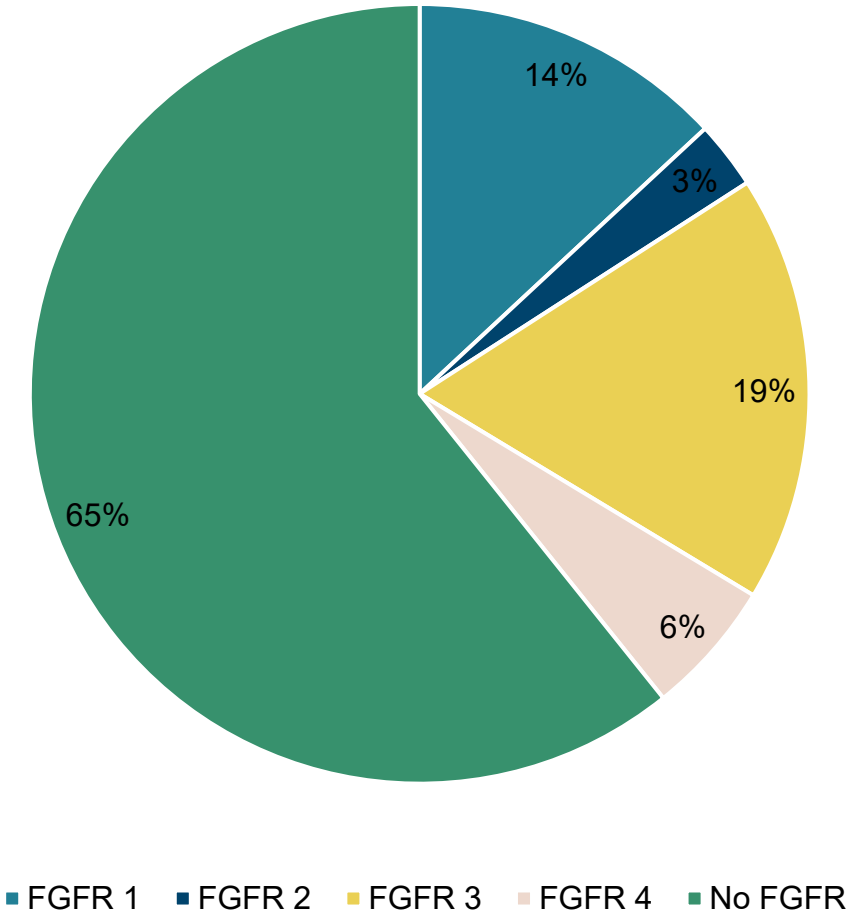
Is the breakdown of life years gained and QALYs between the progression free and progressed disease health states plausible?

Abbreviations: MAIC, matching adjusted indirect comparison; OS, overall survival; PFS, progression free survival; TTNT, time to next treatment

Key issue: Testing costs

Prevalence of FGFR mutations in urothelial cancer

Approximate frequencies by FGF receptor in urothelial cancer



Helsten, T., Schwaederle, M. & Kurzrock, R. Fibroblast growth factor receptor signaling in hereditary and neoplastic disease: biologic and clinical implications. Cancer Metastasis Rev 34, 479–496 (2015). https://doi.org/10.1007/s10555-015-9579-8

Abbreviations: FGFR, fibroblast growth factor receptor

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

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

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

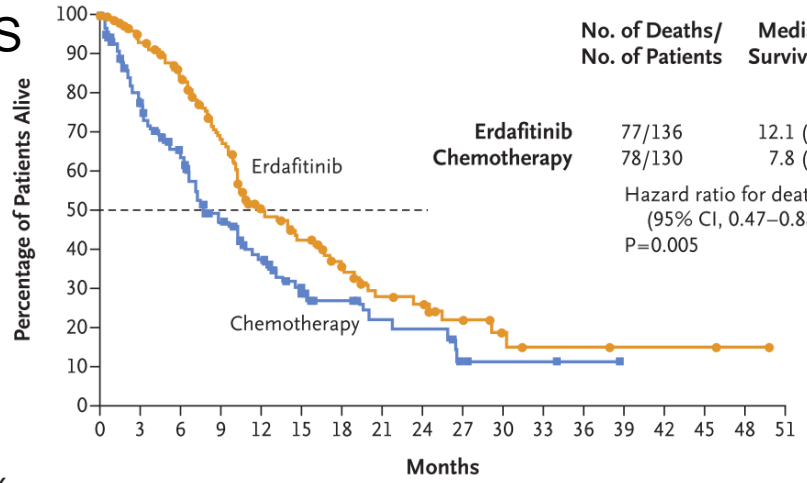
Draft Guidance

"The committee concluded that no equality issues were raised that would have an impact on its decision making, but it would like to hear from stakeholders if any further equality issues should be considered"

Abbreviations: EAG, external assessment group

THOR clinical trial results

OS



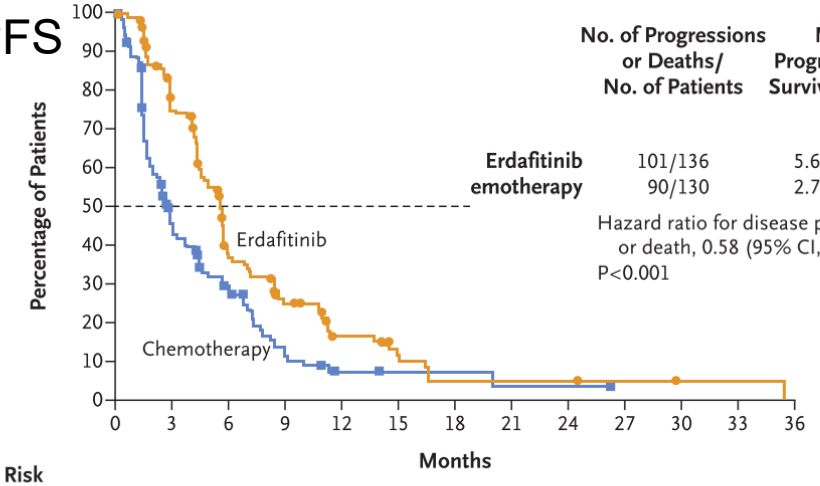
	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI) mo
Erdafitinib	77/136	12.1 (10.3–16.4)
Chemotherapy	78/130	7.8 (6.5–11.1)

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)	

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

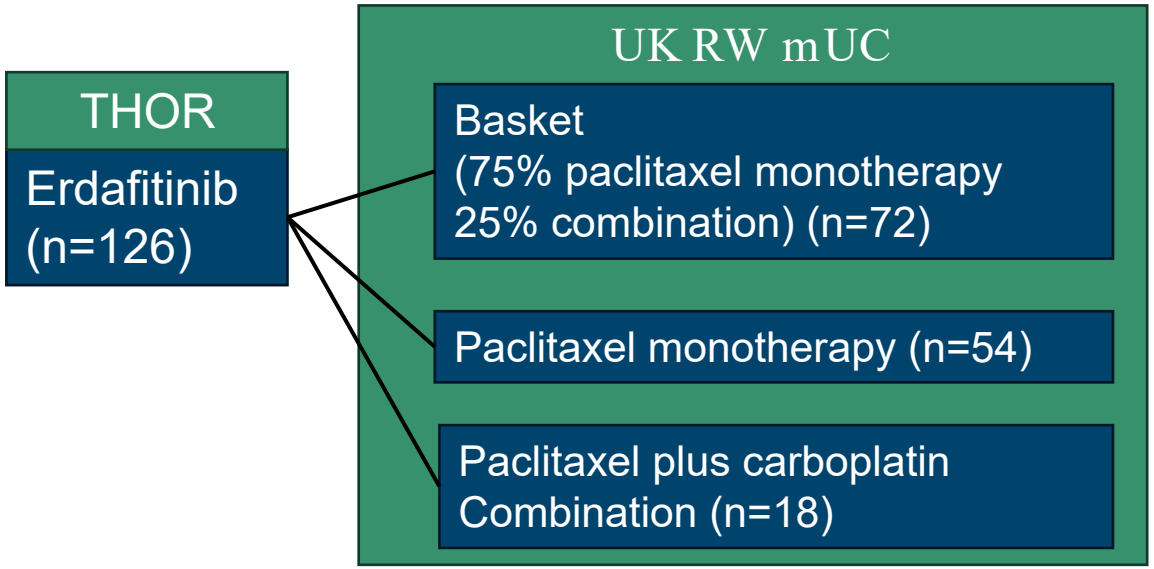
ITC Networks

- 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

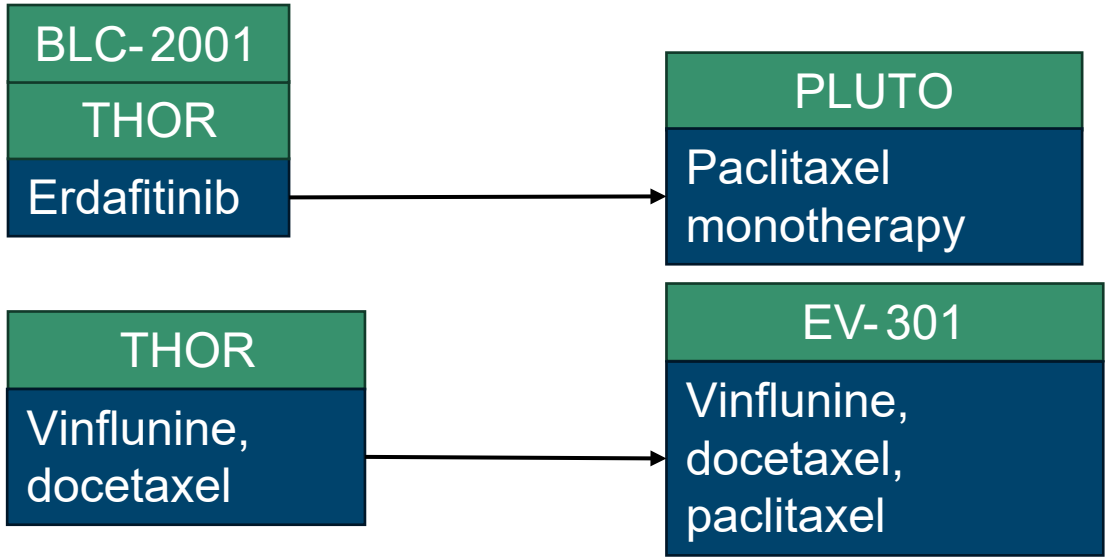
- IPD-ITC compared erdafitinib from the THOR trial to a basket of 75% paclitaxel monotherapy and 25% paclitaxel plus carboplatin (as well as the two regimens separately) from the UK RW mUC study

- 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)



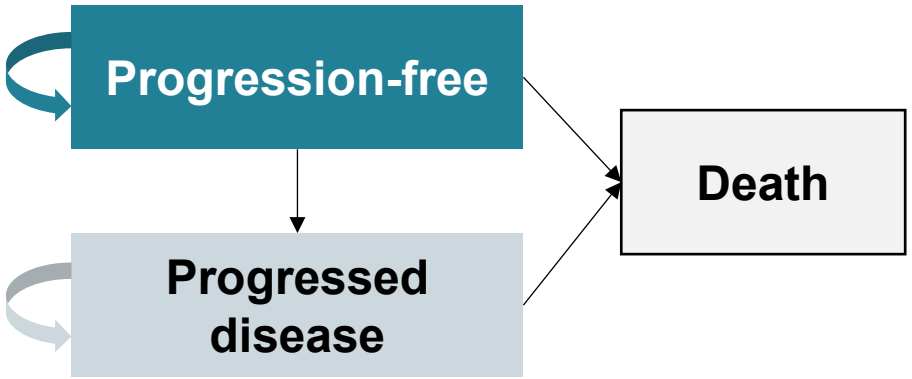
Exploratory MAICs



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

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;

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

Key Clinical Trials

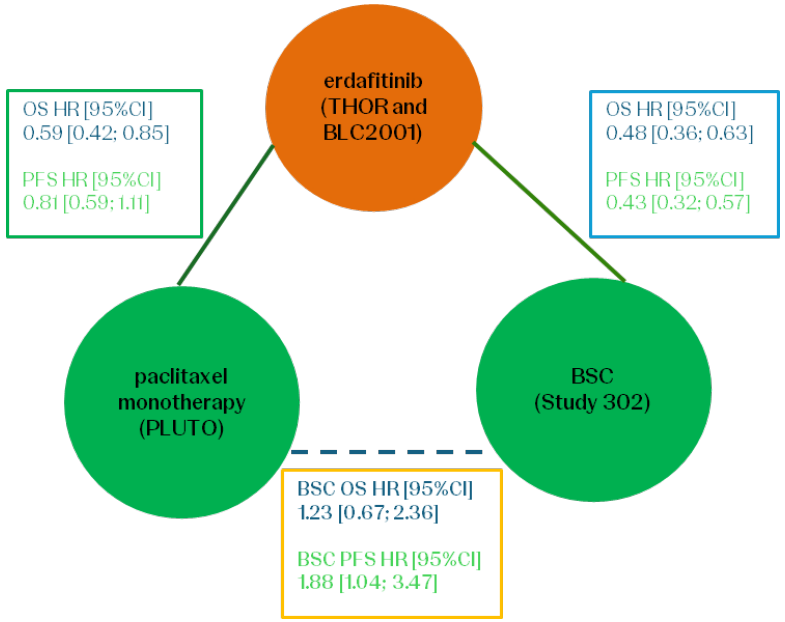
	THOR (n=266)	BLC2001 (n=99)	PLUTO (n=140)	UK RW mUC Study (n=72)
Design	International, Phase III, randomised, open-label	Phase II, single-arm	Phase II, randomised	Real world study
Population	FGFR-altered mUC, progressed after 1-2 treatments including an anti PD-(L)1 agent (Cohort 1)	FGFR-altered mUC, 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;

BSC confirmative analyses

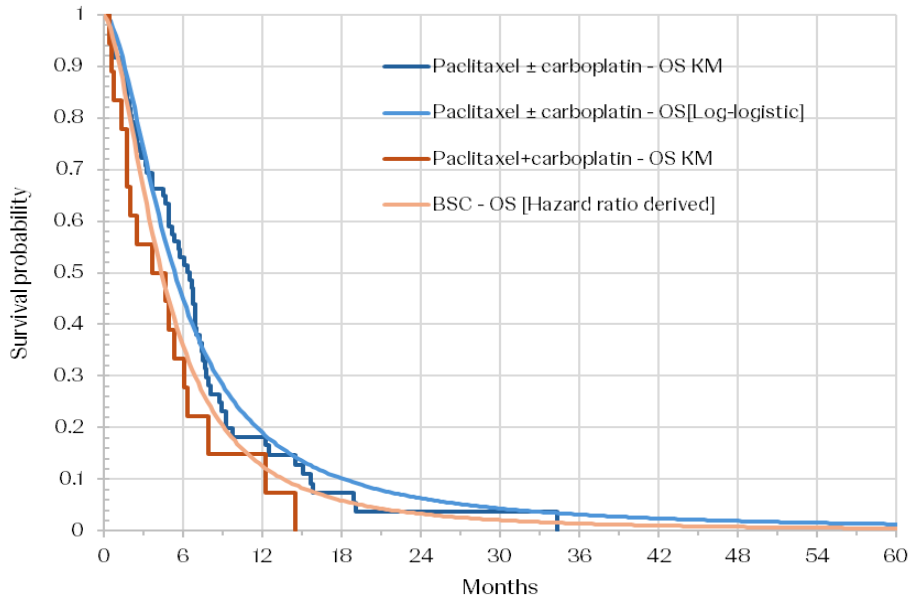
Back to key issue

Network for confirmative analysis

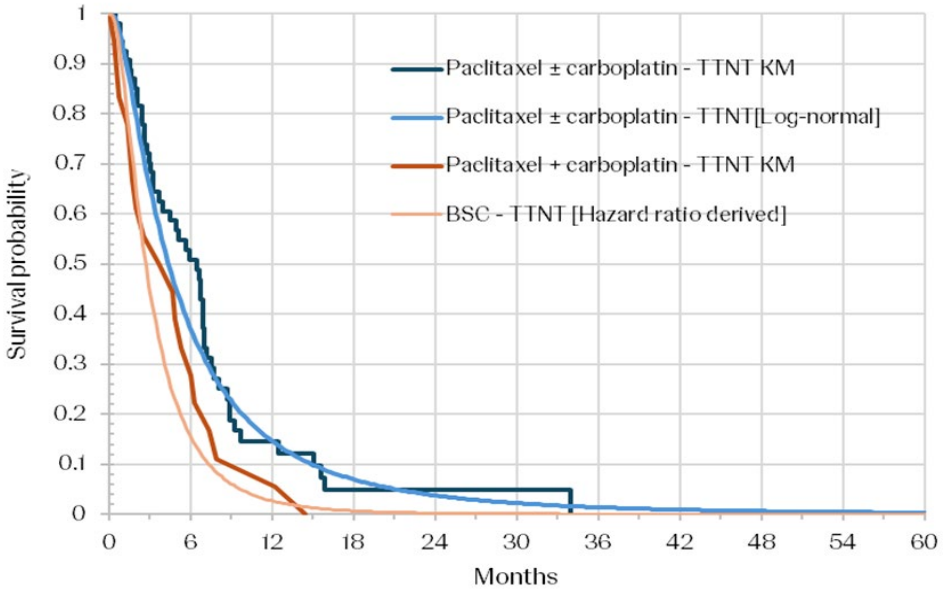


- Study 302 (Bellmunt et al 2009) compared vinflunine with BSC.
- Bucher method used to generate PFS/OS HR for BSC vs paclitaxel monotherapy
- HRs applied to paclitaxel +/- carboplatin to generate curves

OS



TTNT

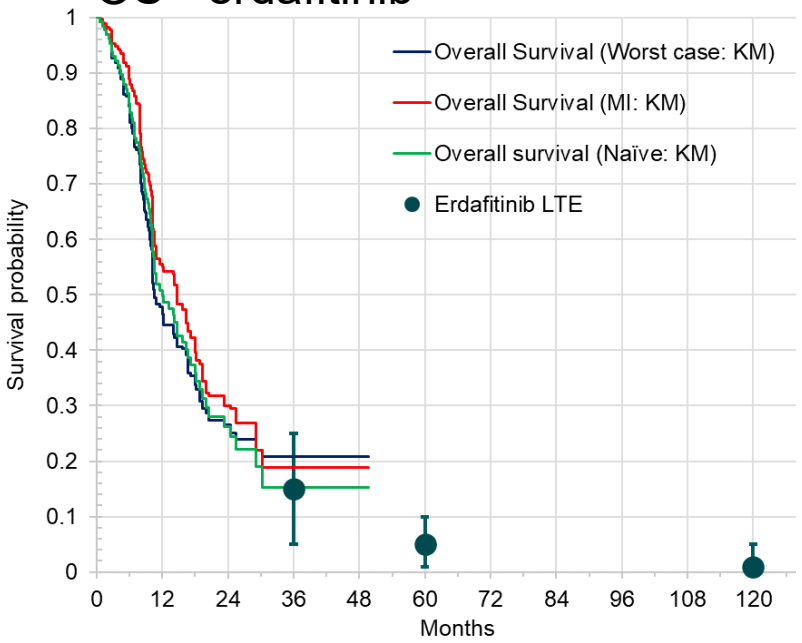


Abbreviations: OS, overall survival

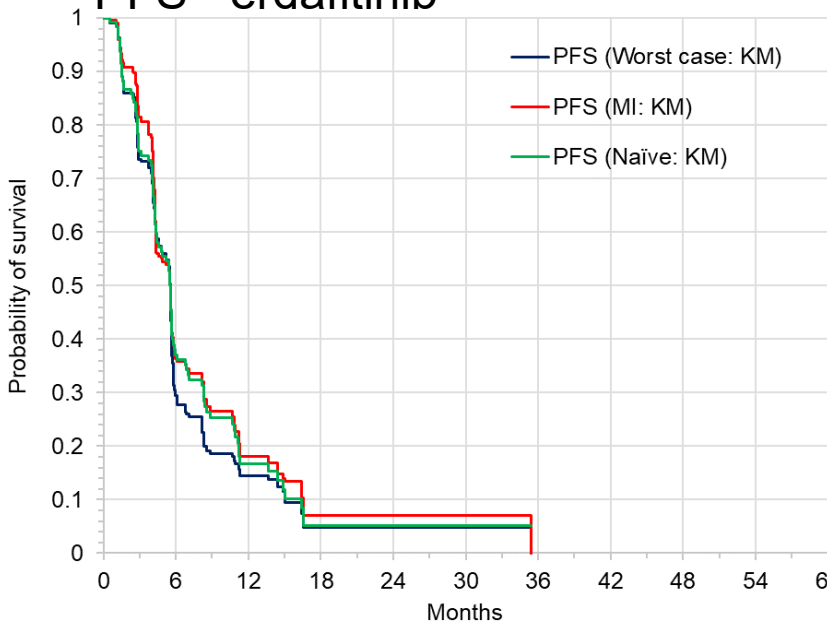
Results of multiple imputation – additional info

Back to key issue

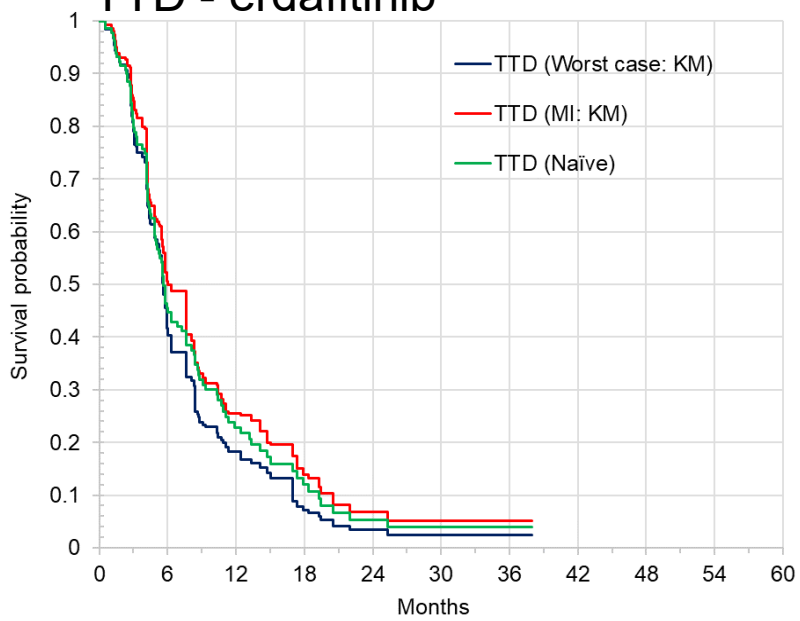
OS - erdafitinib



PFS - erdafitinib



TTD - erdafitinib



Scenario	TTNT HR (95%CI)	OS HR (95%CI)
Base case (worst case)	0.53 (0.37, 0.76)	0.35 (0.23, 0.52)
Multiple imputation	0.42 (0.29, 0.62)	0.28 (0.18, 0.42)

- The same distributions were selected to extrapolate multiple imputation scenario outcomes
- Results in improved PFS and OS but also TTD (and costs). Overall moderate increase in ICER (~£3000)

NICE Abbreviations: OS, overall survival

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"

"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. "

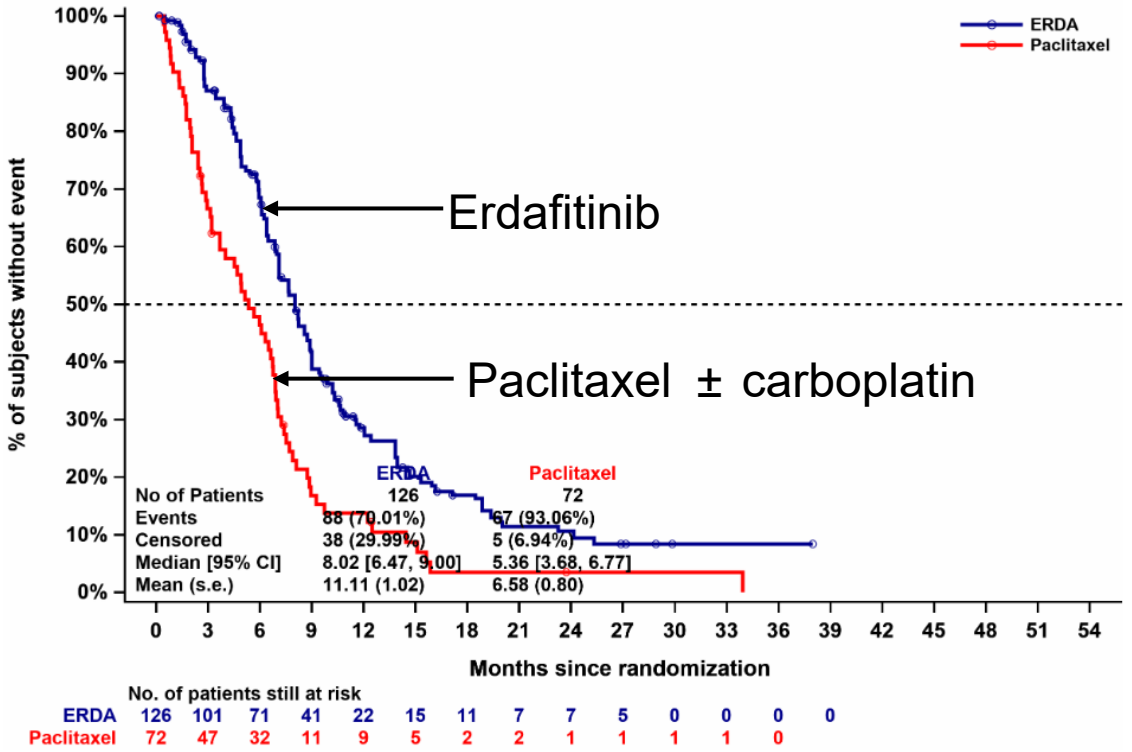
"This drug has a toxicity profile that is broadly similar in frequency and severity overall compared to chemotherapy" - "However. . . a small minority of patients develop central serous retinopathy"

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

Key ITC results

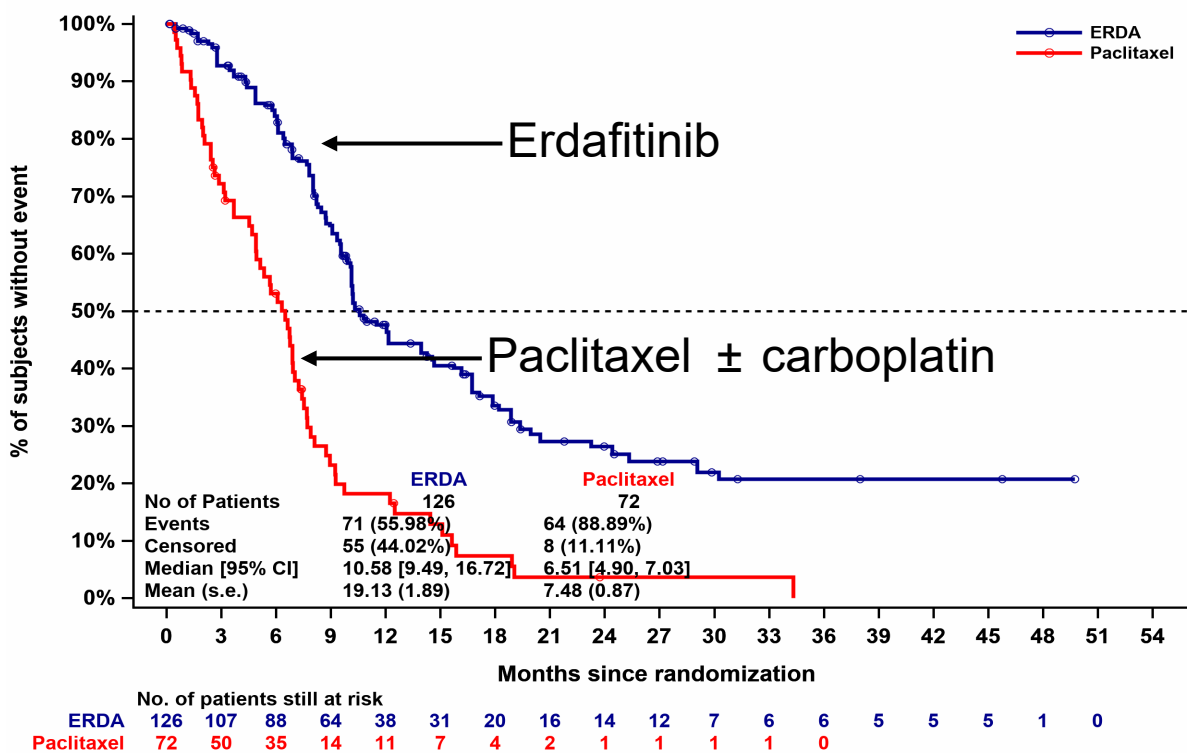
ITC results using ATC weighting (base case) - Erdafitinib improves OS and TTNT (in the absence of PFS) compared to **basket comparator**

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

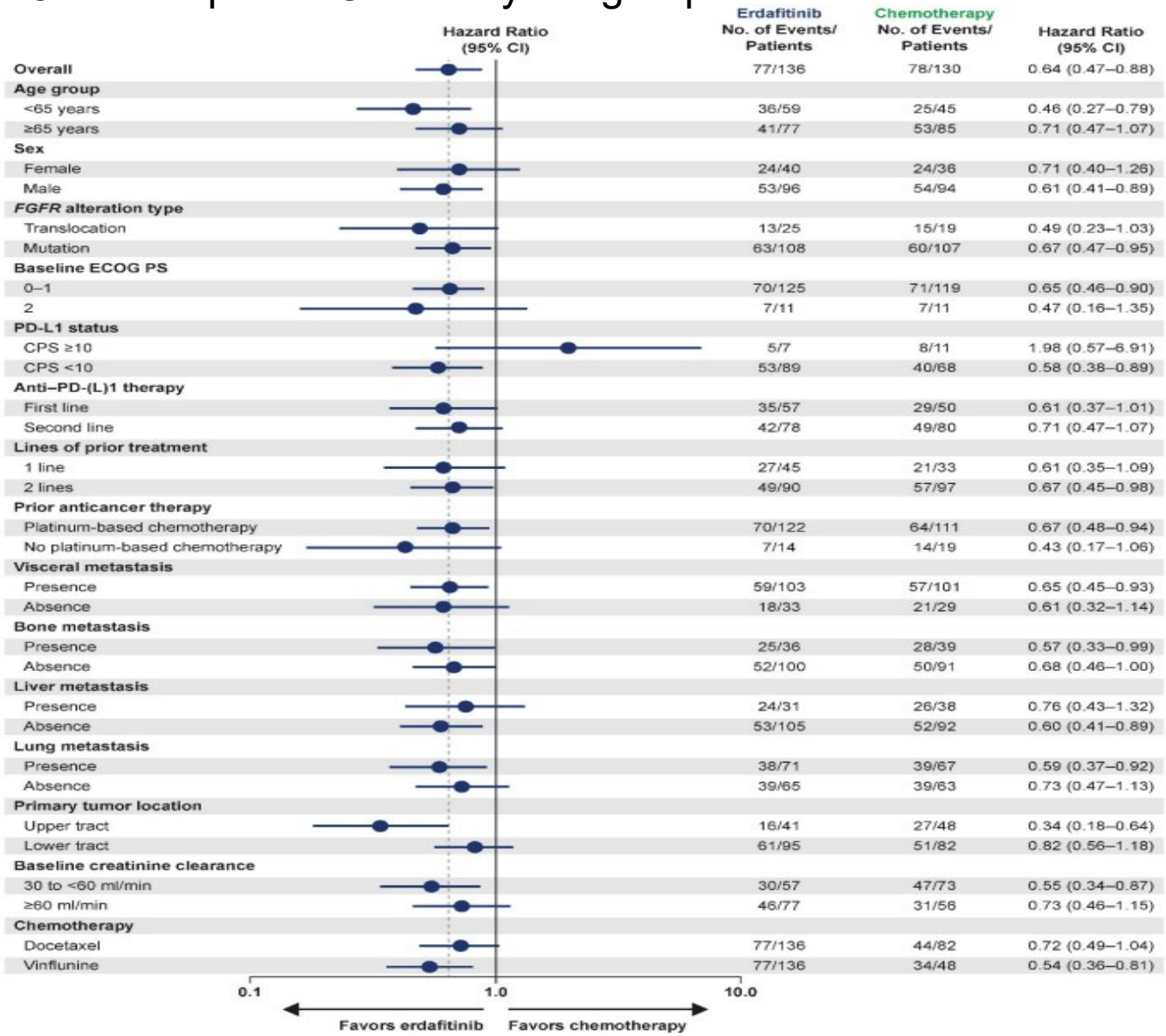


HR (95% CI; p-value),	0.35 (0.23 to 0.52), p < 0.0001

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;

Supplementary slide: THOR trial forest plot

Figure: Forest plot of OS HR by subgroup factors



Abbreviations:

NICE

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;

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

NICE

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;

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?

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;

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	0.861	0.362	0.223	1.660	[redacted]
Progression-free	0.562	0.397	0.022	0.015	0.584	[redacted]
Progressed	0.736	0.464	0.339	0.207	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

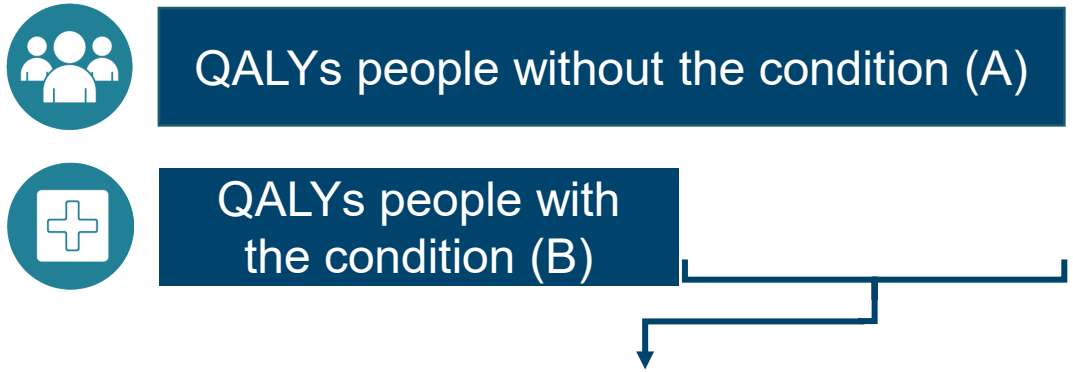
- In the company's revised base-case the majority of the LYs (65%) and QALYs (62%) for erdafitinib were modelled to occur in the PD health state → The same was not seen for paclitaxel ± carboplatin
- Expected most benefits to occur in the PF health state, as erdafitinib was given until progression
- 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;

QALY weightings for severity (1/2)

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

Abbreviations: QALY, quality-adjusted life year

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

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;