Single Technology Appraisal

Erdafitinib for treating metastatic or unresectable FGFR-altered urothelial cancer [ID1333]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Erdafitinib for treating metastatic or unresectable FGFR-altered urothelial cancer [ID1333]

Contents:

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NICE National Institute for Health and Care Excellence

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have

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	regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Johnson and Johnson Innovative Medicine
Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	No disclosures
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No disclosures
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	Thank you for the opportunity to comment on the Appraisal Consultation Document (ACD) regarding the appraisal of erdafitinib for the treatment of adult patients with unresectable or metastatic urothelial carcinoma (mUC) 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. Johnson and Johnson (J&J) are disappointed that the NICE Appraisal Committee has issued a negative preliminary decision not to recommend erdafitinib within its marketing authorisation. As discussed during the appraisal meeting, there is a significant unmet need in this rare, terminal patient population. There are no efficacious treatment options currently available for FGFR3-altered patients who have progressed following immunotherapy. J&J would like to highlight and discuss some concerns regarding the Appraisal

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	Committee's preferred assumptions in the ACD, particularly those related to FGFR3 testing costs and modelling uncertainties, which are addressed in the current document. In addition to the comments below, the Company is pleased to provide further analyses to mitigate some of the uncertainties raised by the Committee, which have been attached alongside this response. These will enable the Committee to make a more informed recommendation for erdafitinib in the treatment of metastatic urothelial carcinoma in adults who harbour susceptible FGFR3 genetic alterations and have previously received at least one line of therapy with a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting.
1	3.19: Testing costs: The committee noted that previous appraisals that the company had based their calculation on had all come from diseases in which there was an existing multi-panel test that was being done routinely. It thought that the cost per test used in the company base case would not reflect the cost to the NHS of implementing new FGFR3 testing for unresectable or metastatic urothelial cancer. It concluded that the full cost of implementing a genomic testing panel for FGFR3 mutations should be applied in the modelling using the: - cost provided by the Cancer Drugs Fund lead, of £1,282 - expected prevalence of FGFR3 alterations of 16.6%. The committee noted that the cost of genetic testing has not been modelled accurately stating that the full cost of £1,282 for implementing a genomic testing panel would be incurred. The committee noted that previous appraisals that the company had based their calculation on precedence, a panel was already being run in routine practice. The committee explained the situation for erdafitinib was different as there are currently no targeted treatments and patients with metastatic urothelial cancer do not have routine genomic testing. **Testing methods to identify FGFR3 genetic alterations and eligibility for erdafitinib** FGFR3 genetic alterations are identified using DNA- or RNA-based assay testing from samples primarily taken either from tumour tissue at the time of diagnosis of metastatic urothelial cancer or from archival tumour tissue samples. Testing can be performed using simple hotspot targeting polymerase chain reaction (PCR) protocols, next-generation sequencing (NGS) at the DNA and RNA level, or by specific RT-qPCR assays that cover FGFR3 mutations and fusions in one assay. In the THOR Cohort 1 phase 3 registrational trial, the majority of randomised patients were molecularly screened based on a PCR diagnostic test. Aware of the NHS England's current and future genomics testing strategy of NGS testing, Johnson & Johnson incorporated NGS testing costs using the approach taken in multiple previous NICE appraisals where testing costs were considered. It is important to note, however, that NGS testing is not necessary to identify patients eligible for erdafitinib and that PCR testing would suffice, i.e., the incremental cost of NGS testing is not solely due to the introduction of erdafitinib but rather a combination of the introduction of erdafitinib and the genomics testing strategy of NHS England.

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	Current availability of FGFR3 testing in the NHS FGFR3 testing using DNA and RNA based NGS technology is already included in the National Directory (https://www.england.nhs.uk/genomics/the-national-genomic-test-directory/). Currently, multiplex sequencing is performed, where a large number of libraries across multiple solid tumours are sequenced simultaneously during a single run (pooling of pan-oncology tumour samples). Even without targeted treatments available via the NHS for patients with unresectable or metastatic urothelial cancer, the FGFR3 test is accessible and already performed in the NHS. Genomic Laboratory Hubs (GLHs) have confirmed the laboratories have the capabilities currently for FGFR3 alteration detection employing the existing technology available as part of routine testing through established pathways (Personal communication with GLHs scientists). Given that the FGFR3 test can be incorporated into an existing multi-panel test covering multiple solid tumours, Johnson & Johnson contend that the statement *"the situation for erdafitinib was different as there are currently no targeted treatments and patients with metastatic urothelial cancer do not have routine genomic testing*" in the draft guidance is factually inaccurate. **Precedence from previous technology appraisals** As stated in the draft guidance, J&J followed the approach taken in previous appraisals to calculate the cost associated with genomic testing (e.g. TA722, TA850, and TA948). Johnson & Johnson consider it important to highlight that the statement in the draft guidance *"previous appraisals that the company had based their calculation on had all come from diseases in which there was an existing multi-panel test that was being done routinely"* is factually inaccurate. Specifically, in relation to TA722, where routine FGFR testing was not previously conducted, yet testing cost calculations were aligned with TA850 and TA948. As such, Johnson & Johnson contend that the approach taken in previous appraisals (regardless of the existence of routine testing) remains applicable to the appraisal of erdafitinib. Following these appraisals, the additional cost of adding a sample to an existing solid tumour panel is £37.33 (£34 based on 2020/2021 price). The testing for FGFR3 requires both RNA and DNA tests, therefore the additional cost would be £74.65 for two tests per sample. Given the expected prevalence of FGFR3 alterations of 16.6%, the total cost comes to £449.70 per eligible patient. **Impact of Committee's conclusion regarding testing costs to be accounted for in the economic modelling** The cost of £1,282 for NGS requested by the Committee to be used in the economic model is 17 times higher than the figure Johnson & Johnson had, based on substantial precedence, originally accounted for in the model. Furthermore, it is not clear what the evidence base is for the £1,282 "*full cost of implementing a genomic testing panel for FGFR3 mutations*". It is inappropriate to accept the costs from a singular source, specifically the Genomic Medicines Service without a comprehensive understanding of the full breakdown to ensure the costs reflect the best value for the healthcare system. The methodology utilised by NHS England in determining the costs associated with testing for FGFR3 mutations, including the underlying assumptions, costs associated with increased activity resourcing and any potential biases, should be thoroughly reviewed and made available for public scrutiny. This cost is excessive, particularly for a rare patient population with a very short life expectancy, as it leads to a huge cost of £7,723 (£1,282/0.166) per eligible

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	patient. With the current discount, this represents [redacted] of the total drug costs versus [redacted] of the original approach. Johnson & Johnson's major concern is the substantial impact that this change of approach (to the calculation of testing costs) is likely to have on NICE's ability to evaluate rare indications with unfortunately, a short life expectancy. The required value assessments are already incredibly challenging for rare and complex conditions, and any further complications introduced would risk preventing any first-to-market targeted medicines receiving a positive recommendation through the NICE evaluation process and ultimately hindering improvement to patient care in England. The application of such a high cost per test divided by prevalence, is difficult to adopt in rare diseases/mutations with very low prevalence, with short duration of survival and therefore duration of treatment. The approach leads to inequity. This is because the proportion of total cost attributed to testing costs over a short time horizon will be much higher than in more common diseases with higher and longer survival. The fundamental issue here is that this approach, if continued, could effectively halt the availability of valuable treatments into clinical practice, especially for rare conditions. More imminently, it highlights the penalty on innovation for erdafitinib and eligible patients. As the first and only targeted precision medicine in its class, Johnson & Johnson simply cannot absorb this excessive cost. If the draft guidance is correct in stating that the cost of £1,282 relates to the *"full cost of implementing a genomic testing panel for FGFR3 mutations"* charging this fee means applying temporary costs to the value of the medicine which will be in effect for the entire lifespan of erdafitinib. This also implies that even if a new targeted therapy were to emerge in this field, erdafitinib would remain the sole treatment responsible for the complete costs, as its service infrastructure should have already been established. Once NGS testing for FGFR3 is set up, there should be no need to incorporate set-up testing costs for this population in the future, only implementation costs should be incurred. If the Committee maintains that the solution is to charge excessive testing costs in the economic modelling for this appraisal, which Johnson & Johnson contest on both principle and precedence, more efficient RT-qPCR approach must be considered. In the THOR trial, the identification of eligible patients with positive FGFR3 alterations was carried out using RT-qPCR (Therascreen Assay, Quiagen; companion diagnostic assay for erdafitinib). Alternatively, identifying eligible patients for erdafitinib can be achieved through collaboration with laboratory partners independent of GLHs. **Conclusion** In conclusion, the most appropriate approach for testing FGFR3 genetic alterations is the cost of £449.70 per identified patient, which is significantly lower than the proposed £7,723. The latter figure imposes an untenable financial burden, particularly given the low FGFR3 prevalence and short life expectancy of the affected patient population. Although Johnson & Johnson understands that no new service is required, the proposed set-up costs of £7,723 should be regarded as a temporary expense. FGFR3 testing will quickly transition to a sustainable routine clinical practice cost of £449.70 per patient until the expiration of the erdafitinib patent. Consequently, setup

	costs should not be considered over the entire duration of erdafitinib's patent life. Following precedence, setup costs were not borne by manufacturers in previous technology appraisals where a new service was required to be implemented. Furthermore, exploring an alternative affordable RT-qPCR method for FGFR3 alterations or collaboration with laboratory partners independent of GLHs could further reduce costs while ensuring access for patients. There is an urgent need to redefine testing cost methodologies in rare diseases to facilitate the introduction of essential therapies.
2	Section 3.2. Treatment pathway. The draft guidance states that "The experts thought that around 70% of people at this point in the pathway may be well enough to have chemotherapy and be offered it but that only 30% to 50% of people would actually have it, with the rest having BSC." There is a lack of data to facilitate a robust modelling analysis. Erdafitinib is indicated for the mUC patient population that has previously been exposed to immunotherapy. To our and clinical expert knowledge, there is no study that has evaluated the clinical efficacy of best supportive care (BSC) in patients who choose or are recommended to receive BSC following immunotherapy, that could be eligible for active treatment (e.g. chemotherapy). The only available clinical evidence from the systematic literature review that was part of the company's submission is a phase III randomised controlled trial (RCT) comparing vinflunine and BSC (https://ascopubs.org/doi/10.1200/JCO.2008.20.5534?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed). However, the population demographics and prior treatments differ significantly from the THOR trial population, and a simple comparison with erdafitinib cannot be made, as this study involved patients who were recently diagnosed and had exclusively been exposed to platinum-based chemotherapy. As such, Johnson & Johnson have utilised the clinical outcomes data from the UK real-world (RW) study involving patients who received a combination of paclitaxel and carboplatin as a proxy for the clinical efficacy of BSC, which could be interpreted as an overestimation of the effect of BSC. The healthcare resource utilisation was primarily informed by the Technology Appraisal 272 (TA272: https://www.nice.org.uk/guidance/ta272) assessment, which we further validated with clinical experts. In the economic model, no subsequent treatments for BSC patients after they progressed were accounted for. Despite the above concerns and limitations, BSC was incorporated in the basket of treatment comparators. Johnson & Johnson conducted a survey with four clinical experts, who confirmed that 50% of patients eligible for active systemic anti-cancer treatment do not receive any form of treatment. Of the 50% of patients who are eligible for SACT, approximately 30% refuse chemotherapy (J&J data on file).
3	Section 3.15. Plausibility of modelled results: The draft guidance states that "So, the committee thought it implausible that the time spent in the progression-free health state would be very similar for both erdafitinib and the basket comparator." The absence of progression-free survival (PFS) data from UK real-world (RW) studies is an inherent limitation in an appraisal for an underserved, rare condition with high unmet need.

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	Firstly, the evidence indicates that the PFS for paclitaxel monotherapy is comparable to that of erdafitinib, as demonstrated by the matching-adjusted indirect comparison (MAIC) analysis (refer to Appendix Q in the Company submission). Secondly, the time to next treatment (TTNT) for both erdafitinib and paclitaxel is much more aligned with the overall survival (OS) curves, so could be seen as an overestimation to the PFS curve.
4	Section 3.21. Committee's preferred assumptions The committee thought that until the uncertainties were addressed it would be unable to establish a plausible incremental cost-effectiveness ratio (ICER) for erdafitinib. The committee outlined additional analyses that could be explored to address some of the uncertainties, which was to use: -BSC as a comparator in the basket (see section 3.3) -alternative imputation methods, such as multiple imputation or assuming the best possible value for the missing data (see section 3.9). -the results from THOR to directly inform the model (see section 3.16) -the relative treatment effect from THOR applied to the baseline risk of OS and TTNT from the mUC RW study (see section 3.16). Johnson & Johnson have included these scenarios in the additional analyses attached to this response; however, there is no evidence to suggest that using the THOR trial to directly inform the model or relying on the relative treatment effects from the THOR explorations, is an appropriate approach within the context of this appraisal. Firstly, docetaxel and vinflunine are not considered standard of care treatments or, in the case of vinflunine, is not available or in the UK, and no comparative studies have been conducted between docetaxel/vinflunine and paclitaxel ± carboplatin to confirm that these chemotherapies are similar or different. In relation to the multiple imputation methods, it is noteworthy that the adjusted overall survival for erdafitinib is superior to the initial results from our THOR trial, with the multiple imputation yielding a survival estimate of 14.7 months (ranging from 10.2 to 19.4 months), compared to 12.1 months (ranging from 10.3 to 16.4 months) observed in the THOR clinical trial. Johnson & Johnson would like to highlight that, while this data is informative, it is not suitable for decision-making purposes. This is mainly because it is improbable that, after adjusting our THOR trial data to UK RWE data, the overall survival would show an improvement compared to the results from a randomised clinical trial. Consequently, the chosen base case, which is based on the *worst-case adjustment* to align with UK clinical practice patients, is likely to yield more realistic results. For the relative treatment effect from THOR applied to baseline risk of OS and TTNT, the lack of time to treatment discontinuation (TTD) data in the UK mUC real-world study requires further assumptions on the erdafitinib TTD curve (we are assuming that it is similar to the observed THOR ITT TTD), thereby introducing a further layer of uncertainty into the analyses.
5	Section 3.5. Generalisability of clinical evidence for erdafitinib

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	Another generalisability concern was that the majority of people in the THOR study had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 1. The EAG explained that this may indicate a healthier population than would be expected in NHS clinical practice. To address concerns about a healthier THOR population than would be expected in NHS practice, a worst-case imputation approach was adopted as the base case in our cost-utility analysis. This method assumes relatively poor ECOG PS for patients without ECOG scores which means that when re-weighting the erdafitinib patient population to match with the UK RW cohort, Johnson & Johnson upweight more severe patients (those with ECOG 1-2) to align with poor PS in the NHS population. The choice was informed by feedback from clinical experts who outlined that 2L+ mUC patients in UK clinical practice are mainly ECOG 1-2 and fewer would be ECOG 0.
6	Section 3.5. Generalisability of clinical evidence for erdafitinib. At the committee meeting, clinical experts explained that they expected people who might have erdafitinib in the NHS to be slightly older than in THOR and suggested an average age of 70 years. As indicated in the draft guidance, the company's real-world cohort study, which included patients who are truly representative of those eligible to receive erdafitinib after immunotherapy in NHS clinical practice, had a median age of 65.5 years. This is comparable to the median age of 66 years in the THOR trial. However, the entire cohort of 10,787 mUC patients in England had a higher mean age of 73.9 (median of 75 years) than our sub-group of patients. A recent, large UK mUC study stated that "*Patients in the cohort with evidence of systemic anti-cancer therapy were younger at diagnosis than those classified as untreated, with mean ages of 67.5 years and 75.7 years, respectively*" (https://www.sciencedirect.com/science/article/pii/S1078143924005477#abs0002), which is in line with our study. It is crucial to acknowledge that patients receiving systemic treatment tend to be significantly younger than the untreated overall cohort of patients. Notably, most individuals are deemed unfit for systemic treatment. Consequently, the age of 70 years cited by clinical experts pertains to the broader, unselected and untreated population of mUC patients within the NHS. In contrast, the specific patient group eligible for erdafitinib treatment, following prior PD-(L)-1 inhibitor treatment has a median age of approximately 65 to 66 years.
7	Section 3.5. Generalisability of clinical evidence for erdafitinib The Committee statement that "It thought that it was plausible that age was a treatment-effect modifier and concluded that there was some uncertainty around the generalisability of the THOR trial to NHS clinical practice." In the subgroup analysis, the median overall survival was 14.0 months (HR: 0.46 (95% CI: 0.27, 0.79) in adults <65 years and 10.9 months (HR: 0.71 (95% CI: 0.47, 1.07) for adults 65+ years, demonstrating a consistent efficacy for erdafitinib in all age groups. It is essential to exercise caution and avoid reading too much the results from subgroup analysis, as we are already working within a rare and relatively small patient population, even in the trial. It is also worth noting that THOR has

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	investigated the efficacy of a targeted agent in rare driver alterations within a pre-defined small group of patients who have been treated with a PD-(L)1 inhibitor. Any trends are simply hypothesis generating and are inappropriate for decision making. Besides this general statement, the subgroup analysis in the THOR trial was not adequately powered to test specific hypotheses. Johnson & Johnson advise caution in the overinterpretation of results, as the analyses were defined post hoc, and the findings are based on small sample sizes with wide confidence intervals. Additionally, they did not include appropriate adjustments for potential confounding factors and/or multiple testing, which increases the risk of chance findings.
9	3.24. Uncaptured benefits The draft guidance states that "the committee did not identify additional benefits of erdafitinib not captured in the economic modelling. So, the committee concluded that all additional benefits of erdafitinib had already been taken into account." Johnson & Johnson are of the view that in addition to the clinical and economic value, additional benefits of erdafitinib that are not captured in the QALY framework include the intangible value of hope in dire end-of-life circumstances as heard from patients during the first committee meeting, the ease of use of treatment for the patient, the alleviation of carer burden and the value derived from innovation, which acts as a bridge for current and future patients, enabling them to access forthcoming advances in medical care.
10	3.12. Stopping rule for paclitaxel with or without carboplatin The EAG explained that TTD was not captured in the RW mUC study. So, its base case assumes TTD is equal to PFS. But the EAG said that people may stop treatment for reasons other than progression, so this approach may still overestimate TTD. The committee concluded that a 6-cycle stopping rule for paclitaxel with or without carboplatin should be applied in the modelling. Johnson & Johnson are of the view that, while this represents an acceptable compromise, using time to next treatment (TTNT) as a proxy for progression-free survival (PFS) may also overestimate PFS for paclitaxel ± carboplatin. The implementation of a stopping rule after 6 cycles for chemotherapy's time to treatment discontinuation (TTD) somewhat alleviates the potential overestimation of TTD.
11	3.22. Acceptable ICER. The committee concluded that given the uncertainties in the evidence, an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained). This cancer is extremely rare and aggressive, affecting a small patient population that faces a dire prognosis with practically no options available for those fortunate enough to be alive. Johnson & Johnson believe that, considering the severity of the disease, the small size of the patient population, the significant improvement erdafitinib delivers, the additional analyses provided addressing remaining uncertainty and demonstrating the robustness of the cost-effectiveness results, the risk associated with funding erdafitinib is low. Therefore, the acceptable ICER should be positioned at the upper end of the range that NICE considers to be a cost-effective use of NHS resources (i.e., £30,000 per QALY gained).

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

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Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Company Additional Analyses

[January 2025]

File name	Version	Contains confidential information	Date
ID1333_Erdafitinib_Additional_Analyses_[CON].docx	V1	Yes	January 2025

Introduction

These supplementary analyses explore the addition of best supportive care (BSC) to the basket and other scenarios' impact on the incremental cost-effectiveness of erdafitinib. We anticipate that this additional evidence will be useful to support a recommendation for erdafitinib in treating metastatic or unresectable FGFR-altered urothelial cancer population, thereby addressing a significant unmet need.

Section A: Summary of the updated base case and additional scenarios

Given the request to add BSC as a comparator to the company's base case, Johnson & Johnson have revised and updated the base case. The committee's preferred assumptions including a 6-cycle stopping rule for paclitaxel with or without carboplatin, time to next treatment (TTNT) data from the RW mUC study as a proxy to inform the PFS for paclitaxel with or without carboplatin, the severity weight of x1.7 (note that a basket of paclitaxel ± carboplatin and BSC gives a x1.7 severity weight), the regression model to estimate utility values and lower progression-free per-cycle costs in the erdafitinib have been incorporated. A PAS of [redacted] and testing costs of £74.65 per test are applied in all scenarios. Deterministic and probabilistic results of the updated analyses are presented in

Table 1 and Table 2, respectively.

Table 1. Deterministic analyses based on the committee's preferred assumptions and results from additional scenarios requested by the committee to address uncertainty

	Total outcomes by treatment			**Incremental outcomes**			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
Base case							
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	[redacted]	0.630	0.705	[redacted]	1.030	[redacted]	£28,182
Multiple imputation							
Erdafitinib	[redacted]	1.751	[redacted]	-	-	-	-
Paclitaxel ± carboplatin	[redacted]	0.733	0.823	[redacted]	1.018	[redacted]	£30,981
BSC	[redacted]	0.527	0.588	[redacted]	1.223	[redacted]	£31,490
Basket	[redacted]	0.630	0.706	[redacted]	1.121	[redacted]	£31,261
Applying the relative effect from THOR to the risk of OS and TTNT from the mUC RW study							
Erdafitinib	[redacted]	1.423	[redacted]	-	-	-	-
Paclitaxel ± carboplatin	[redacted]	0.733	0.823	[redacted]	0.691	[redacted]	£33,691
BSC	[redacted]	0.527	0.588	[redacted]	0.896	[redacted]	£33,699
Basket	[redacted]	0.630	0.706	[redacted]	0.793	[redacted]	£33,695
THOR ITT							
Erdafitinib	[redacted]	1.632	[redacted]	-	-	-	-

Chemotherapy (docetaxel, vinflunine)	[redacted]	1.041	1.104	[redacted]	0.591	[redacted]	£36,977

Key: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LY, Life years; QALY, Quality adjusted life year; Basket, Paclitaxel ± carboplatin and BSC; OS, Overall survival; TTNT, Time to next treatment; mUC, Metastatic urothelial carcinoma; RW, real-world

Table 2. Probabilistic analyses based on the committee's preferred assumptions and results from additional scenarios requested by the committee to address uncertainty

	Total outcomes by treatment			**Incremental outcomes**			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
Base case							
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	[redacted]	0.659	0.730	[redacted]	1.023	[redacted]	£28,265
Multiple imputation							
Erdafitinib	[redacted]	1.770	[redacted]	-	-	-	-
Paclitaxel ± carboplatin	[redacted]	0.744	0.832	[redacted]	1.025	[redacted]	£31,061
BSC	[redacted]	0.574	0.628	[redacted]	1.196	[redacted]	£31,816
Basket	[redacted]	0.659	0.730	[redacted]	1.111	[redacted]	£31,473
Applying the relative effect from THOR to the risk of OS and TTNT from the mUC RW study							
Erdafitinib	[redacted]	1.485	[redacted]	-	-	-	-
Paclitaxel ± carboplatin	[redacted]	0.744	0.832	[redacted]	0.741	[redacted]	£32,923
BSC	[redacted]	0.574	0.628	[redacted]	0.912	[redacted]	£33,458
Basket	[redacted]	0.659	0.730	[redacted]	0.826	[redacted]	£33,220
THOR ITT							
Erdafitinib	[redacted]	1,661	[redacted]				

Chemotherapy (docetaxel, vinflunine)	[redacted]	1,047	1,111	[redacted]	0.613	[redacted]	£36,121

Key: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LY, Life years; QALY, Quality adjusted life year; Basket, Paclitaxel ± carboplatin and BSC; OS, Overall survival; TTNT, Time to next treatment; mUC, Metastatic urothelial carcinoma; RW, real-world

Section B: Additional evidence requested by the committee

Best supportive care as a comparator in the basket

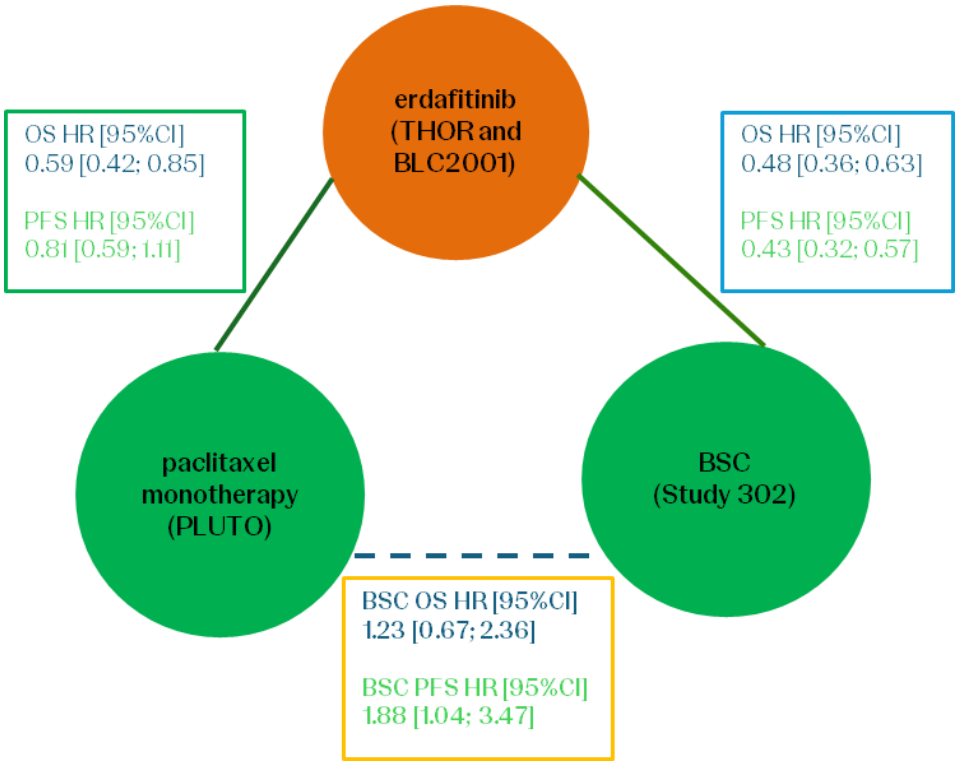
Efficacy data

There is no clinical efficacy data for BSC in mUC patients who progressed after PD-1 or PD-L1 inhibitors. In a different patient population in mUC however, a phase III trial compared the efficacy of vinflunine against BSC after platinum-based chemotherapy [1, 2]. For this analysis, Johnson & Johnson explored two options. For the base case, Johnson & Johnson used the efficacy data (OS and TTNT) from the paclitaxel + carboplatin arm from the UK RW study as a proxy for the efficacy for BSC, which was also suggested by NICE. The chosen parametric curves for OS and TTNT are log-logistic and log-normal, respectively. No treatment is required by patients on BSC, apart from pain medication, so time to treatment discontinuation (TTD) is not required.

In another option, which is presented as a confirmative scenario analysis, Johnson & Johnson estimated the relative efficacy of BSC (from the 302 study[2]) versus paclitaxel monotherapy (from the PLUTO study[3]) using the Bucher method[4]. Due to the lack of clinical trial data, we used the unanchored MAIC results of erdafitinib versus paclitaxel monotherapy and BSC (see

Figure 1 and more details in the Annex: MAIC analyses).

Figure 1. Network for erdafitinib versus paclitaxel monotherapy and BSC

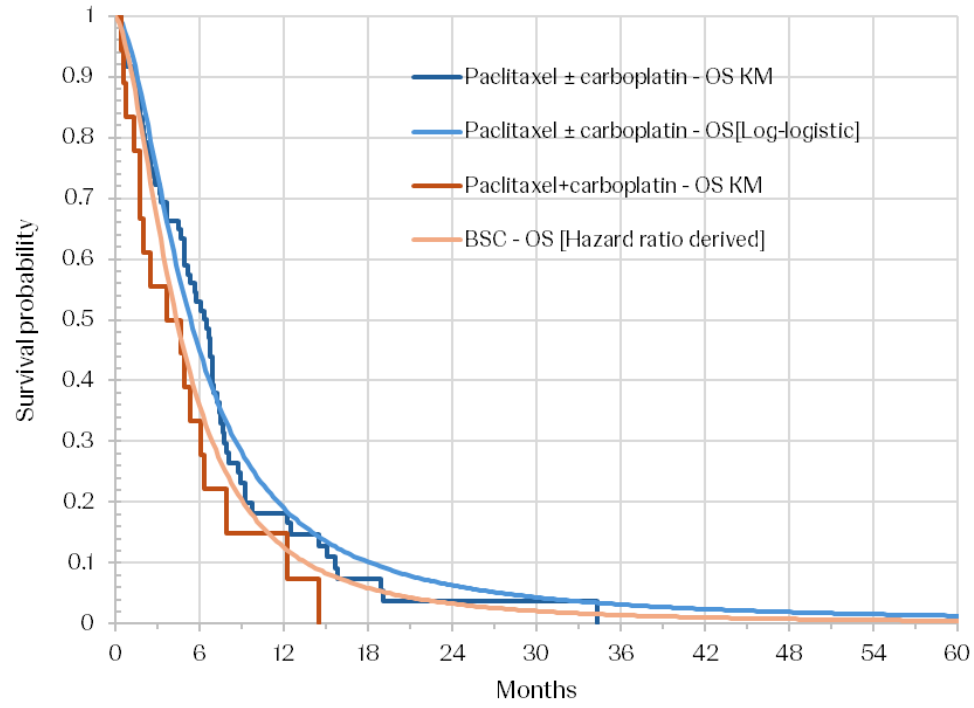


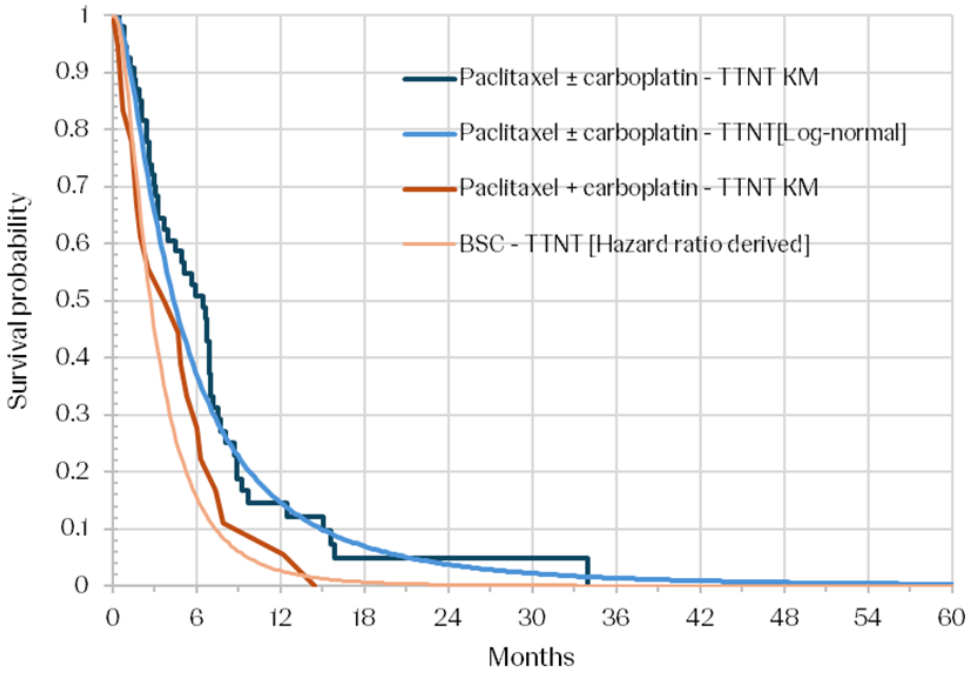
OS and PFS risk curves for BSC derived from applying the hazard ratios (HRs) shown in

Figure 1 to the UK RW paclitaxel ± carboplatin OS and TTNT (proxy for PFS) were compared to the paclitaxel + carboplatin OS and TTNT for UK RW study. These results demonstrate that the HR-derived curves (OS and TTNT) and combination treatment (paclitaxel + carboplatin) OS and TTNT curves are similar (

Figure 2).

Figure 2. Comparison of OS (top) and TTNT (bottom) curves for paclitaxel + carboplatin and those derived from applying the hazard ratios of BSC versus paclitaxel monotherapy.





Key: BSC, best supportive care; TTNT, time to next treatment; OS, overall survival; KM, Kaplan Meier.

Healthcare resource utilisation

Published evidence on resource use for patients with locally advanced or metastatic urothelial carcinoma treated with BSC is limited. In this analysis, resource utilisation was informed by a previous submission for mUC for patients who received BSC (TA272[5]). Some of the resource frequencies were informed by clinical experts[6]. Both pre and post progression resource use are presented in Table 3.

Table 3. Healthcare resource utilisation by patients on BSC

Cost component	Description	Disease state	Item	Resource use	Source
Treatments and procedures	Blood transfusion	Pre- and post-progression	Blood transfusion	10% of patients	Clinical experts[6]
	Pain medication	Pre- and post-progression	Prednisolone	10mg/day (pack size 140mg)	Clinical experts[6]
		Pre- and post-progression	Morphine	40mg/day (pack size 200mg)	Clinical experts[6]
		Pre- and post-progression	Gabapentin	300mg/day (pack size 30,000mg)	Clinical experts[6]
	Palliative radiotherapy	Pre-progression	Radiotherapy	22.2% of patients (once before progression)	TA272[5] and Clinical experts[6]
		Post-progression	Radiotherapy	15.7% of patients (once after progression)	TA272[5] and Clinical expert
Community care	GP home visits	Pre-progression	GP home visits	1 per month	TA272[5]
		Post-progression	GP home visits	1 per month	TA272[5]
	Community/district nurse visits	Pre-progression	Community nurse visit	4 per month	TA272[5]
		Post-progression	Community nurse visit	4 per month	TA272[5]

	Consultant visits	Pre-progression	Consultant led oncologist visit	1 per month	TA272[5], TA788[7]
		Post-progression	Non-consultant oncologist follow-up visit	1 per month	TA272[5], TA788[7]
	Hospice care	Post-progression	Hospice day visits	30% of patients once per week	TA272[5]
			Inpatient hospice care	40% of patients averaging 5 nights	TA272[5]

Key: BSC, best supportive care; GP, General practitioner; CT, Computed tomography

Adverse events

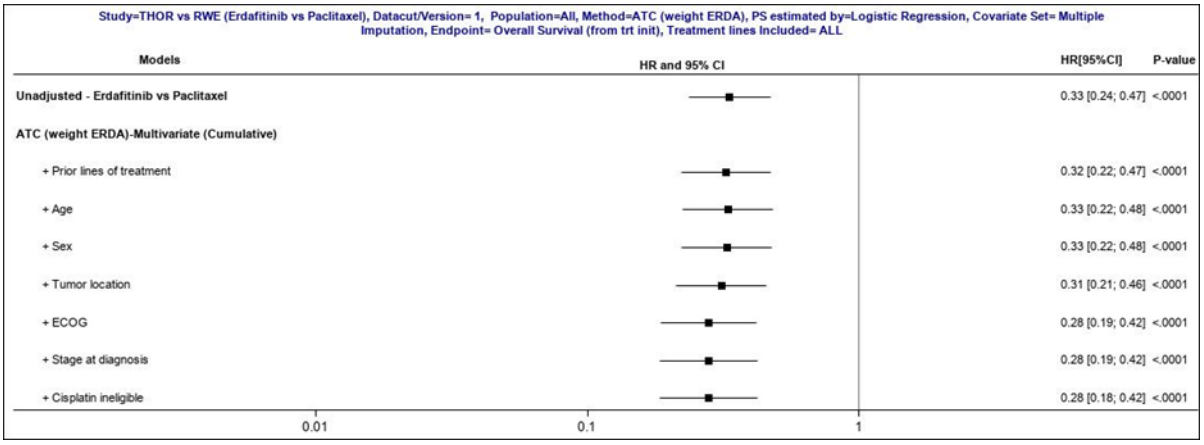
The model considers grade 3 or more adverse events that occurred in at least 5% of the patients. Based on this criteria, only 3 adverse events were included for BSC, based on Study 302 (TA272)[5] and these were anaemia (8.1%), fatigue (17.9%) and neutropenia (1.7%), with the latter included as it was included for other comparators.

Multiple imputation

The missing variables—27% for disease stage and 57% for ECOG PS—were imputed using multiple imputation. Across multiple imputation (MI) method was used to generate 50 imputations using SAS v9.4. In summary, after imputing the missing values and calculating the propensity scores for each imputed dataset, the propensity scores were pooled together before calculating the weights and running the survival models.

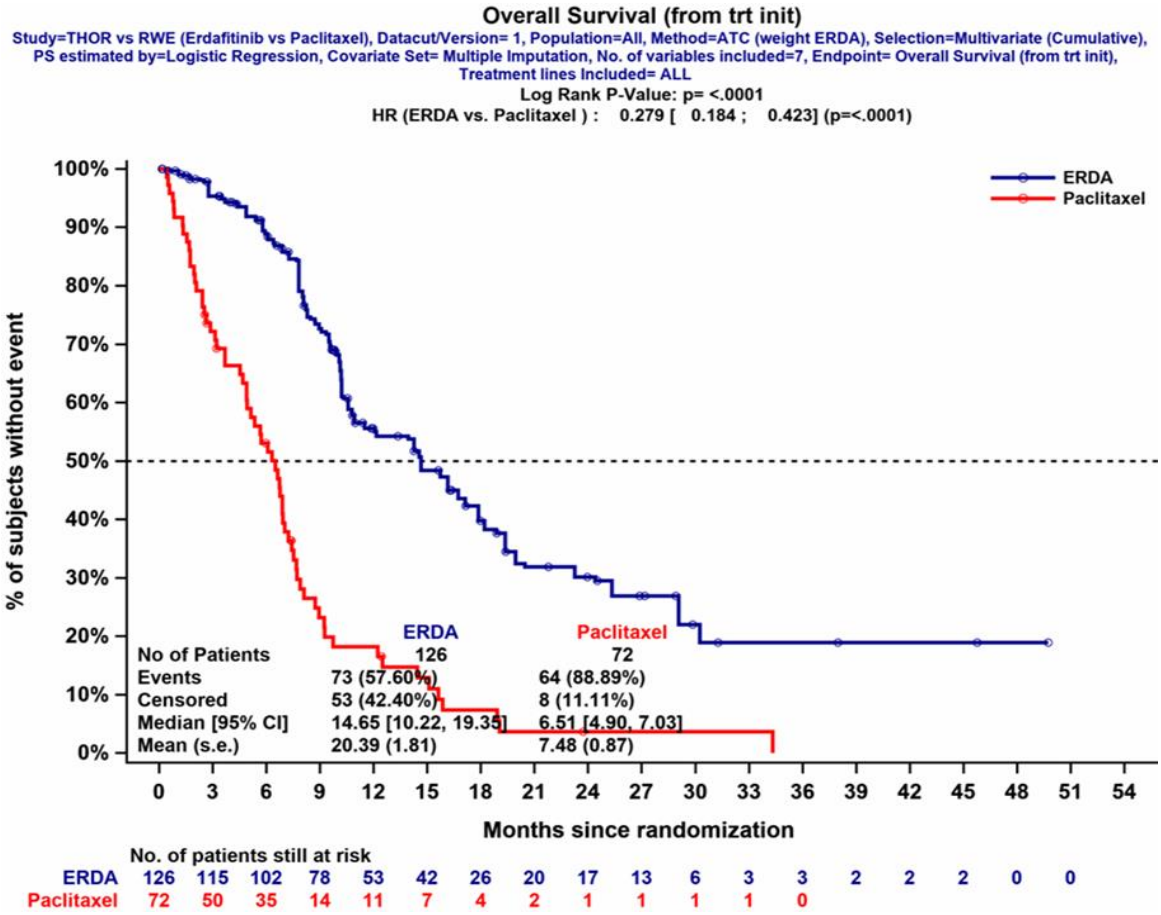
The impact of adding covariates cumulatively on OS is presented in Figure 3, where the addition of covariates did not impact much the hazard ratio from the unadjusted analysis. However, these hazard ratios are more in favour of erdafitinib. The Kaplan-Meier curve for ATC-adjusted OS comparison for erdafitinib versus paclitaxel ± carboplatin is presented in Figure 4, with the median OS of 14.7 months (95% CI: 10.2, 19.4) for erdafitinib and 6.5 months (95% CI: 2.5, 7.0) for paclitaxel ± carboplatin.

Figure 3. Forest plot for ATC-adjusted OS comparison for erdafitinib versus paclitaxel ± carboplatin (Multiple imputation)



Key: ERDA, Erdafitinib; ATC, average treatment effect for the control; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, Overall survival; Paclitaxel, Paclitaxel ± carboplatin

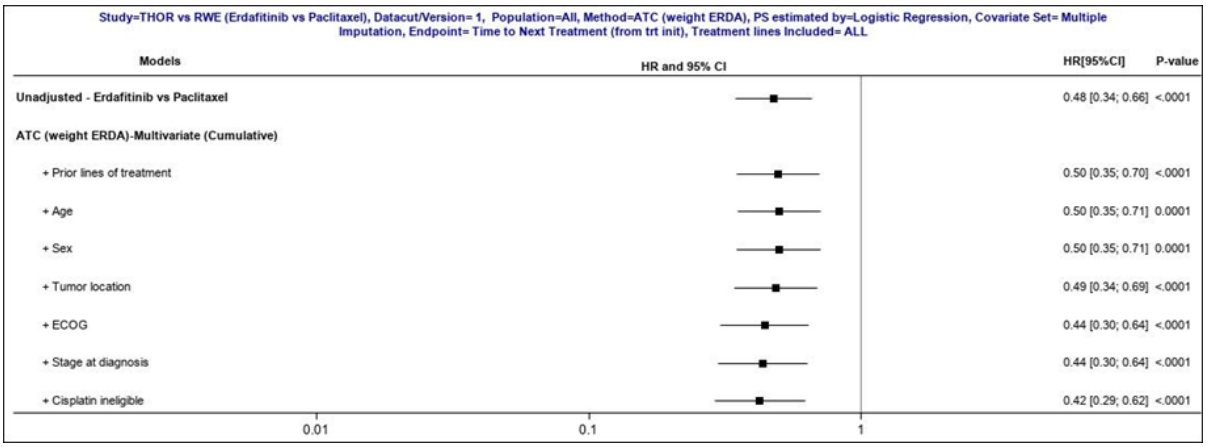
Figure 4. Kaplan-Meier curve for ATC-adjusted OS comparison for erdafitinib versus paclitaxel ± carboplatin (Multiple imputation)



Key: ERDA, Erdafitinib; ATC, average treatment effect for the control; Paclitaxel, Paclitaxel ± carboplatin; CI, Confidence interval; s.e, standard error; OS, Overall survival

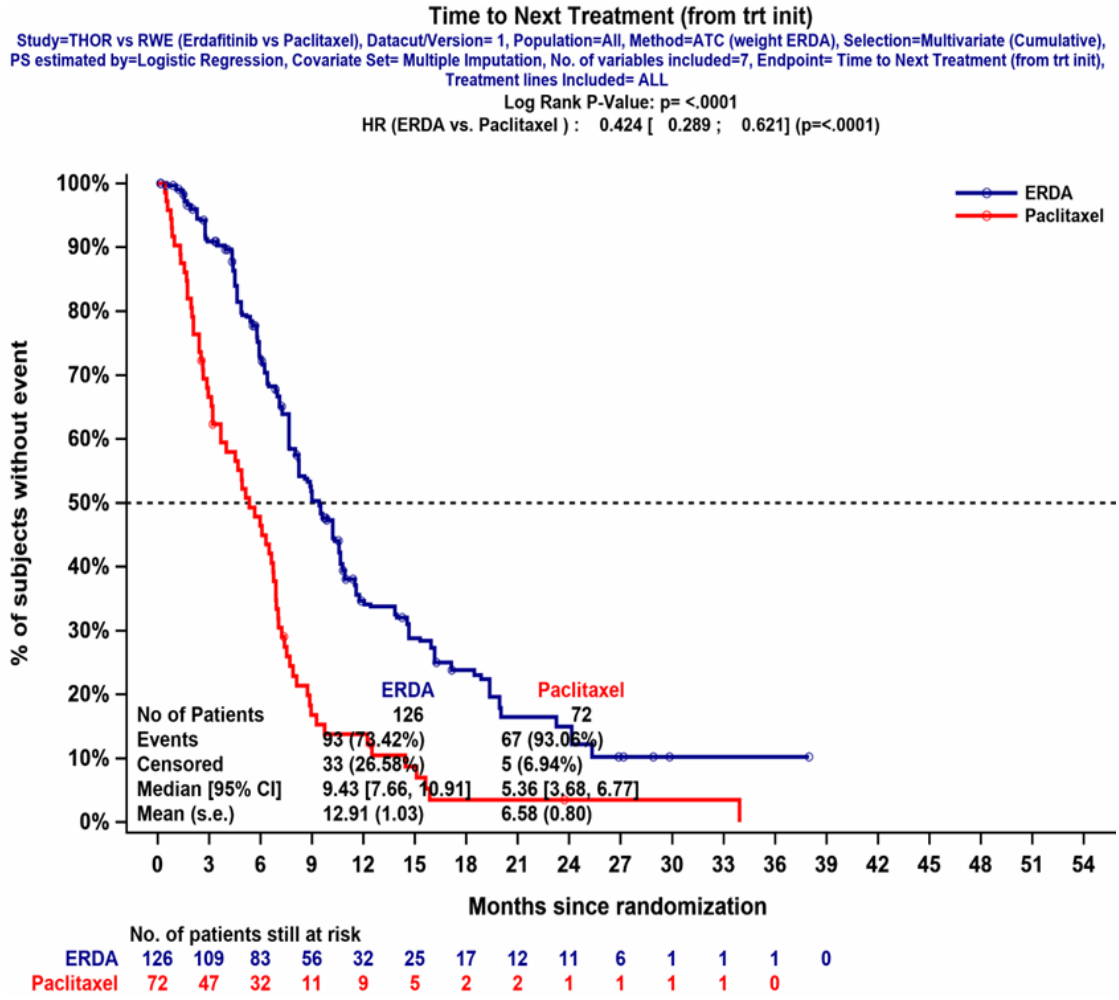
The addition of covariates did not impact much the HR for TTNT from the naïve comparison (Figure 5). The Kaplan-Meier curve for comparison for erdafitinib versus paclitaxel ± carboplatin is given in Figure 6, with the median TTNT of 9.4 months (95% CI: 7.7, 10.9) for erdafitinib and 5.4 months (95% CI: 3.7, 6.8) for paclitaxel.

Figure 5. Forest plot for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel ± carboplatin (Multiple imputation)



Key: ERDA, Erdafitinib; PS, propensity score; ATC, average treatment effect for the control; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; CI, Confidence interval; HR, Hazard ratio

Figure 6. Kaplan-Meier curve for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel ± carboplatin (Multiple imputation)



Key: ERDA, Erdafitinib; ATC, average treatment effect for the control; Paclitaxel, Paclitaxel ± carboplatin; CI, Confidence interval; s.e, standard error; TTNT, Time to next treatment

A comparison of the base case (worst case) and multiple imputation scenario is presented in Table 4. As stated in the company's response to the EAG's report, any other imputation values would lead to a better treatment estimate (higher relative effect) for erdafitinib versus paclitaxel ± carboplatin. With multiple imputation, slightly fitter patients (compared to the worst-case approach) are weighted up leading to better outcomes. On the other hand, fitter patients are likely to be treated for much longer than patients with worse Eastern Cooperative Oncology Group performance status (ECOG PS) scores as shown by the increase in median TTNT. The HRs for the worst-case and multiple imputation scenarios are shown in Table 4 for paclitaxel ± carboplatin.

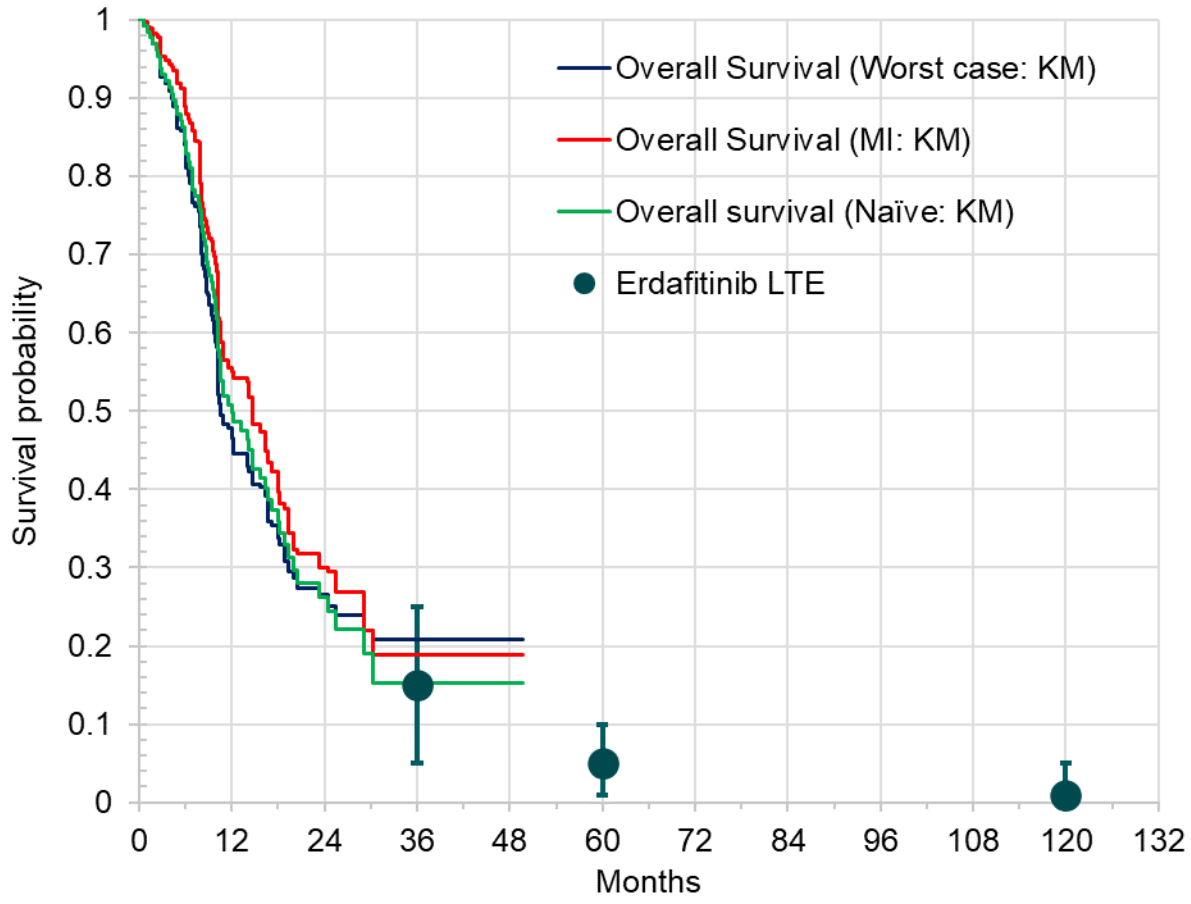
Table 4. Summary of ITC (ATC) results for paclitaxel ± carboplatin

Scenarios for handling missing ECOG scores and tumour stage	**Erdafitinib**	**Paclitaxel ± carboplatin**
Base case (worst case)		
No of patients	126	72
Median OS, months (95% CI)	10.6 (9.5, 16.7)	6.5 (4.9, 7.0)
Hazard ratio		0.35 (0.23, 0.52)
Median TTNT, months (95% CI)	8.0 (6.5, 9.0)	5.4 (3.7, 6.8)
Hazard ratio (95% CI)		0.53 (0.37, 0.76)
Multiple imputation		
No of patients	126	72
Median OS, months (95% CI)	14.7 (10.2, 19.4)	6.5 (4.9, 7.0)
Hazard ratio		0.28 (0.18, 0.42)
Median TTNT, months (95% CI)	9.4 (7.7, 10.9)	5.4 (3.7, 6.8)
Hazard ratio		0.42 (0.29, 0.62)

Key: ECOG, Eastern Cooperative Oncology Group; ATC, Average treatment effect for the control; ITC, Indirect treatment comparison; CI, Confidence interval; TTNT, Time to next treatment; OS, Overall survival

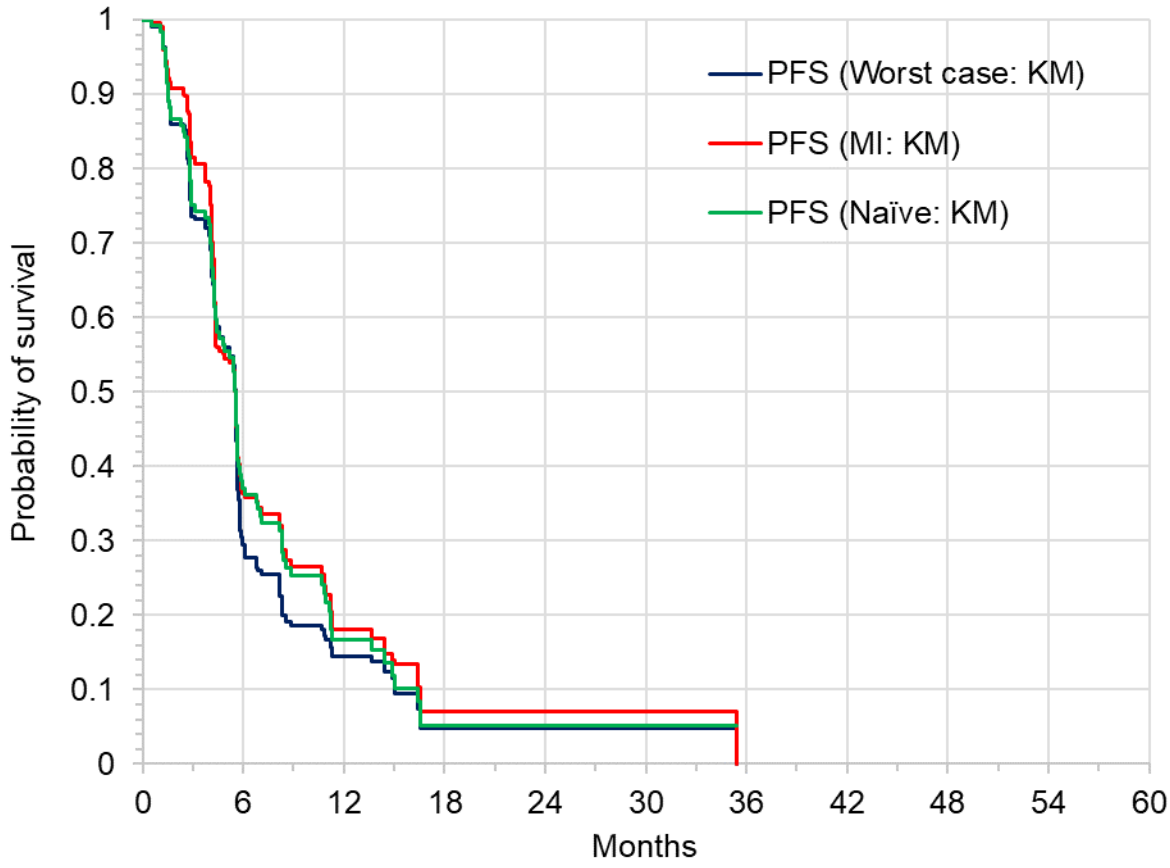
The overall survival, progression-free survival and time to treatment discontinuation Kaplan-Meier curves for erdafitinib derived using the worst case and multiple imputation are shown in Figure 7, Figure 8 and Figure 9, respectively. We also present the unadjusted curves from the erdafitinib arm of the THOR ITT population to demonstrate consistency and plausibility of the results.

Figure 7. ATC-adjusted OS of erdafitinib for worst-case, multiple imputation and best-case scenarios



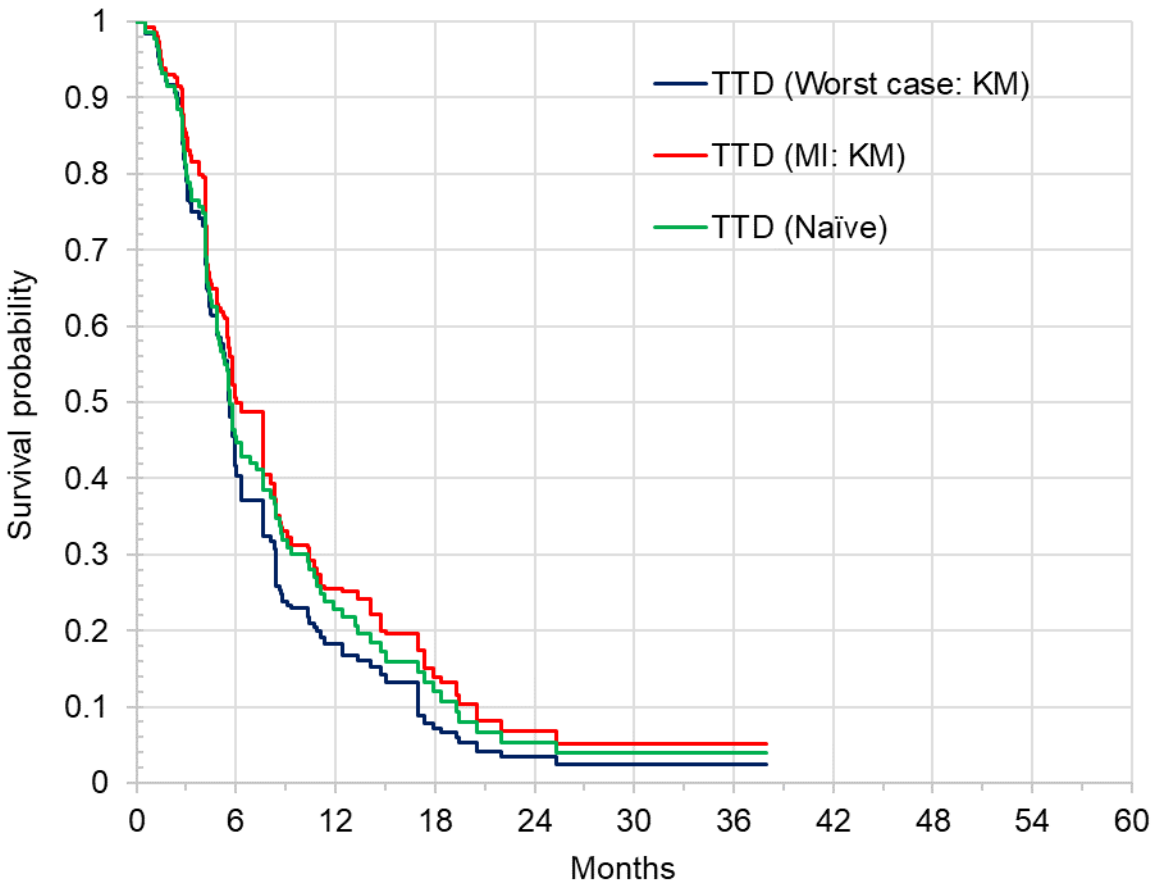
Key: ATC, Average treatment effect for the control; MI, Multiple imputation; OS, Overall survival; KM, Kaplan Meier; LTE, long-term estimates

Figure 8. ATC-adjusted PFS of erdafitinib for worst-case, multiple imputation and best-case scenarios



Key: ATC, Average treatment effect for the control; PFS, Progression-free survival; MI, Multiple imputation; KM, Kaplan Meier

Figure 9. ATC-adjusted TTD of erdafitinib for worst-case, multiple imputation and best-case scenarios



Key: ATC, Average treatment effect for the control; TTD, Time to treatment discontinuation; MI, Multiple imputation; KM, Kaplan Meier

In Table 5, we present the selected curves for the worst case and multiple imputation scenarios. Note that the same best fitting curves for the worst case are still valid for multiple imputation.

Table 5. Model selection assumptions

	Overall survival	Progression-free survival	Time to treatment discontinuation	Time to next treatment
Worst-case				
Erdafitinib	Log-logistic	Log-logistic	Log-logistic	Log-logistic
Paclitaxel ± carboplatin	Log-logistic	TTNT as PFS	Equal to PFS with a stopping rule after 6 cycles	Log-normal
Multiple imputation				
Erdafitinib	Log-logistic	Log-logistic	Log-logistic	Log-logistic
Paclitaxel ± carboplatin	Log-logistic	TTNT as PFS	Equal to PFS with a stopping rule after 6 cycles	Log-normal

Key: PFS, Progression-free survival; TTNT, Time to next treatment

The cost-effectiveness results for the multiple imputation scenario are presented in Table 6. These results show an increase in health outcomes (LYs and QALYs), and drug acquisition costs as these patients were treated for a bit longer and consequently resulting in an increase of the ICER by £3,079.

Table 6. Multiple imputation cost-effectiveness results

	Total outcomes by treatment			Incremental outcomes			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
Erdafitinib	[redacted]	1.751	[redacted]	-	-	-	-
Paclitaxel ± carboplatin	[redacted]	0.733	0.823	[redacted]	1.018	[redacted]	£30,981
BSC	[redacted]	0.527	0.588	[redacted]	1.223	[redacted]	£31,490
Basket	[redacted]	0.630	0.706	[redacted]	1.121	[redacted]	£31,261

Key: BSC, Best supportive care; ICER, Incremental cost-effectiveness ratio; LY, Life years; QALY, Quality adjusted life year; Basket, Paclitaxel ± carboplatin and BSC

In relation to the multiple imputation methods, it is noteworthy that the adjusted overall survival for erdafitinib is superior to the initial results from our THOR trial, with the multiple imputation yielding a survival estimate of 14.7 months (ranging from 10.2 to 19.4 months), compared to 12.1 months (ranging from 10.3 to 16.4 months) observed in the THOR clinical trial. Johnson & Johnson would like to highlight that, while this data is informative, it is not suitable for decision-making purposes. This is mainly because it is improbable that, after adjusting our THOR trial data to UK RWE data, the overall survival would show an improvement compared to the results from a randomised clinical trial. Consequently, the chosen base case, which is based on the *worst-case adjustment* to align with UK clinical practice patients, is likely to yield more realistic results.

Applying the relative effect from THOR to the risk of OS and TTNT from the mUC RW study

The OS and TTNT hazard ratios for erdafitinib versus chemotherapy based on the THOR trial are given in

Table 7. These were applied to the UK RW OS and TTNT curves to derive erdafitinib OS and PFS curves. Given that TTD was not available from the UK RW study, Johnson & Johnson used the observed erdafitinib TTD curve from the THOR trial and assumed that the patient characteristics for the model were similar to the observed values in THOR.

For this scenario analysis, it is important to mention that there is no evidence to suggest that relying on the relative treatment effects from the THOR explorations, is an appropriate approach within the context of this appraisal.

Firstly, docetaxel and vinflunine are not considered standard of care treatments or, in the case of vinflunine, is not available or in the UK, and no comparative studies have been conducted between docetaxel/vinflunine and paclitaxel ± carboplatin to confirm that these chemotherapies are similar or different.

Additionally, the lack of time to treatment discontinuation (TTD) data in the UK mUC real-world study requires further assumptions on the erdafitinib TTD curve (we are assuming that it is similar to the THOR ITT TTD), thereby introducing a further layer of uncertainty into the analyses.

Table 7. Hazard ratios for OS and TTNT from THOR ITT

	Erdafitinib (n=136)	**Chemotherapy (n=130)**
OS		
Number of events (%)	77 (56.6%)	78 (60.0%)
Median, months (95% CI)	12.1 (10.3, 16.4)	7.8 (6.5, 11.1)
HR (95% CI)	-	0.64 (0.47, 0.88)
TTNT		
Number of events (%)	93 (68.4%)	100 (76.9%)
Median, months (95% CI)	9.0 (7.1-10.7)	4.2 (3.3-5.9)
HR (95% CI)	-	0.49 (0.37, 0.65)

Key: CI, confidence interval; HR, Hazard ratio; ITT, Intent to treat; TTNT, Time to next treatment; OS, Overall survival

The newly derived risk of OS and TTNT (proxy for PFS) for erdafitinib give the cost-effectiveness results presented in Table 8.

Table 8. Cost-effectiveness results of erdafitinib versus paclitaxel ± carboplatin when THOR hazard ratios are applied.

	Total outcomes by treatment			**Incremental outcomes**			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
Erdafitinib	[redacted]	1.423	[redacted]	-	-	-	-
Paclitaxel ± carboplatin	[redacted]	0.733	0.823	[redacted]	0.691	[redacted]	£33,691
BSC	[redacted]	0.527	0.588	[redacted]	0.896	[redacted]	£33,699
Basket	[redacted]	0.630	0.706	[redacted]	0.793	[redacted]	£33,695

The results from THOR to directly inform the model

Johnson & Johnson also used the THOR ITT trial population to inform the cost-effectiveness model. Model inputs and the justification for curve selection are provided in Appendix R in the Company submission. The best-fitting curves using joint-fitting are presented in Table 9, with the corresponding cost-effectiveness results in Table 10.

As highlighted in the preceding chapter regarding relative effect from THOR, it is crucial to note that there is currently no evidence to support the notion that utilising the THOR trial data to inform the model is a suitable approach within the scope of this appraisal. The comparators utilised in the THOR trial are either unavailable or not recognised as standard care treatments in the UK. Furthermore, there have been no comparative studies conducted between docetaxel and vinflunine and paclitaxel ± carboplatin to ascertain whether these chemotherapy regimens demonstrate similarities or differences.

Table 9. Selected parametric survival curves for THOR ITT

Treatment arm	**OS**	**PFS**	**TTD**
Erdafitinib	Log-logistic	Log-normal	Log-logistic
Chemotherapy (docetaxel, vinflunine)	Exponential	Log-normal	Log-logistic

Table 10. Cost effectiveness of erdafitinib versus chemotherapy

	Total outcomes by treatment			Incremental outcomes			
	Costs	**LYs**	**QALYs**	**Costs**	**LYs**	**QALYs**	**ICER**
Erdafitinib	[redacted]	1.632	[redacted]	-	-	-	-
Chemotherapy (docetaxel, vinflunine)	[redacted]	1.041	1.104	[redacted]	0.591	[redacted]	£36,977

Annex: MAIC analyses

An unanchored matched-adjusted indirect comparison (MAIC) of erdafitinib versus paclitaxel monotherapy is presented in Appendix Q in the Company submission. A MAIC analysis using the PLUTO trial[3] data on paclitaxel monotherapy and pooled data from THOR and BLC2001 yielded a base case OS HR of 0.59 (95% CI: 0.42, 0.85), demonstrating a reduction in the risk of death of 41% compared to paclitaxel. The PFS HR of 0.81 (95% CI: 0.59, 1.11) was observed, demonstrating a reduction in risk of progression with erdafitinib, although it was not statistically significant.

In this Annex, we summarise the MAIC analysis for erdafitinib versus BSC. Study 302 is a randomized phase III study of vinflunine and best supportive care (BSC) versus BSC alone in the treatment of patients with advanced mUC who had experienced progression after a first-line platinum-containing regimen[1, 2, 5]. Three hundred and seventy patients were randomly assigned in a phase III trial and allocated (2:1) to vinflunine (320 or 280 mg/m2) plus BSC (n = 253) or BSC alone (n = 117) between May 2003 and August 2006.

The initial analysis compared the inclusion/exclusion criteria of the two trials (THOR/BLC2001 and Study 302). For the base case analysis, patients with ECOG>2 and patients with zero or more than 2 prior lines of therapy or no platinum-based prior line of therapy were excluded from the BLC2001 and THOR IPD data. This decreased the sample size from 237 to 176. The base case matched ECOG performance status, haemoglobin levels, and visceral disease, resulting in an effective sample size of 159 and when all variables were matched, the effective

sample size decreased to 144. Table 11 reports the values of the baseline characteristics before and after matching for the four scenarios: 1) before applying the exclusion criteria and matching; 2) after exclusion and before matching; 3) after exclusion and matching of the three characteristics mentioned in the previous paragraph, and 4) after exclusion and fully matched on all available characteristics.

Figure 10 is the forest plot for the MAIC adjusted HRs of OS. In the plot, we listed the observed HR, the observe HR after excluding patients, the MAIC adjusted HR starting from matching on most important variables, i.e., ECOG performance status, haemoglobin levels, and visceral disease, and each time with one more variable being additionally adjusted based on its importance (i.e. cumulative from the top to the bottom). For OS, the point estimates with confidence interval of the MAIC adjusted HRs were consistently below 1, so, suggesting statistically significant longer survival with patients receiving erdafitinib. The naïve observed OS HR of patients receiving erdafitinib patients versus patients receiving BSC was 0.45 (95% CI, 0.35, 0.57). The base case OS HR was 0.48 (95% CI, 0.36, 0.63) and when all available characteristics were matched, the HR of OS remained robust at 0.48 (95% CI, 0.36, 0.64). This demonstrates the robustness of the results in all matching scenarios.

Similarly, the point estimates and confidence intervals for the PFS HR were consistently below 1 (Figure 11), suggesting a statistically significant delayed progression in patients receiving erdafitinib.

The OS KM curves for the main scenarios are presented in Figure 12. The median OS before matching was 12.0 months (95% CI: 10.3, 14.7) with erdafitinib versus 4.8 months (95% CI: 4.1, 6.7) with BSC. The median OS for erdafitinib was 11.6 months (95% CI: 10.0, 14.1) in the base case.

The base case median PFS was 5.5 months (95% CI: 4.9, 5.6) versus 1.6 months (95% CI: 1.4, 2.5) with BSC (Figure 13).

Table 11. Baseline characteristics of erdafitinib-treated (BLC2001 and THOR) and patients on BSC (Study302) before and after matching.

Baseline characteristics before and after matching

	BSC Study302 (Bellmunt2012)	ERDA POOL (THOR and BCL2001)		ERDA arm from POOL (THOR and BCL2001) matched to BSC arm from Study302 (Bellmunt2012)						
	N = 117	N =237	Exclusion N =176	Match7 (SA) N =176 Neff =144 (Weights)	Match6 N =176 Neff =148 (Weights)	Match5 N =176 Neff =148 (Weights)	Match4 N =176 Neff =157 (Weights)	Match3 (BC) N =176 Neff =159 (Weights)	Match2 N =176 Neff =159 (Weights)	Match1 N =176 Neff =162 (Weights)
% ECOG=0	38	48	53	38	38	38	38	38	38	38
% ECOG>=1	62	52	47	62	62	62	62	62	62	62
% Hemoglobin < 10g/dl	12	16	16	12	12	12	12	12	12	17
% Visceral disease	74	76	74	74	74	74	74	74	75	75
% Creatine clearance <=60	39	47	45	39	39	39	39	45	45	45
% Prior Cisplatin	80	60	68	80	80	80	69	68	68	68
% Age >= 65	49	59	57	49	49	52	56	58	58	57
% age < 65	51	41	43	51	51	48	44	42	42	43
% Male	81	73	74	81	75	76	76	75	75	74

Figure 10. Erdafitinib vs BSC: Hazard ratios for overall survival from pooled THOR and BCL2001 compared to overall survival from Study302

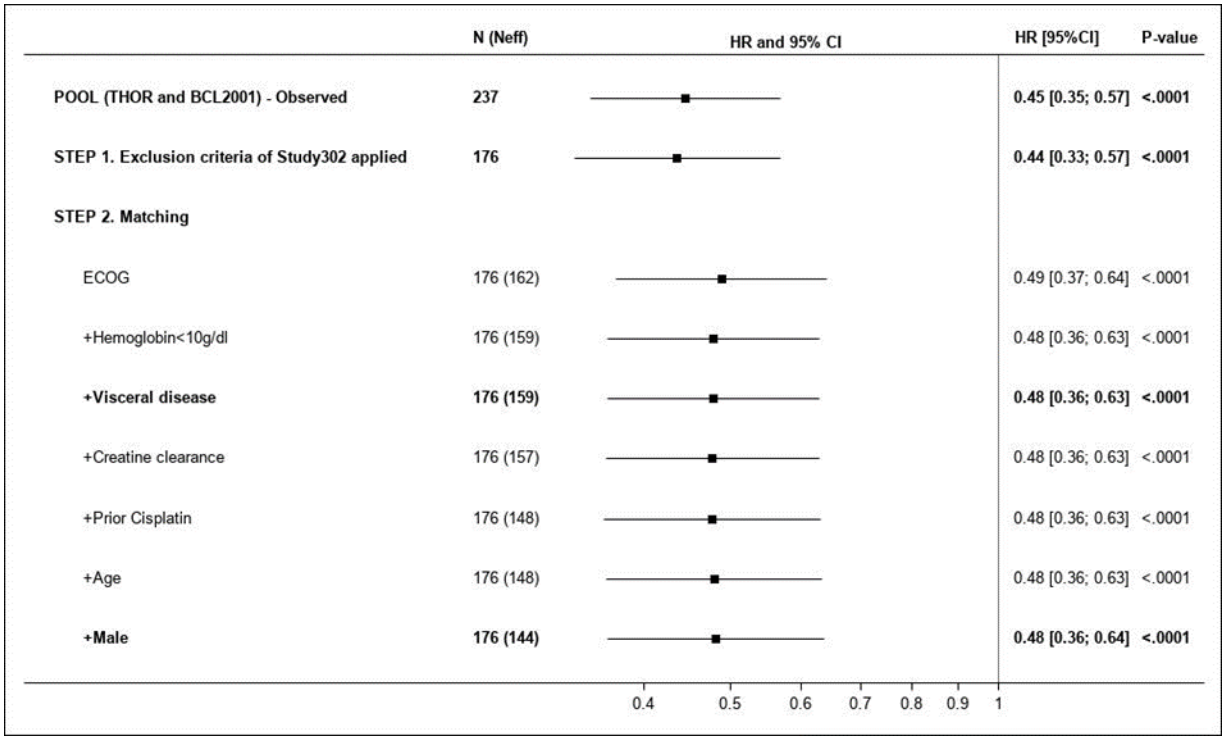


Figure 11. Erdafitinib vs BSC: Hazard ratios for progression-free survival from pooled THOR and BCL2001 compared to overall survival from Study302.

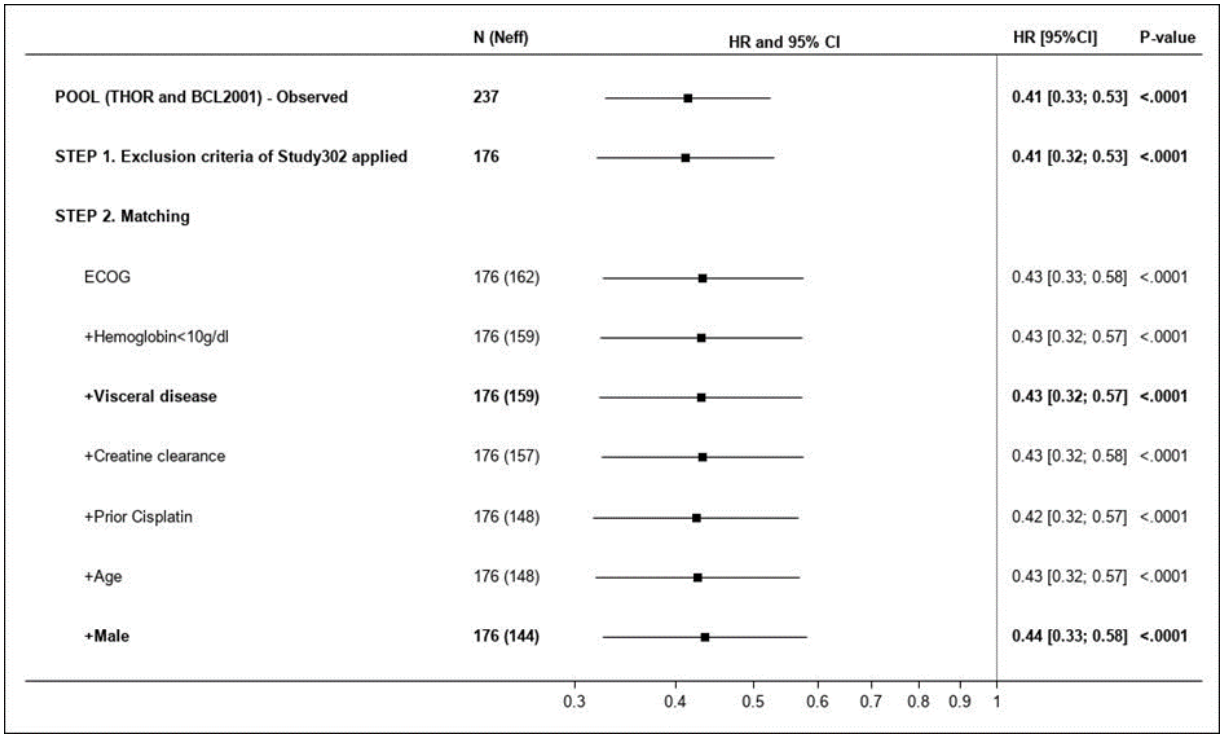
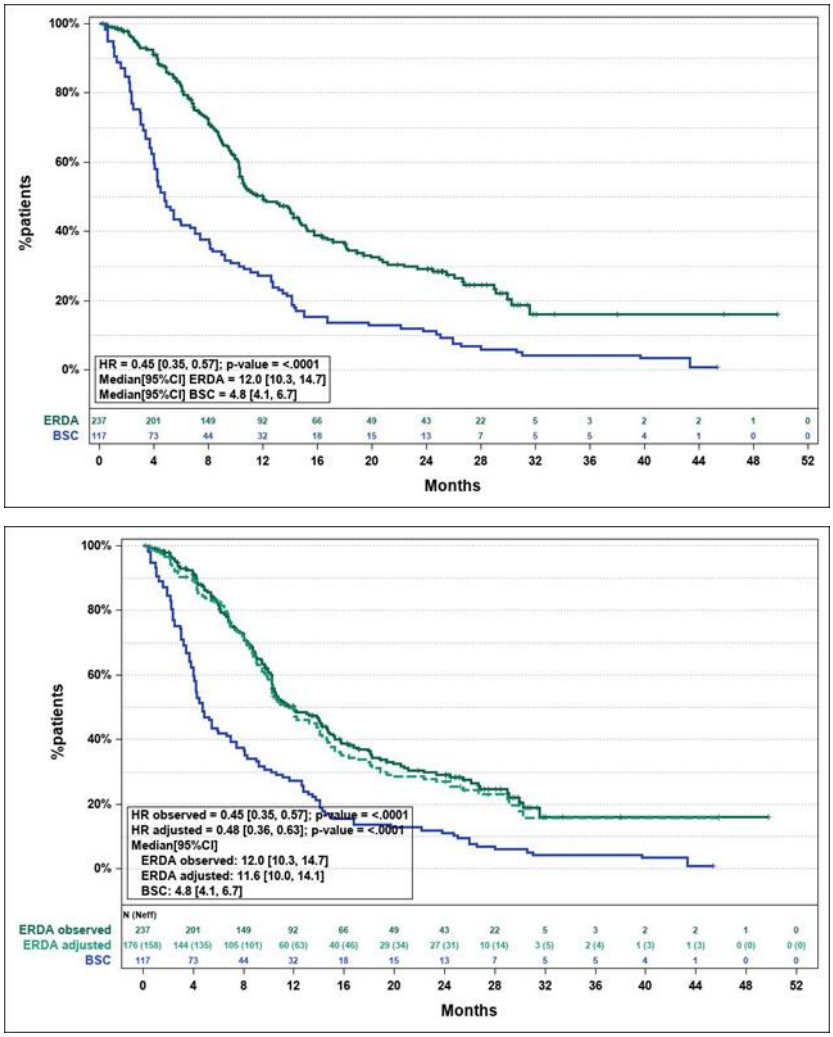
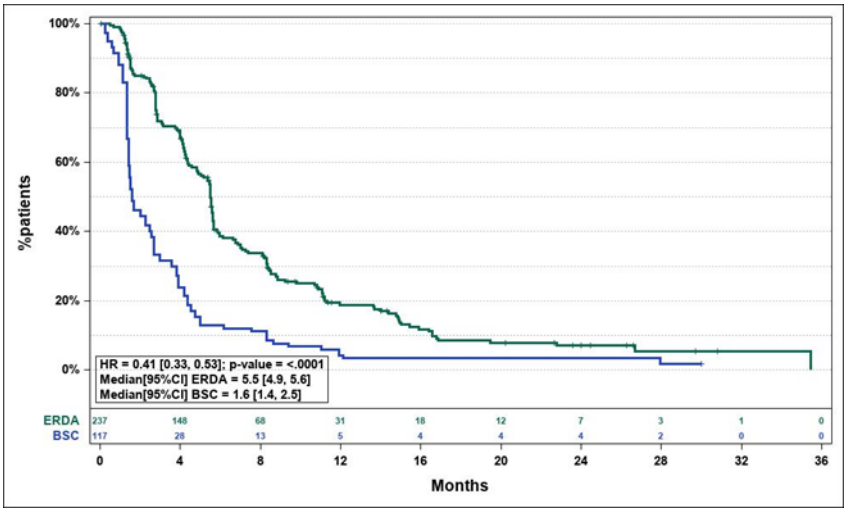


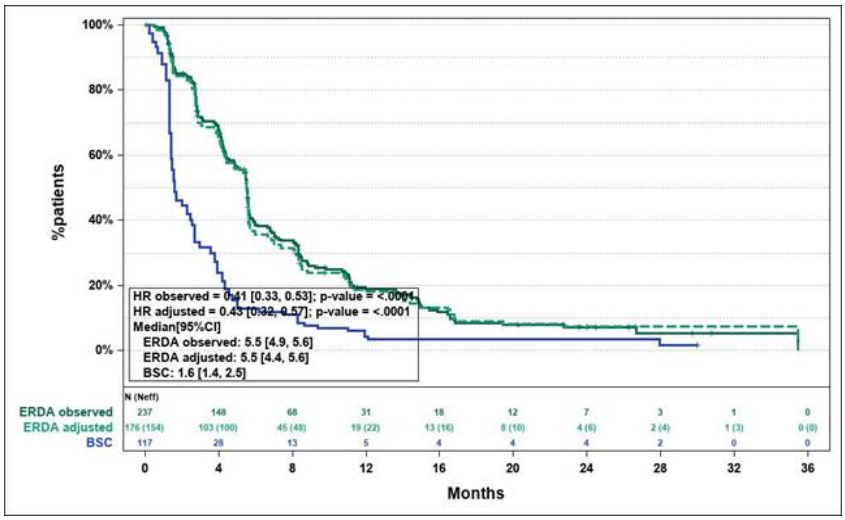
Figure 12. Naïve unadjusted and MAIC-adjusted comparisons of OS from pooled THOR and BCL2001 among patients treated with erdafitinib versus BSC from Study302



Key: Top: Naïve unadjusted comparison (observed); Bottom: Adjusted comparison (base case); HR, hazard ratio; ERDA, erdafitinib; BSC, best supportive care; CI, confidence interval

Figure 13. Naïve unadjusted and MAIC adjusted comparisons of PFS from pooled THOR and BCL2001 among patients treated with erdafitinib versus BSC from Study302





Key: Top: Naïve unadjusted comparison (observed); Bottom: Adjusted comparison (base case); HR, hazard ratio; ERDA, erdafitinib; BSC, best supportive care; CI, confidence interval

References

1. Bellmunt, J., et al., *Long-term survival results of a randomized phase III trial of vinflunine plus best supportive care versus best supportive care alone in advanced urothelial carcinoma patients after failure of platinum-based chemotherapy.* Ann Oncol, 2013. **24**(6): p. 1466-72.
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NICE National Institute for Health and Care Excellence

Erdafitinib for treating metastatic or unresectable FGFR-altered urothelial cancer [ID1333]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 30 January 2025. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	ACTION BLADDER CANCER UK

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NICE National Institute for Health and Care Excellence

Erdafitinib for treating metastatic or unresectable FGFR-altered urothelial cancer [ID1333]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 30 January 2025. Please submit via NICE Docs.

Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Janssen June 2024 One-off Arms length grant of £9,500 Purpose: to support ABC UK Nurse Education Programme
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	JEANNIE RIGBY, CEO Action Bladder Cancer UK

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	ABC UK are concerned that a potential, and badly needed, new treatment for this poorly served patient group is not to be approved for wider use and that, despite positive clinical trial evidence and strong evidence from patient groups of the paucity of treatments, the often debilitating

Please return to: **NICE DOCS**

Erdafitinib for treating metastatic or unresectable FGFR-altered urothelial cancer [ID1333]

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	treatment effects from only existing current treatments, poorer quality of life and poorer survival outcomes, that Erdafitinib is not considered of value to this patient group.
2	ABC UK are concerned that the costs of any necessary genetic testing, if included in the cost per patient assessment, would impose barriers to wider use by patients. We have been surprised to learn that NICE have requested that the full costs of genetic testing are included as part of their value assessment. ABC UK's understanding is that, once a process is established, genetic testing costs are in fact covered by payments from NHSE. We are unclear whether NICE intend to rule that in this case these costs should be a factor in per patient costs for Erdafitinib. If this is the case, we would ask why this is? ABC UK would question as to whether other precision therapies are asked to, as a matter of course, include the cost of necessary genetic testing into the treatment cost per patient? Would not this policy then make any precision medicine which requires this kind of test too expensive for any disease area or patient cohort? This would severely impact on the use of any such therapies within the NHS, limit progress on new cancer treatments and deny patients access to a newer area of effective treatments – as well as deny access to erdafitinib to a patient population which is suffering severe, terminal disease with no other treatment options available. We would struggle to understand how the instigation of such a practice, particularly in the area of new therapies in disease areas of great need, could not but result in the setting up additional barriers to treatment access for patients.
3	ABC UK are concerned that the attitude towards inclusion of full cost of genetic testing in any cost per patient calculations would not take into account that, after any process set up costs, we understand that the necessary information could be drawn from test results already banked for a patient from previous diagnostic procedure or biopsies. Therefore a higher level of cost for full genetic testing would not be an on-going cost.
4	ABC UK are concerned that the draft guidance implies that best supportive care is able to be consistently measured to provide a realistic comparator for Erdafitinib. ABC UK are concerned that best supportive care has been suggested as the direct comparator for Erdafitinib. As was discussed at the Appraisal, and acknowledged by NICE in previous appraisals for bladder cancer (for example, the use of Atezolizumab) there is no data which is consistently collected for Best Supportive Care to enable accurate, or robust, direct comparison with Erdafitinib to be made.
5	ABC UK are also concerned that Best Supportive Care might be considered as an acceptable comparator. We feel that the poorer quality of life, poor survival and potential higher financial cost due to resources required for a patient with best supportive care have not been taken into consideration. Also we feel that the severity of the potential negative impact of best supportive care on the patient and carers should be taken into consideration.
6	

Insert extra rows as needed

Checklist for submitting comments

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NICE National Institute for Health and Care Excellence

Erdafitinib for treating metastatic or unresectable FGFR-altered urothelial cancer [ID1333]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments 5pm on Thursday 30 January 2025. Please submit via NICE Docs.

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Single Technology Appraisal

Erdafitinib for treating metastatic or unresectable FGFR-altered urothelial cancer [ID1333]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	N/A
Conflict	None
Comments on the DG:	

Has all of the relevant evidence been taken into account?

I consider the THOR trial the most relevant clinical trial evidence to consider regarding Erdafitinib. This has been considered in detail.

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

From what I can see (although as a busy consultant it is difficult to get through all the details), the interpretations are reasonable

Are the recommendations sound and a suitable basis for guidance to the NHS?

The recommendations not to recommend Erdafitinib to patients with metastatic urothelial cancer with susceptible FGFR3 genetic alterations is extremely disappointing. I do not consider this recommendation sound or a suitable guidance. I have introduced FGFR testing into my NHS clinic, this is easy to do and an important direction of travel for the NHS. I have seen very good responses and quality of life benefits for patients receiving Erdafitinib under my care. These patients have very limited systemic therapy choices and the THOR trial speaks clearly of the overall survival benefit. I firmly believe it is in the best interests of our patients to be able access Erdafitinib.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, sex, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Not to my knowledge

Name	[redacted]
Organisation	Fight Bladder Cancer
Conflict	None
Comments on the DG:	

Are the summaries of clinical and and cost effectiveness reasonable interpretations of the evidence?

No, we do not believe they are.
We are so disappointed to see NICE's refusal to approve this drug on the basis that Erdafitinib has not been directly or indirectly compared with Best Supportive Care(BSV), making "the clinical and cost-effectiveness of Erdafitinib uncertain". As a patient group, we do not see BSV as a treatment, but rather a lack of one. It is devastating to think that the cost-effectiveness of a lack of treatment should be compared to the cost-effectiveness of a treatment that delivers far better survival and, more importantly, a lack of disease progression. This analysis does not seem to the patient as a person. It does not take into account the emotional toll on the patient and their families of having no possible treatment options to prevent disease progression and ensure their last months, weeks and days can be as fulfilling and enjoyable as possible, for as long as possible. As a patient group, we have seen patients and heard carers speak of these patients in this stage of the disease being constantly in and out of the hospital and having no real life to speak of. The term "Best Supportive Care" glosses over the ugly and devastating reality that this can be for a patient and their family. We urge NICE to consider the costs both to the NHS of caring for someone whose more rapid disease progression requires more around-the-clock care and also to the patients themselves, along with their families and carers, who would be losing the opportunity to spend time in the sort of state where they can cherish and enjoy that irreplaceable time with their loved ones. There is no way to put a price on something like that, and we understand that NICE has a difficult job in trying to do so. In this case, we are convinced that the Committee hasn't given proper weight to these concerns.

Are the recommendations sound and a suitable basis for guidance to the NHS?

We do not believe that they are. As representatives of this small group of patients who meet the eligibility criteria for this drug, we cannot see how the Committee's request to include the full cost of genetic testing as part of the value assessment seems fair or beneficial to innovation in this space. As we are regularly involved with clinicians and the research community, we have been excited about the potential for genetic testing to support bladder cancer care in the UK. We are concerned that this analysis will set a precedent that will hinder the ability of many small subsets of patients to access innovative treatments in the UK. As we go forward and more targeted therapies become available, conducting genetic testing of all tumours is likely to become routine best practice around the world and in the UK. NHS England and NHS Improvement have already undertaken to

fund genetic testing across England to deliver world-leading personalised cancer care. It seems unfair to require the cost of setting up the test to be attributed to that small subset of patients who would qualify to receive one of the first treatments that have been innovated for them, especially since in this case it has meant they will now not be able to access that treatment due to the Committee's decision. While we can understand the Committee's desire to consider all the costs associated with genetically testing a population that would originally not be tested, the outcome of this decision is that many new genetically targeted therapies that are geared towards small populations of patients will be excluded from NICE approval, completely de-incentivising any innovation for these smaller patient groups.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Erdafitinib for treating metastatic or unresectable FGFR-altered urothelial cancer [ID1333]

Critique of response to draft guidance

Produced by: Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed: 07 February 2025

Confidential data (CON) are highlighted in blue throughout the report.

This document refers back to the company draft guidance (DG) comments. Of note, the document covered 10 issues, namely issues 1 to 7 as well as 9 to 11 i.e., omitted issue 8.

3.2 Treatment pathway (issue 2 in DG response)

EAG comment: In the draft guidance, it is highlighted that *"the experts thought that around 70% of people at this point in the pathway may be well enough to have chemotherapy and be offered it but that only 30% to 50% of people would actually have it, with the rest having BSC"*.

The External Assessment Group (EAG) noted that the company in its updated base-case assumed that 50% of patients would have chemotherapy and the remaining 50% of patients would be on best supportive care (BSC). In line with the statement in the draft guidance above, the EAG provided a scenario analysis assuming 30% of patients would have chemotherapy and the remaining 70% of patients would be on BSC.

The EAG agrees that using paclitaxel and carboplatin as a proxy for the modelling of BSC clinical efficacy is likely conservative. The company stated that published evidence on resource use for patients with locally advanced or metastatic urothelial carcinoma treated with BSC is limited, and used inputs from technology appraisal (TA) 272 and clinical experts to inform health care healthcare resource use (HCRU) for BSC in the economic model.

While EAG considers these sources to be reasonable, it noted that a per cycle HCRU cost rather than a one-off cost for radiotherapy was modelled for patients on BSC despite Table 3 of the company's additional analyses post-ACM1 (1st appraisal committee meeting) document stating that this was given only once for 22.2% and 15.7% of patients before and after progression respectively. The EAG noted that this per cycle radiotherapy cost comprises a substantial part of the total per cycle HCRU costs for BSC. Considering the limited published evidence on resource use for patients on BSC and the issue related to radiotherapy costs, the EAG explored a scenario analysis where pre- and post-progression HCRU costs for BSC were assumed equal to the pre and post progression HSCRU costs of paclitaxel and carboplatin.

3.5 Generalisability of clinical evidence for erdafitinib (issues 5 to 7 in DG response)

The company DG comments referred to three aspects related to generalisability:

1. Issue 5 (ECOG performance status in THOR trial)
2. Issue 6 (Age of participants of THOR trial)
3. Issue 7 (Age as treatment effect modifier)

EAG comment: The EAG acknowledges that the company provided a *"worst-care imputation approach"*, upweighting *"more severe patients (those with ECOG 1-2) to align with poor PS in the NHS population. The choice was informed by feedback from clinical experts who outlined that 2L+ mUC patients in UK clinical practice are mainly ECOG 1-2 and fewer would be ECOG 0"*. This relates to key issues 3 and 6 of the EAG report which remain unresolved.

The EAG remains concerned about a potential mismatch of the age of participants of the THOR study and NHS patients, as discussed in detail in Section 3.2.3 of the EAG report.

While the EAG agrees with the company to *"exercise caution"* when interpreting the results of subgroup analyses, it also agrees with the committee that *"it thought that it was plausible that age was a treatment-effect modifier and concluded that there was some uncertainty around the generalisability of the THOR trial to NHS clinical practice"*.

3.12 Stopping rule for paclitaxel with or without carboplatin (issue 10 in DG response)

The company aligned its base-case with the EAG base-case by applying a stopping rule after 6 treatment cycles.

EAG comment: None.

3.15 Plausibility of modelled results (issue 3 in DG response)

In their draft guidance, the committee stated that it was considered implausible that the time spent in the progression-free health state would be very similar for both erdafitinib and the basket comparator.

In response to the draft guidance, the company repeated the appraisals limitation regarding the absence of progression-free survival (PFS) data from UK real-world (RW) studies. It further argued that results of the matching-adjusted indirect comparison (MAIC) suggest that the PFS for paclitaxel monotherapy is comparable to that of erdafitinib. In addition, the company stated that time to next treatment (TTNT) for both erdafitinib and paclitaxel is much more aligned with the overall survival (OS) curves, and hence could be seen as an overestimation to the PFS curve.

EAG comment: No compelling new arguments or evidence were provided by the company to address this issue.

3.19 Testing costs (issue 1 in DG response)

The company included the cost of adding a mutation to a next generation sequencing panel that was already being run in routine practice. In their draft guidance, the committee stated that the situation for erdafitinib was different as there are currently no targeted treatments and people with unresectable or metastatic urothelial cancer do not routinely have genomic testing. It concluded that the full cost of implementing a genomic testing panel for FGFR3 mutations should be applied in the modelling using the cost provided by the Cancer Drugs Fund lead of £1,282, and the expected prevalence of FGFR3 alterations of 16.6%.

In their response to the draft guidance, the company argued that next-generation sequencing (NGS) testing is not necessary to identify patients eligible for erdafitinib and that polymerase chain reaction (PCR) testing would suffice. In addition, it was stated that even without targeted treatments available via the NHS for patients with unresectable or metastatic urothelial cancer, the FGFR3 test is accessible and already performed in the NHS.

Furthermore, the company stated that it followed the approach taken in previous appraisals (e.g. TA722, TA850, and TA948), and that it was unclear what the committees evidence base was for the £1,282 cost. The company argued that the committees approach leads to inequity, as the proportion of total cost attributed to testing costs over a short time horizon will be much higher than in more common diseases with higher and longer survival.

Finally, it stated that more efficient RT-qPCR approach must be considered, as was used in the THOR trial. In its updated base-case, the company modelled a per identified patient cost of £449.70, which is substantially lower than the committee proposed cost of £7,723 per identified patient.

EAG comment: Whilst the EAG is unsure what the exact cost associated with diagnostic testing for FGFR3 alterations in people with urothelial cancer who would not otherwise have been tested should be, it adjusted its base-case testing cost to £74.65 for two tests per sample to reflect both RNA and DNA tests (in line with the company's updated base-case). In addition, the EAG provided a scenario analysis assuming a testing cost of £1,282, reflecting the full cost of implementing a genomic testing panel for FGFR3 mutations.

3.20 Severity

In its draft guidance, the committee concluded that although uncertain, the severity weight of 1.7 applied to the quality-adjusted life years (QALYs) was likely to be appropriate. Although, it noted that it would reconsider the severity weighting once the additional comparator of BSC had been explored.

EAG comment: The EAG noted that the company did not provide an updated assessment of the severity weighting for BSC and the updated basket (which now also includes BSC). The EAG additionally noted

that the company's initial economic model included a model sheet including calculations related to severity weighting, but this model sheet was not part of the company's updated model post ACM1.

The EAG would like to see an updated severity weighting assessment as well as an overview of the company's calculations. In anticipation of this assessment, the EAG assumed a severity weight of 1.7 in its analyses.

3.21 Committee's preferred assumptions (issue 4 in DG response)

In their draft guidance, the committee highlighted the following additional analyses to be explored:

- BSC as a comparator in the basket
- Alternative imputation methods, such as multiple imputation or assuming the best possible value for the missing data
- The results from THOR to directly inform the model
- The relative treatment effect from THOR applied to the baseline risk of OS and TTNT from the mUC RW study

The company provided these scenario analyses and highlighted the limitations of each of them, concluding that their chosen base case, which is based on the worst-case adjustment to align with UK clinical practice patients, is likely to yield more realistic results.

EAG comment: The EAG acknowledges that best supportive care as a comparator in the basket was explored in two scenarios by the company, see Section B of the additional analysis, namely a base case aligning with suggestions by NICE as well as a *"confirmative scenario analysis"*.

The EAG appreciates the company's effort of providing the abovementioned scenario analyses. However, it noted that the best-case adjustment as an alternative to the company's worst-case adjustment to explore uncertainty in the handling of missing disease stage and ECOG performance status data was not provided, despite the EAGs and committees request to do so.

Assuming that multiple imputations were used correctly, the EAG agrees with the company that *"it is improbable that, after adjusting [the] THOR trial data to UK RWE data, the overall survival would show an improvement compared to the results from a randomised clinical trial"*. The scenario analyses applying the treatment effect or using THOR directly were referred to as exploratory in the draft guidance, and the EAG also regards them in this way.

3.22 Acceptable ICER (issue 11 in DG response)

EAG comment: The company commented on the *"acceptable ICER"* which should be considered.

3.24 Uncaptured benefits (issue 9 in DG response)

EAG comment: The company commented on conclusions by the committee.

EAG analyses

Table 1. EAG base-case – erdafitinib versus basket of paclitaxel ± carboplatin (PAS price, 1.7x severity modifier applied)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
Deterministic company and EAG base-case							
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	[redacted]	0.630	0.705	[redacted]	1.030	[redacted]	£28,182
Probabilistic company and EAG base-case							
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	[redacted]	0.659	0.730	[redacted]	1.023	[redacted]	£28,265
Deterministic scenario 1 – Full cost of implementing a genomic testing panel for FGFR3 mutations							
Erdafitinib	[redacted]	1.660	[redacted]	-	-	-	
Paclitaxel ± carboplatin	[redacted]	0.733	0.822	[redacted]	0.927	[redacted]	£35,411
BSC	[redacted]	0.527	0.588	[redacted]	1.133	[redacted]	£35,077
Basket	[redacted]	0.630	0.705	[redacted]	1.030	[redacted]	£35,225
Probabilistic scenario 1 – Full cost of implementing a genomic testing panel for FGFR3 mutations							
Erdafitinib	[redacted]	1.682	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.744	0.832	[redacted]	0.938	[redacted]	£35,693
BSC	[redacted]	0.573	0.628	[redacted]	1.108	[redacted]	£35,684
Basket	[redacted]	0.659	0.730	[redacted]	1.023	[redacted]	£35,688
Deterministic scenario 2 – Assume BSC HCRU costs equal to paclitaxel+-carboplatin							
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]	£30,415
Basket	[redacted]	0.630	0.705	[redacted]	1.030	[redacted]	£29,108
Probabilistic scenario 2 – Assume BSC HCRU costs equal to paclitaxel+-carboplatin							
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]	£30,962
Basket	[redacted]	0.659	0.730	[redacted]	1.023	[redacted]	£29,380

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
Deterministic scenario 3 – 70% of comparator basket receiving BSC							
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	[redacted]	0.589	0.658	[redacted]	1.071	[redacted]	£28,425
Probabilistic scenario 3 - 70% of comparator basket receiving BSC							
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	[redacted]	0.625	0.689	[redacted]	1.057	[redacted]	£28,547

CS = company submission; EAG = Evidence Assessment Group; HCRU = healthcare resource use; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; PFS = progression-free survival; QALY = quality-adjusted life year

Table 2. EAG base-case – erdafitinib versus basket of paclitaxel ± carboplatin (PAS price, no severity modifier applied)*

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
Deterministic company and EAG base-case							
Erdafitinib	[redacted]	1.660	[redacted]	-	-	-	
Paclitaxel ± carboplatin	[redacted]	0.733	0.484	[redacted]	0.927	[redacted]	£46,690
BSC	[redacted]	0.527	0.346	[redacted]	1.133	[redacted]	£48,880
Basket	[redacted]	0.630	0.415	[redacted]	1.030	[redacted]	£47,909
Probabilistic company EAG base-case							
Erdafitinib	[redacted]	1.682	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.744	0.490	[redacted]	0.938	[redacted]	£46,662
BSC	[redacted]	0.573	0.369	[redacted]	1.108	[redacted]	£49,187
Basket	[redacted]	0.659	0.429	[redacted]	1.023	[redacted]	£48,050
Deterministic scenario 1 – Full cost of implementing a genomic testing panel for FGFR3 mutations							
Erdafitinib	[redacted]	1.660	[redacted]	-	-	-	
Paclitaxel ± carboplatin	[redacted]	0.733	0.484	[redacted]	0.927	[redacted]	£60,199
BSC	[redacted]	0.527	0.346	[redacted]	1.133	[redacted]	£59,631
Basket	[redacted]	0.630	0.415	[redacted]	1.030	[redacted]	£59,883
Probabilistic scenario 1 – Full cost of implementing a genomic testing panel for FGFR3 mutations							
Erdafitinib	[redacted]	1.682	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.744	0.490	[redacted]	0.938	[redacted]	£60,679

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
BSC	[redacted]	0.573	0.369	[redacted]	1.108	[redacted]	£60,663
Basket	[redacted]	0.659	0.429	[redacted]	1.023	[redacted]	£60,670
Deterministic scenario 2 – Assume BSC HCRU costs equal to paclitaxel+-carboplatin							
Erdafitinib	[redacted]	1.660	[redacted]	-	-	-	
Paclitaxel ± carboplatin	[redacted]	0.733	0.484	[redacted]	0.927	[redacted]	£46,690
BSC	[redacted]	0.527	0.346	[redacted]	1.133	[redacted]	£51,705
Basket	[redacted]	0.630	0.415	[redacted]	1.030	[redacted]	£49,483
Probabilistic scenario 2 – Assume BSC HCRU costs equal to paclitaxel+-carboplatin							
Erdafitinib	[redacted]	1.682	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.744	0.490	[redacted]	0.938	[redacted]	£46,662
BSC	[redacted]	0.573	0.369	[redacted]	1.108	[redacted]	£52,636
Basket	[redacted]	0.659	0.429	[redacted]	1.023	[redacted]	£49,947
Deterministic scenario 3 – 70% of comparator basket receiving BSC							
Erdafitinib	[redacted]	1.660	[redacted]	-	-	-	
Paclitaxel ± carboplatin	[redacted]	0.733	0.484	[redacted]	0.927	[redacted]	£46,690
BSC	[redacted]	0.527	0.346	[redacted]	1.133	[redacted]	£48,880
Basket	[redacted]	0.589	0.387	[redacted]	1.071	[redacted]	£48,323
Probabilistic scenario 3 - 70% of comparator basket receiving BSC							
Erdafitinib	[redacted]	1.682	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.744	0.490	[redacted]	0.938	[redacted]	£46,662
BSC	[redacted]	0.573	0.369	[redacted]	1.108	[redacted]	£49,187
Basket	[redacted]	0.625	0.405	[redacted]	1.057	[redacted]	£48,531

* Probabilistic results without severity modifier were manually calculated by the EAG by dividing the total QALYs for each treatment option by 1.7 and subsequently re-calculate incremental effects and outcomes

CS = company submission; EAG = Evidence Assessment Group; HCRU = healthcare resource use; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; PFS = progression-free survival; QALY = quality-adjusted life year

GMS's preferred approach to identify FGFR3 genetic alterations in the NHS.

The NHS Genomic Medicine Service's (GMS) preferred approach to somatic genomic testing for multiple diagnostic testing indications is to use large NGS panels to deliver efficiencies. The current method for FGFR3 testing on the National Genomic Test Directory (NGTD) includes two panels, a DNA and RNA panel.

However, for this medicine, where current use of 'diagnostic genomic testing' to inform any treatment or surgical options is low, we have considered potential delivery options and are recommending a medium panel.

An explanation around the testing costs for identifying FGFR3 genetic alterations in people with metastatic urothelial cancer.

The preferred approach to testing is as listed on the NGTD. Operational delivery would require two panels to identify FGFR3 mutations (DNA targets) and structural variants (RNA targets), each panel attracting a tariff. Each genomic test listed on the NGTD has a specified test method, which has a designated tariff.

Confirmation around if the unit costs as per your tariff for additional activity is per person tested or per person treated.

As this 'diagnostic' genomic testing is not done routinely in current clinical practice, determining eligibility for this medicine will significantly increase activity. As the test is already on the NGTD and available through the GMS, a ***% marginal rate tariff for medium panels has been applied: this equates to £*** per person/case.

Consideration as to whether multiplex sequencing and pooling of pan-oncology tumour samples affects testing costs.

The strategic approach of the GMS is to use large panels wherever possible to optimise workflows, turnaround times and cost effectiveness. Medium panels for this use case are not deliverable within the current infrastructure across all seven Genomic Laboratory Hubs (GLH). However, in this instance it has been considered for appropriate costing purposes, and given there are currently limited targets routinely tested in this patient pathway, a revised cost for medium panels (at marginal cost) should be applied. This does not necessarily mean that the testing would be delivered by a medium panel as the panel size will be determined by the workflow of each GLH.

Alternative approaches to testing costs for FGFR3 mutations in different disease areas such as cholangiocarcinoma or NSCLC.

Cholangiocarcinoma: There is no testing for FGFR3 available on the NGTD for the clinical indication.

NSCLC: There is no testing available for FGFR3 available on the NGTD for this clinical indication.