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

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Contents:

The following documents are made available to stakeholders:

Access the **final scope** and **final stakeholder list** on the NICE website.

1. **Company submission from Johnson & Johnson:**
   a. Full submission
   b. Summary of Information for Patients (SIP)

2. **Clarification questions and company responses**
   a. Priority questions
   b. Non-priority questions

3. **Patient group, professional group, and NHS organisation submissions** from:
   a. Action Bladder Cancer UK – written by patient expert, Jeannie Rigby
   b. Fight Bladder Cancer
   c. British Uro-oncology Group

4. **External Assessment Report** prepared by Kleijnen Systematic Reviews
   a. Appendix

5. **External Assessment Report – factual accuracy check**

6. **Statements from experts:**
   a. Prof. Robert Huddart, Professor of Urological Cancer and Hon Consultant Clinical Oncologist – clinical expert, nominated by Johnson & Johnson
   b. Jeannie Rigby, Chief Executive – patient expert, nominated by Action Bladder Cancer UK

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

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Document B

Company evidence submission

June 2024

File name	Version	Contains confidential information	Date
Document B	**V1**	**Yes**	**26 June 2024**

Contents

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Abbreviations

Abbreviation	Definition
1L	First line
2L	Second line
3L	Third line
4L	Fourth line
AE	Adverse event
ADC	Antibody-drug conjugate
BSC	Best supportive care
CI	Confidence interval
CPI	Checkpoint inhibitor
CR	Complete response
DCR	Disease control rate
DOR	Duration of response
ESMO	European Society for Medical Oncology
FGFR	Fibroblast growth factor receptor
HR	Hazard ratio
HRQL	Health-related quality of life
ITT	Intention-to-treat
IV	Intravenous
mUC	Metastatic urothelial carcinoma
NCRAS	National Cancer Registration and Analysis Service
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed death protein 1
PD-(L)1	Programmed death-ligand 1
PFS	Progression-free survival
PR	Partial response
PS	Performance status
RW	Real world
RWE	Real-world evidence
SAEs	Serious adverse events
SD	Stable disease
SHELF	Sheffield Elicitation Framework
SLR	Systematic literature review
SoC	Standard of care
TA	Technology appraisal

TEAEs	Treatment-emergent adverse events
TRAEs	Treatment-related adverse events
UC	Urothelial carcinoma

B.1. Decision problem, description of the technology and clinical care pathway

B.1.1. Decision problem

The submission covers the technology's anticipated full marketing authorisation for this indication:

[redacted]

The decision problem addressed in this submission is presented in Table 1.

Table 1: The decision problem

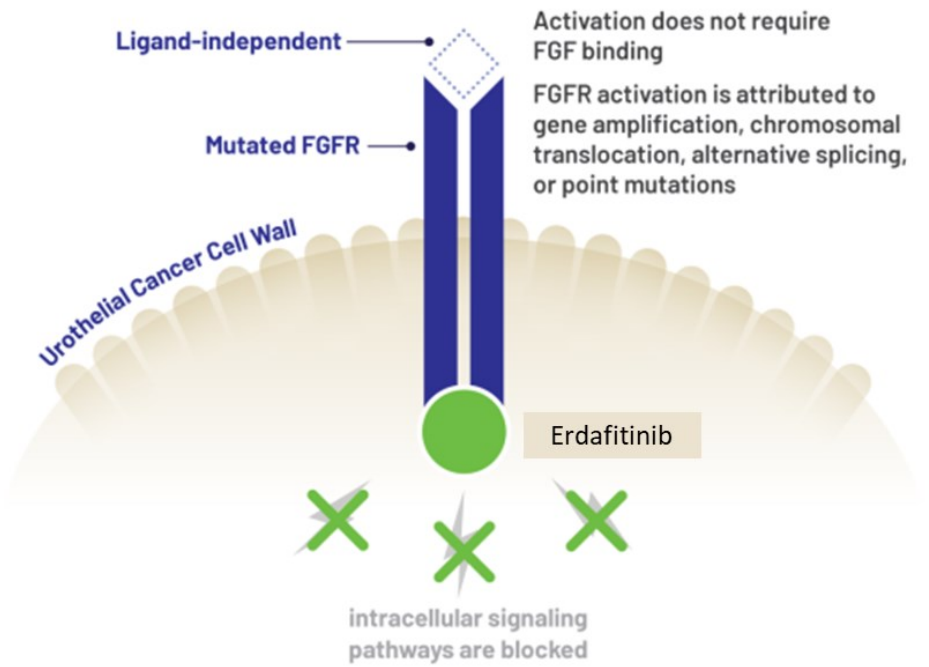
	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with metastatic or unresectable *FGFR*-altered UC	[redacted][1]	To align with the final marketing authorisation
Comparator(s)	Established clinical management without erdafitinib, including but not limited to: • Chemotherapy (including docetaxel, paclitaxel) • Atezolizumab • BSC	Paclitaxel as a monotherapy, or in combination with carboplatin (paclitaxel ± carboplatin)	Clinical experts and real-world evidence confirmed that the relevant comparator is paclitaxel ± carboplatin. Docetaxel's use is restricted to clinical trials and is not current standard of care in England and Wales. Atezolizumab re-treatment is not considered established practice by UK-based clinicians due to the lack of evidence on the efficacy of re-treating with a PD-(L)1 inhibitor. Given the population of this appraisal focuses on those already treated with anti-PD-(L)1 therapy, atezolizumab is not an appropriate comparator. For BSC, there is no evidence available in patients after exposure to PD-(L)1 inhibitors, and therefore a comparative analysis could not be conducted.
Outcomes	The outcome measures to be considered include:	As per NICE scope	N/A

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
	• OS • PFS • Response rates (including type and duration of response) • Adverse effects of treatment • HRQL		
Subgroups to be considered	• *FGFR* alteration type • Previous anti-PD-(L)1 treatment • People with upper tract urothelial cancer	• People with upper tract urothelial cancer	The proposed subgroups of *FGFR* alteration type and previous anti-PD-(L)1 treatment make up the relevant population, i.e., patients with *FGFR3* alterations with disease progression during or following at least one line of therapy containing a PD-1 or PD-(L)1 inhibitor. Therefore, these subgroups do not need to be considered separately.
Key: BSC, best supportive care; *FGFR*, fibroblast growth factor receptor; HRQL, health-related quality of life; N/A, not applicable; NICE, National Institute for Health and Care Excellence; OS, overall survival; PD-1, programmed death receptor-1; PD-(L)1, programmed death-ligand 1; PFS, progression-free survival; UC, urothelial carcinoma.			

B.1.2. Description of the technology being evaluated

Erdafitinib is a first-in-class, potent, oral pan-FGFR inhibitor with a novel mechanism of action.[2-4] It is a highly selective tyrosine kinase inhibitor that suppresses FGFR phosphorylation and signalling, thereby decreasing the viability of cell lines with *FGFR* alterations. Erdafitinib has high affinity and inhibitory activity at low nanomolar levels for all FGFR family members (i.e., FGFR1, FGFR2, FGFR3 and FGFR4). Aberrant *FGFR3* alterations are common in approximately 20% of patients with advanced or mUC, causing constitutive FGFR signalling contributing to oncogenesis and are thus of clinical importance.[5, 6] The antitumour activity of erdafitinib has been demonstrated in *FGFR*-driven cell lines and xenograft models derived from multiple tumour types, including bladder cancer.[2] Erdafitinib is rapidly absorbed, with a terminal half-life of 50–60 hours.[3] It is taken up by lysosomes, resulting in sustained intracellular release, which may contribute to its long-lasting activity.[7]

Figure 1: Erdafitinib mode of action schematic



Key: FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor.
Source: Balversahcp.com (mode of action diagram).[8]

The draft Summary of Product Characteristics (SmPC) is provided in Appendix C.

Table 2: Technology being evaluated

UK approved name and brand name	Erdafitinib (Balversa®)
Mechanism of action	Erdafitinib is a pan-FGFR tyrosine kinase inhibitor. It inhibits FGFR phosphorylation and signalling and decreases cell viability in cell lines expressing *FGFR* alterations, including point mutations, amplifications, and fusions.[9]
Marketing authorisation/CE mark status	The application for marketing authorisation with the MHRA is currently ongoing, with the submission expected in [redacted]. Marketing authorisation is expected in [redacted].
Indications and any restriction(s) as described in the Summary of Product Characteristics (SmPC)	The anticipated indication under appraisal is: '[redacted]'.[1]
Method of administration and dosage	Treatment should be initiated and supervised by a physician experienced in the use of anticancer therapies.[1] The recommended starting dose for adults (18+ years) is 8 mg orally once daily.[1] This dose should be maintained, and serum phosphate level should be assessed 14–21 days after initiating treatment. The dose should be increased to 9 mg once daily if serum phosphate < 9.0 mg/dL and there is no drug-related toxicity.[1] Treatment should continue until disease progression or unacceptable toxicity occurs.[1] The tablets should be swallowed whole, with or without food, at about the same time each day. If vomiting occurs any time after taking erdafitinib, the next dose should be taken the next day. If a dose is missed, it can be taken as soon as possible, and the regular daily dose schedule can resume the next day. Additional tablets should not be taken to make up for the missed dose.[1] For information on dose reduction recommendations, please refer to the SmPC.[1]
Additional tests or investigations	The use of erdafitinib is conditional on the presence of a *FGFR3* gene alteration. Diagnostic testing for *FGFR3* gene alteration should be carried out through an NGS panel, which is already commissioned by NHS England through the National Genomic Test Directory.
List price and average cost of a	List price: £12,750.00 per pack (28 days)

course of treatment	Net price: £[redacted] (28 days)
Patient access scheme (if applicable)	This submission includes a confidential simple discount PAS for erdafitinib, representing a discount to the list price of [redacted].
Key: FGFR, fibroblast growth factor receptor; MHRA, Medicines and Healthcare products Regulatory Agency; NGS, next-generation sequencing; NHS, National Health Service; PAS, patient access scheme; PD-1, programmed death receptor-1; PD-(L)1, programmed death-ligand 1; SmPC, Summary of Product Characteristics; UC, urothelial carcinoma.	

B.1.3. Health condition and position of the technology in the treatment pathway

Summary of key points:

Unresectable or metastatic urothelial carcinoma

- In the UK, UC accounts for approximately 90% of bladder cancers, and can be broadly categorised into three key stages: non-muscle invasive, muscle invasive, and locally advanced or metastatic.[10-13] Metastatic bladder cancer carries a dismal prognosis, with a 5-year overall survival (OS) rate of 5%.[14] Approximately 10% of patients in England have unresectable metastatic disease at diagnosis.[15]
- Alterations of the *FGFR* gene are observed in approximately 20% of metastatic UC (mUC), suggesting a significant role for FGFR targeting in mUC.[16-19]
- A Johnson & Johnson-initiated UK real-world (RW) mUC study of clinical practice in England has demonstrated that, from the point of diagnosis, median OS of patients with mUC is just 5.4 months (95% confidence interval [CI]: 5.2, 5.6).[20]
- The high symptom burden and nature of current treatments mean that mUC is associated with high psychological and physical impacts, resulting in low health-related quality of life (HRQL). [21-23]

Current clinical pathway of care

- At first line (1L), a cisplatin-based chemotherapy (such as cisplatin plus gemcitabine or dose-dense methotrexate, vinblastine, doxorubicin, cisplatin [ddMVAC]) is recommended for patients who are physically fit, and carboplatin plus gemcitabine is recommended for patients who are ineligible for cisplatin.[22] Following these treatments, patients with a response or stable disease are recommended the anti-PD-(L)1 avelumab for 1L maintenance.[24] Beyond 1L treatment, guidelines are unclear yet triangulation of real-world evidence (RWE) and expert clinical opinion shows that paclitaxel or paclitaxel + carboplatin is the most relevant comparator in England and Wales.[20, 25, 26]

- The UK RW mUC study indicates that some of the second-line (2L) and later lines of treatment options for patients who have previously received treatment with an anti-PD-(L)1 include: treatment with paclitaxel or paclitaxel + carboplatin (36.4%; n = 72); with platinum-based chemotherapy (30.8%; n = 61); or retreatment with a PD-(L)1 inhibitor (23.7%; n = 47).[20]
- Clinical experts and clinical guidelines do not endorse retreatment with PD-(L)1 inhibitors, and it is considered a last-resort choice due to limited treatment alternatives.[25, 27, 28] Additionally, UK clinicians have stated that patients are rarely rechallenged with platinum-based chemotherapy due to the high level of fitness required in order to tolerate the treatment, with only 8 patients (4.0%) receiving platinum-based retreatment in the UK RW mUC study.[26]
- Importantly, UK clinical experts have highlighted the impact of the COVID-19 pandemic on the UK RW mUC study cohort timeline. During the pandemic, oncologists were not prescribing 1L chemotherapy during the study period, and more patients were prescribed immunotherapy at 1L and platinum-based chemotherapy or immunotherapy retreatment at 2L, which is not current standard practice.[25] This means that the use of platinum-based chemotherapy in the UK mUC RW study in 2L is inflated versus current and future standard clinical practice. Current clinical practice predominantly supports the utilisation of platinum-based chemotherapy as a 1L treatment option, with only limited instances of retreatment in later lines should disease progression occur $\geq$12 months after completion of a 1L platinum-regimen.[27]

Unmet need

- Patients with mUC who progress during or after one or more lines of systemic therapy have poor prognosis and reduced survival. Among the 2L treatments currently approved, the associated median OS is < 1 year.[29-33]
- Current mUC treatments have a substantial negative impact on patients' physical, emotional wellbeing and quality of life.[23]
- The UK RW mUC study shows that only ~15% of patients in England receive subsequent anticancer treatment after anti-PD-(L)1 discontinuation at 1L and

2L, highlighting the need for safe and effective treatment options with innovative mechanisms of action after anti-PD-(L)1 therapy.[5, 20, 32]

- Erdafitinib represents a first-in-class FGFR-targeted treatment and will be a critical addition to the treatment pathway for patients with *FGFR*-positive unresectable or mUC, who have progressed on or following treatment with an PD-(L)1 inhibitor.

B.1.3.1. Disease background

UC is cancer of the cells that form the inner lining of the bladder, urethra, ureter, or renal pelvis (called transitional or urothelial cells) and is defined as C65 – C68 topographies using the International Classification of Diseases, version 10 (ICD-10).[34, 35] UC accounts for approximately 90% of bladder cancers, with the remaining 10% having either small cell, adenocarcinoma or squamous cell carcinoma histology.[36] Though most cases of UC originate in the bladder, UC may also originate in the renal pelvis and ureter, known as upper tract UC. UCs can be split into four molecular subtypes: luminal 1, luminal 2, basal 3 and basal 4.[37]

Tobacco smoking is the greatest risk factor for bladder cancer, accounting for approximately 50% of cases[28], followed by occupational exposure to ionising radiation and chemicals such as aromatic amines and polycyclic aromatic hydrocarbons.[28, 38]

Staging is based on the results of the physical exam, biopsy and imaging tests, and the results of surgery. The stages of bladder cancer according to Tumour, Node, Metastasis (TNM) classification are outlined in Table 3. They can be broadly categorised into three key groups: non-muscle-invasive (Stage 0–I), muscle-invasive (Stage II–III) and metastatic (Stage IV).[13, 39] Non-invasive bladder cancers have not invaded the surrounding tissues, whereas muscle-invasive bladder cancer means the cancer has grown into a deeper muscle layer of the bladder, or beyond.[10] Muscle-invasive bladder cancer has a higher risk of invading the bladder wall and becoming mUC, commonly invading the pelvic or abdominal wall (T4b), spread to one or more lymph nodes (N1–N3) and metastasising to distant sites (M1).[40, 41]

Table 3: Stages of bladder cancer, as per the TNM classification system

Stage	TNM classification*			Stage description
0	Ta or Tis	N0	M0	Non-muscle invasive
I	T1	N0	M0	
II	T2a or T2b	N0	M0	Muscle invasive
IIIA	T3a–T3b or T4a T1–4a	N0 N1	M0 M0	
IIIB	T1–T4a	N2 or N3	M0	
IVA	T4b Any T	Any N Any N	M0 M1a	Metastatic
IVB	Any T	Any N	M1b	

Key: TNM, tumour, node, metastasis
Notes: *Ta = non-invasive papillary carcinoma; Tis = flat, non-invasive carcinoma; N0 = cancer has not spread to nearby lymph nodes; M0 = no distant metastasis; T1 = cancer has grown into the layer of connective tissue under the lining layer of the bladder; T2a = cancer has grown into the inner muscle layer of the bladder wall; T2b = cancer has grown into the outer muscle layer of the bladder wall; T3a = cancer invades the layer of fatty tissue surrounding the bladder (microscopically); T3b = cancer invades the layer of fatty tissue surrounding the bladder (macroscopically); T4a = cancer invades prostate, seminal vesicles, uterus or vagina; N1 = metastasis in one lymph node in the true pelvis; N2 = metastasis in multiple lymph nodes in the true pelvis; N3 = metastasis in lymph node(s) along common iliac arteries; T4b = cancer invades pelvic wall or abdominal wall; M1a = metastasis to distant lymph nodes; M1b = metastasis to distant organs.
Source: European Association of Urology Guidelines[42]

B.1.3.1.1. FGFR alterations in UC

FGFR family genes can be activated by: gene amplification leading to receptor overexpression; translocations resulting in activating gene fusions; or mutations.[43] These abnormalities in the FGFR pathway can drive abnormal morphogenesis and the progression of bladder cancers.[43]

Alterations of *FGFR* genes are observed in approximately 20% of cases of mUC, suggesting a significant role for FGFR targeting in mUC.[16-19, 44] They are particularly enriched in the luminal 1 subtypes of UC.[5, 45] The luminal 1 tumours are reported to be enriched for *FGFR3* mutations, lacking in immune marker expression and immune cell infiltrate.[7, 33, 46, 47] Differential response to immunotherapy has been

observed across urothelial cancer subtypes, with the luminal 1 subtype showing the lowest response rate to the anti-PD-(L)1 inhibitors versus with other urothelial cancer subtypes.[7, 33, 47]

Objective response rate (ORR) to PD-1 and PD-(L)1 inhibitors appears to be lower in luminal 1 tumours compared with luminal 2 and basal 3 tumours, suggesting that the tumour subgroup enriched with *FGFR3* alterations also benefits the least from immunotherapy.[45]

B.1.3.2. Epidemiology

As per the 2020 National Health Service (NHS) cancer statistics, there were 16,547 cases of bladder cancer diagnosed in England in 2020.[48] Bladder cancer incidence is greater in men than in women; in the UK, 73% of bladder cancer cases are in men, and 27% are in women, and it is the seventh and 17th most common cancer, respectively.[49] The prognosis in women can be less favourable, as women have between 15% and 45% higher odds of being diagnosed with advanced disease compared with men in England and Wales.[41] The incidence of bladder cancer is strongly related to age, with most people diagnosed over the age of 60. In the UK, between 2016 and 2018, 56% of all new bladder cancer cases were diagnosed in people aged 75 and older.[49]

Most patients are diagnosed with localised disease (approximately 55% of patients are Stage I or II). However, in patients who undergo radical treatment for muscle-invasive disease, approximately 50% experience relapse and are likely to develop distant metastases.[27] Approximately 10% of patients have locally advanced or metastatic disease (Stage IV) at diagnosis.[27, 50]

A UK RW mUC study was initiated by Johnson & Johnson, with the aim of collecting RW treatment and health outcomes data from an evolving cohort of patients with mUC in England.[20] The study utilised several linked datasets available through the National Cancer Registration and Analysis Service (NCRAS), one of the two disease registration services under the responsibility of NHS England.[51] The NCRAS provides near real-time, comprehensive data collection and quality assurance over

the entire cancer care pathway using data received from across the NHS[51, 52] Between January 2016 and December 2021, 61,816 patients were diagnosed with UC in England. Of these patients, 13,902 (22.5%) had no stage data at diagnosis; 37,120 (60.0%) were diagnosed at Stage I–III and were not flagged to have progressed during the time period (approximated via algorithm); and 10,787 (17.5%) patients were Stage IV at diagnosis or Stage I–III with progression to metastatic disease during the time period. Further details on the UK RW mUC study can be found in Section B.2.9 and Appendix O.

B.1.3.3. Mortality and morbidity

The survival rates for patients with UC are poor. Approximately 5,600 deaths in the UK are attributed to bladder cancer annually, accounting for 3% of all cancer deaths.[53] In England, the 5-year OS rate is 53.8% in patients across all disease stages, with survival rates decreasing with advancing stage.[54] One-year OS rates are 92.5% for Stage I, 73.6% for Stage II, 63.7% for Stage III, and 29.1% for Stage IV.[54]

Data from the UK RW mUC cohort study introduced in Section B.1.3.2 showed that, from diagnosis, the median OS of patients with mUC is just 5.4 months (95% CI: 5.2, 5.6).[20] Further details on the UK RW mUC study can be found in Section B.2.9 and Appendix O. Additionally, the median OS associated with most of the currently approved therapies for mUC across 1L and 2L is only 10–14 months, and in that time, many patients will relapse or experience disease progression.[32]

B.1.3.4. Burden of disease

B.1.3.4.1. Clinical and humanistic burden

Patients diagnosed with UC experience high symptom burden. Most patients (approximately 80%) will experience blood in their urine, which is usually painless.[28, 55] Patients may also experience irritative symptoms, such as painful urination and increased urination frequency and/or urgency.[55] Patients who progress to/are diagnosed with late-stage disease tend to experience a higher symptom burden. Patients with unresectable or mUC can experience flank pain, caused by

retroperitoneal metastases or ureteral obstruction, or bone pain/skeletal complications caused by bone metastasis.[28] The high symptom burden results in frequent hospital visits for managing disease symptoms, which has a serious impact on the HRQL of a patient and reduces their time available to spend with friends and family.[56-59]

The nature of the current treatments for unresectable or mUC result in high psychological and physical impacts, resulting in low HRQL.[56-58] Current treatment for unresectable or mUC commonly involves multiple cycles of IV-administered chemotherapy. This treatment often leads to treatment-related adverse events (TRAEs), including: neutropenia, anaemia, diarrhoea, pneumonia, fatigue, pain, nausea/vomiting, bone marrow suppression, peripheral neuropathy, arthralgia/myalgia, injection site reactions, ototoxicity, and hair loss.[60, 61] These TRAEs add to disease symptoms, at further detriment to a patient's quality of life. Frequently, these chemotherapy-related adverse events (AEs) require hospital admission. For instance, the average hospital stay for chemotherapy-related anaemia is one day-long stay; for diarrhoea, it is two short stays of less than a day; and for neutropenia it is two day-long stays for affected patients (10% of patients).[57] These disease symptoms and/or TRAEs can result in a detrimental effect on HRQL due to an impaired ability to perform daily tasks, decreased energy, and mobility restrictions (particularly in cases of metastases).[56]

A study investigating patient-reported symptoms and the impact of unresectable or mUC after chemotherapy followed by a PD-(L)1 checkpoint inhibitor (CPI) described noticeable impact on emotional functioning and family relationships. Some patients reported challenges with essential activities of daily living, such as shopping and cooking. Most patients also reported an increased reliance on friends and relatives for assistance.[60]

A comprehensive survey, developed by the World Bladder Cancer Patient Coalition to collect real-world experiences of patients with bladder cancer, found that financial toxicity is a major concern, particularly in patients with advanced/metastatic disease.[62] It reported that 57% of patients with advanced/metastatic disease

believed bladder cancer impacted them financially, and that patients with advanced/metastatic disease were more vulnerable to changes in employment status. Early retirement was taken by a reported 26% of patients with advanced/metastatic disease; 19% said they voluntarily left their job and only 15% reported experiencing no change to their employment status.[62, 63] It is noted that only 2% of survey respondents had a primary diagnosis of advanced or mUC; therefore, the sample size for this population was limited (n = 28). The survey also assessed the impact of bladder cancer diagnosis on the carer; 91% of carers confirmed it had impacted them emotionally.[62]

B.1.3.4.2. Economic burden

UC also imposes a substantial economic burden in the UK. In 2012, the financial burden of bladder cancer on the UK was around £441 million.[64] This total included approximately £232 million in healthcare costs, with the largest portion, around £124 million, attributed to inpatient care (costs have been converted to GBP from EUR).[64] To align with the base case, we have focused specifically on the economic burden caused by paclitaxel ± carboplatin. The current treatment administration costs per cycle of paclitaxel ± carboplatin treatment is high, at £406.63 per cycle of paclitaxel (every week).[57-59, 65] Similarly, administration cost for carboplatin (every 3 weeks) is £253.32. The costs of AEs can increase the economic burden of mUC. The cost of AEs as a result of treatment with paclitaxel ± carboplatin also poses a substantial economic burden, as these can be systemic and require hospitalisation. The most expensive AEs to treat are neutropenia and fatigue, estimated to cost £4,111 and £3,083 per patient, respectively, in the UK.[57-59, 65]

B.1.3.5. Clinical care pathway and proposed positioning of the technology

B.1.3.5.1. Diagnostic pathway

In the UK, there is currently no national screening programme for detecting bladder cancer.[66] Cases are usually identified on the basis of painless macroscopic haematuria (i.e. blood in the urine). On presentation of haematuria, patients are referred for urine cytology, cystoscopy, and upper tract imaging. If muscle-invasive

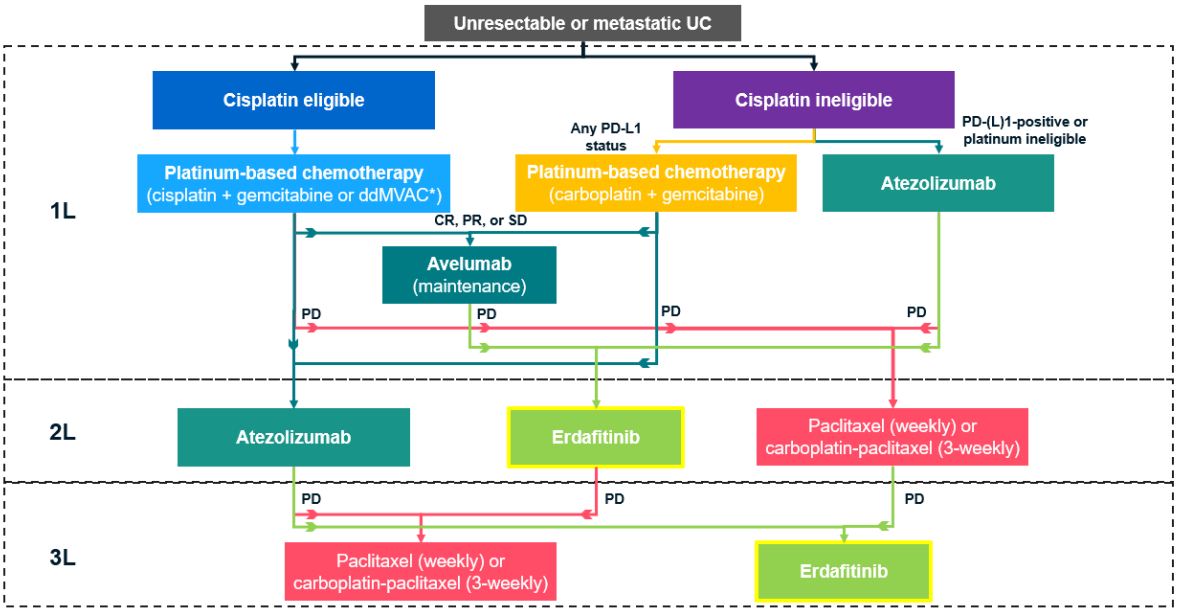
bladder cancer is suspected at cystoscopy, it is recommended to consider computed tomography (CT) or magnetic resonance imaging (MRI) staging before transurethral resection of bladder tumour (TURBT). If abnormalities are identified, the National Institute for Health and Care Excellence (NICE) recommends white-light-guided TURBT, an operation in which abnormal areas of tissue can be removed and biopsied.[22]

B.1.3.5.2. Treatment pathway

The goal of treatment for patients with unresectable or mUC is to provide relief from cancer symptoms, maintain HRQL, delay disease progression, prolong time to the next treatment, and extend survival.[27] The current treatment options in the UK are limited, and despite some developments, such as avelumab maintenance and atezolizumab in 1L and 2L, there has been a lack of progress on the introduction of new effective treatments. The most recent UK-specific guidelines for bladder cancer (NG2) were published by NICE in 2015 (and reassessed in 2019).[22] These guidelines do not include the above recently licensed and appraised treatments for mUC. Incorporating existing NICE guidance and updating the guideline regarding treatments and holistic patient care was identified as crucial by UK healthcare professionals and patients.[67]

Figure 2 represents the current clinical pathway of care for patients with unresectable or mUC, aligned with UK clinical expert opinion, and the proposed positioning of erdafitinib.

Figure 2: Clinical pathway of care for patients with unresectable or mUC, and the proposed positioning of erdafitinib



Key: 1L, first-line; 2L, second-line; 3L, third-line; CR, complete response; ddMVAC, dose dense methotrexate, vinblastine, doxorubicin, cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; PD, progressive disease; PD-L1, programmed death-ligand 1; PR, partial response; SD, stable disease; UC, urothelial carcinoma.
Note: * Patients can be treated with ddMVAC if their renal function is adequate (typically defined as a GFR of ≥ 60 ml/min/1.73 m^2) and they are otherwise physically fit (have an ECOG PS of 0–1).[22]

In England, the SoC for 1L treatment for patients with unresectable or mUC is a platinum-based chemotherapy, as recommended by NICE (NG2) and confirmed in the UK oncologist perspective review by Jones et al., and the UK RW mUC study.[20, 22, 27] In patients who are physically fit (have an Eastern Cooperative Oncology Group performance status [ECOG PS] of 0 or 1) and have adequate renal function (GFR ≥ 60 ml/min/1.73 m^2), cisplatin-based chemotherapy (such as cisplatin plus gemcitabine or ddMVAC) is recommended.[22] For patients who are ineligible for cisplatin due to poor performance status, inadequate renal function or other comorbidities, carboplatin plus gemcitabine is recommended.[22] Patients who are ineligible for chemotherapy and have PD-(L)1-positive tumours (approximately 10% of patients) may be offered anti-PD-(L)1 therapies.[23, 68] The only anti-PD-(L)1 therapy currently recommended by NICE for the treatment of patients at 1L+ is atezolizumab (Tecentriq®) (TA739/TA492).[26, 27, 69]

For patients with an objective response or stable disease after 1L platinum-based chemotherapy, the anti-PD-(L)1 agent avelumab (Bavencio®) (TA788) is recommended for 1L maintenance.[24, 27] UK clinicians, have spoken to the increased avelumab uptake for those patients who have not progressed after platinum-based chemotherapy. This was unable to be captured within the UK RW mUC data since avelumab was approved after the end of the study data collection period.[20, 25] The outcomes presented in THOR (see Section B.2.7) were consistent regardless of type of prior PD-(L)1 received. As such, it is unlikely that the type of prior PD-(L)1 patients received has a significant effect on outcomes or affects the generalisability of the UK RW mUC study.

The choice of 2L treatment is dependent on the 1L treatment received. For patients treated with platinum-based chemotherapy followed by avelumab maintenance, a rechallenge with a platinum-based chemotherapy (cisplatin plus gemcitabine or ddMVAC) is an option if progression occurs more than 12 months after completion of the prior platinum regimen.[27] Rechallenge however, confirmed in both the UK RW mUC study and clinical advisory boards, is rare,[20, 25] only reserved for a limited proportion of physically fit patients, with no evidence to support this approach.[27] Alternatively, paclitaxel in combination with carboplatin or gemcitabine is an option for patients who are ineligible for, or choose not to have cisplatin-based chemotherapy.[22] In 2L+, taxanes, specifically paclitaxel ± carboplatin, are largely ineffective in 90% of patients and is offered to help symptom relief.[26] In England, atezolizumab is recommended at 2L, irrespective of PD-(L)1 status, however is not used following avelumab maintenance or atezolizumab frontline treatment due to the lack of data and clinical rationale to use a second PD-(L)1 inhibitor after progression on a prior PD-(L)1 inhibitor.[27, 58] In 2L or later lines, prognosis is poor with limited effective treatment options available and recommended.[26]

The UK RW mUC study was conducted and validated with clinicians based in the UK, giving greater clarity on the current standard of treatment practice for those with mUC.[20, 25] The study found that in the cohort of 10,787 patients, 36.5% (n = 3,942) received active 1L treatment, with the remainder either receiving best supportive care (BSC) or not surviving long enough to start treatment.[20] This aligns with

observations by UK clinicians: that many patients are either ineligible for, or choose not to have, chemotherapy, and will therefore receive BSC.[25, 26] Of the patients who received 1L treatment, only 24.3% (n = 959), 4.0% (n = 158), and 0.5% (n = 19) received 2L, third-line (3L), and fourth-line (4L) treatments, respectively.[20] A total of 834 patients (7.7%) received a PD-(L)1 inhibitor at 1L (including avelumab maintenance), while 515 patients (4.8%) received it at 2L. Of the 834 patients who received a PD-(L)1 inhibitor at 1L, 135 patients (16.2%) received subsequent anti-cancer treatment. Of these patients approximately 26.7% (n = 36) received paclitaxel monotherapy or a combination of paclitaxel and carboplatin, 40.0% (n = 54) received platinum-based chemotherapy (gemcitabine + carboplatin/cisplatin), and 21.5% (n = 29) underwent retreatment with a PD-(L)1 inhibitor. Of the 515 patients who received a PD-(L)1 inhibitor at 2L, 63 patients (12.2%) proceeded to subsequent treatment. The most common therapies were paclitaxel monotherapy or a combination of paclitaxel and carboplatin, accounting for 57.1% (n = 36) of cases. Additionally, 28.6% (n = 18) received a PD-(L)1 inhibitor, and 11.1% (n = 7) received platinum-based chemotherapy.

The results demonstrate a significant use of PD-(L)1 inhibitors in 1L setting. Of the 3,942 patients receiving 1L treatment, 21.2% (n = 834) of patients received PD-(L)1 inhibitors.[20] Furthermore, a considerable prevalence of re-challenge with PD-(L)1 inhibitors in 2L setting was observed, as evidenced by 21.5% of patients receiving such treatment. Additionally, platinum-based chemotherapy was utilised as 2L treatment in 40.0% of cases following PD-(L)1 inhibitor therapy.[20] Although this UK RW mUC study presented evidence of patients with mUC being retreated with immunotherapies, this approach is not supported by UK clinical experts or clinical guidelines as eluded to above.[22, 25] Importantly, UK clinical experts highlighted the impact of the COVID-19 pandemic on the UK RW mUC study timeline.[25] During the COVID-19 pandemic, clinicians were prescribing chemotherapy in limited capacity at 1L. In interim guidance from NHS England, atezolizumab as first-line immunotherapy instead of chemotherapy was permitted as a treatment option to reduce the number of admissions and reduce the risk of neutropenia.[70] Whilst not standard practice, this was conducted as immunotherapy is less immunosuppressive and resource

intensive than chemotherapy making better use of clinical capacity. This was supported by UK clinical experts who highlighted ethical concerns of subjecting patients to chemotherapy exposure.[25] Consequently, the number of patients receiving 1L chemotherapy will have been lower and experienced disruption to their chemotherapy administration.[71] The effects of COVID-19 on the study period are expected to have lasted at least 12 months.[25]

Patients who receive platinum-based chemotherapy as their 1L treatment therefore tend to receive 2L treatment with carboplatin-paclitaxel [3-weekly], paclitaxel [weekly], or docetaxel. It should be noted that treatment with docetaxel and ddMVAC is very limited in clinical practice in England, and docetaxel is not recommended in the NICE guidelines.[26] This aligns with the UK RW mUC study, where only four (2.0%) patients received treatment with docetaxel at 2L or beyond following treatment with a PD-(L)1 inhibitor.[20]

Additionally, within clinical practice in the 2L, there is a significant proportion of patients with unresectable or mUC that were not fit for a 2L chemotherapy, due to a poor performance status (defined as ECOG PS 3–4) or due to patient preference. These patients were therefore only eligible to receive BSC. It is anticipated that erdafitinib could be a treatment option for a limited proportion of these patients with mUC who have progressed on or following treatment with a PD-(L)1 inhibitor. However, considering the critical analysis of the UK RW mUC study, clinician recommendation and the available data, the main comparator for erdafitinib is anticipated to be paclitaxel, as a monotherapy or in combination with carboplatin (denoted paclitaxel ± carboplatin).[20, 25, 26] UK clinicians mentioned that patients who are currently receiving BSC or not receiving systemic treatment after prior exposure to anti-PD-(L)1 inhibitors may be eligible for erdafitinib if they have *FGFR*-positive disease.[25] However, given the absence of evidence available following up BSC patients after exposure to PD-(L)1 inhibitors, a comparative analysis could not be conducted.

B.1.3.5.3. Unmet need in the treatment of unresectable or mUC

Unresectable or mUC is very difficult to treat, and the lack of tolerable and effective treatments for patients with unresectable mUC – especially of recommended options offering proven survival benefit in the 2L setting – is widely recognised.[27] Patients with unresectable or mUC have a poor prognosis, with a median OS of just 5.4 months from diagnosis.[20] Qualitative research investigating the experiences of individuals living with mUC was conducted.[23] This involved conducting in-depth interviews with a total of four patients diagnosed with metastatic bladder cancer and three of their caregivers (n=3). The aim of this research was to gain a comprehensive understanding of the physical, social and emotional challenges faced by mUC patients, as well as the impact of these challenges on their daily lives and well-being of their caregivers. The findings of the research highlighted the striking physical impact of mUC and current treatments on patients, with direct repercussions on their emotional well-being and overall quality of life. Additionally, there was a clear, direct impact on caregivers, who shared the emotional burden with the patients and faced challenges to their own emotional well-being. Furthermore, caregivers were required to assume additional tasks, resulting in diminished social interactions and reduced engagement in activities. Both patients and caregivers expressed their desire for novel and supplementary treatment options and emphasised the advantages of home-based administration compared to hospital administration.[23]

There are limited treatment options available, and few patients receive anticancer treatments due to age, comorbidities, patient preference, and the lack of tolerable efficacious treatments. The UK RW mUC study of patients with mUC in England demonstrated that a relatively high proportion of patients are not receiving active treatment, including at frontline.[20] This is supported by literature, in which global RW studies have shown that only approximately 40% of patients receive 1L treatment, with 15–20% receiving treatment in the 2L+ setting.[27] Without active treatment, these patients experience an immense impact on their survival, quality of life and productivity.

Of the patients with unresectable or mUC who do receive treatment, the existing treatment options frequently fail to meet their needs, are associated with high

toxicity, and often lead to poor clinical outcomes. Patients who progress on or after 1L systemic therapy have poor prognosis, and a large proportion of patients opt for BSC versus current 2L treatment options due to tolerability. Almost all approved 2L treatments in unresectable or mUC are associated with a median OS of < 1 year.[5, 31-33] Additionally, current therapies for unresectable or mUC, specifically systemic chemotherapy, require frequent hospital visits and lead to harmful TRAEs that are detrimental to a patient's HRQL.[60, 72]

Furthermore, there is an unmet need for post-immunotherapy treatments in the unresectable or mUC population in the UK. It has been reported that nearly 70% of patients with mUC fail to respond to immune CPIs, and there are limited treatment options after progression on immune CPIs.[73, 74] In the UK RW mUC study, 14.7% (n = 198) of patients in England received subsequent anticancer treatment after anti-PD-(L)1 discontinuation at 1L or 2L (n = 1349).[20] The prognosis for these patients is poor, as observed in the study where median OS was found to be below 9 months for all treatments, even including patients who were rechallenged by immunotherapies (Appendix O). Patients experience anxiety and concern when 1L treatments, especially CPIs fail as options are limited to clinical trials.[23] This highlights the urgent need for additional treatment options after anti-PD-(L)1 therapy.

There are no targeted treatments currently available for patients with unresectable or mUC. Apart from PD-(L)1 testing at 1L, routine clinical practice does not use molecular biomarkers to predict sensitivity to specific agents to guide treatment selection. As discussed in Section B.1.3.1.1, luminal 1 tumours are enriched with *FGFR3* mutations; patients with luminal 1 tumours benefit the least from immunotherapy, reflecting a particular unmet need for *FGFR* alteration testing and FGFR-targeted therapies in this population following anti-PD-(L)1 therapy.[45, 75]

Both patients receiving chemotherapy and those not currently receiving active treatment could benefit from a targeted oral treatment. This approach offers a less disruptive hospital administration schedule, maintains HRQL, minimises AEs and extends survival.

B.1.4. Equality considerations

No equality considerations relating to the use of erdafitinib have been identified or are anticipated.

B.2. Clinical effectiveness

Summary of key points:

Study identification

- A clinical systematic literature review (SLR) was conducted to identify all Phase II, III, or IV RCT evidence on the efficacy and safety of systemic therapies for patients with locally advanced, unresectable or mUC who have received one prior line of systemic therapy. Only one study reported on patients [redacted]:
  - THOR: an ongoing, international, Phase III, randomised, open-label trial investigating erdafitinib versus chemotherapy in patients with advanced UC and susceptible *FGFR* alterations who had progressed on or after one or two prior treatments, where at least one of the prior treatments was an anti-PD-(L)1 agent (Cohort 1).[5]
- Supportive evidence is provided by the earlier BLC2001 study, a Phase II, single-arm trial conducted in patients with locally advanced and unresectable or metastatic UC with *FGFR* alterations.[6]
- The THOR trial, being conducted on a global scale, is not entirely reflective of clinical practices in the UK. The comparator arm of THOR comprises chemotherapy regimen consisting of vinflunine and docetaxel.[20] It is important to note that vinflunine is not reimbursed in the UK, while docetaxel is reimbursed, but not recommended in NICE guidelines nor widely used.[22, 26, 59] Therefore, the comparator arm of the THOR trial does not fully align with the SoC in the UK clinical practice.
- To provide a more accurate representation of the current clinical management for patients with advanced UC in England, Johnson & Johnson conducted a UK RW mUC study using datasets available through the NCRAS. This UK RW mUC study provides insight into England-specific data on comparators to erdafitinib and patient profiles in the NHS and reflects the RW population likely to receive erdafitinib in clinical practice in England. Given the large sample size (n = 10,787) and true representativeness of the unresectable or mUC patient

population in England (in terms of patient characteristics and current clinical management), this UK RW mUC study serves as the primary comparative efficacy evidence for erdafitinib in this submission.[25]

The THOR trial

Efficacy

- At the March 2023 database lock (median follow-up of 15.9 months), erdafitinib demonstrated superior efficacy when compared with chemotherapy:[5, 76]
  - Median OS: 12.1 months versus 7.8 months (hazard ratio [HR]: 0.64; 95% CI: 0.47, 0.88; p = 0.005)
  - Median progression-free survival (PFS): 5.6 months versus 2.7 months (HR: 0.58; 95% CI: 0.44, 0.78; p=0.0002)
  - ORR: 45.6% versus 11.5% (relative risk: 3.94; 95% CI: 2.37, 6.57; p < 0.001)
- The results from subgroup analyses were consistent to the main analyses for erdafitinib compared with chemotherapy, irrespective of: the number of prior lines of therapy; prior line of anti-PD-(L)1 therapy; prior treatment with platinum-based chemotherapy; primary tumour location; *FGFR* alteration type; and type of chemotherapy (docetaxel or vinflunine).[5]

HRQL

- HRQL was maintained on treatment, with few differences between treatment groups.[76]

Safety

- The safety profile of erdafitinib in the confirmatory THOR trial was characterised by different AEs compared with chemotherapy, however, AEs were shown to be manageable with dose modifications and consistent with the known safety profile for erdafitinib in patients with unresectable or mUC.[5, 76]
- As of the March 2023 database lock, the incidence of Grade 3/4 TRAEs was similar between erdafitinib and chemotherapy groups, and erdafitinib resulted in fewer TRAEs that had an outcome of death, were serious, or led to treatment discontinuation compared with chemotherapy.[5, 76]

Indirect treatment comparisons (ITCs) (Appendix P)

- An ITC was conducted to compare the efficacy of erdafitinib to paclitaxel as a

monotherapy or in combination with carboplatin, denoted by paclitaxel ± carboplatin.

- Three analytical approaches explored for robustness are regression adjustment, inverse probability weighting method, and the doubly robust estimator.
- The results of the ITC show that, irrespective of the selected method of matching, erdafitinib provides substantial clinical benefit compared with paclitaxel ± carboplatin. With the ATC-adjusted weighting, erdafitinib is estimated to reduce the risk of death by 65% (HR: 0.35; 95% CI: 0.23, 0.52) compared with paclitaxel ± carboplatin, with a median OS of 10.6 months (95% CI: 9.5, 16.7) for erdafitinib and 6.5 months (95% CI: 4.9, 7.0) for paclitaxel ± carboplatin.
- The time to next treatment (TTNT) HR of 0.33 (95% CI: 0.22, 0.49) indicates erdafitinib reduces the hazard of progression to the next treatment line by 67% versus paclitaxel ± carboplatin, with the median TTNT of 10.2 months (95% CI: 9.3, 13.9) for erdafitinib and 5.4 months (95% CI: 3.7, 6.8) for paclitaxel ± carboplatin.

B.2.1. Identification and selection of relevant studies

An SLR was conducted to identify and select evidence of the efficacy and safety of treatments available in the UK for patients with locally advanced, metastatic or unresectable UC with progressive disease after receiving at least one prior systemic therapy. The SLR covered a broad range of interventions used globally in the relevant population. The first search was conducted on 10 March 2023; these searches identified relevant evidence published since 2006 and conference abstracts from 2021. The initial search strategy was further refined, and searches were run on 1 May 2024 to align with the decision problem presented within this submission. A total of six studies were identified globally for patients with locally advanced, metastatic, or surgically unresectable (stage IV) UC who have received one prior line of systemic therapy. Full details of the SLR are provided in Appendix D.

However, none of these six RCTs, except for THOR, are relevant for inclusion in the indirect treatment comparisons (ITCs) necessary for this appraisal (i.e. [redacted]). To resolve this evidence gap, Johnson & Johnson initiated an RW study conducted in England that provides a strong source of data for clinical outcomes for patients treated with SoC in the UK, utilised in an ITC (presented in Section B.2.9).[20]

B.2.2. List of relevant clinical effectiveness evidence

A summary of the clinical effectiveness evidence for erdafitinib is presented in Table 4.

The pivotal evidence used to support erdafitinib for the treatment of [redacted], is the confirmatory registrational THOR trial.5, 76 This primary source of evidence provides information on 266 patients relevant to the decision problem, with a median follow-up for survival of 15.9 months (database lock: 2 March 2023).[5, 76] Further details of THOR are provided in Sections B.2.3–B.2.6 of this submission.

Supportive evidence is provided by the earlier BLC2001 study, a Phase II, two-arm trial conducted in patients with metastatic or surgically unresectable UC with *FGFR* alterations.[6, 77] BLC2001 demonstrated the efficacy and safety of erdafitinib in patients with advanced UC who have susceptible *FGFR* alterations. The trial was also key in ascertaining the optimal therapeutic dosing regimen for erdafitinib: 8 mg once daily with pharmacodynamically guided up-titration to 9 mg once daily.[6] Efficacy and safety results of the BLC2001 trial have been presented in Section B.2.6.2 and Section B.2.10.2, respectively. All other data for this trial, including methodology, are presented in Appendix N.

As discussed in Section B.1.3, further supportive evidence was generated through the UK RW mUC study, with the aim to identify a standing cohort of adults diagnosed with mUC in England between January 2016 to December 2021, and to follow them

through the study period (up to March 2023) to provide insight into NHS clinical practice.[20] This was a retrospective, cohort study, aiming to describe the demographic and clinical characteristics of patients, molecular diagnostic tests, the type and frequency of NHS healthcare resource utilisation and the lines of systemic anticancer therapy. The study aimed to understand the patient treatment pathway in England, and to report key treatment milestones (including OS and TTNT) from the date of diagnosis and the initiation of 1L, 2L, and 3L systemic anticancer therapy.[20] This UK RW mUC study has been used to support ITCs for erdafitinib compared with UK-relevant comparators. For further information regarding these analyses, including the methodology of the RW study, please refer to Section B.2.9 and Appendix O.

Table 4: Clinical effectiveness evidence

Trial	THOR, Cohort 1
Trial title	A Phase III Study of Erdafitinib Compared With Vinflunine or Docetaxel in Patients With Advanced Urothelial Cancer and Selected *FGFR* Gene Aberrations
Trial number	NCT03390504
Study design	Phase III, randomised, open-label, multicentre trial
Population	Patients with advanced UC harbouring selected *FGFR* aberrations who had progressed after one or two prior treatments, at least one of which included an anti-PD-(L)1 agent.
Intervention(s)	Erdafitinib (8 mg oral tablet administered once daily for 21 days in a 21-day cycle)
Comparator(s)[a]	Vinflunine (320 mg/m^2 as a 20-minute IV infusion every 3 weeks) Docetaxel (75 mg/m^2 as a 1-hour IV infusion every 3 weeks)
Indicate if study supports application for marketing authorisation	Yes
Indicate if study used in the economic model	Yes
Rationale if study not used in the model	NA
Reported outcomes specified in the decision problem[b]	• **OS** • **PFS** • Objective response rates (complete or partial) • DOR • **Adverse effects of treatment**

Trial	THOR, Cohort 1
	• **HRQL**
Key: DOR, duration of response; *FGFR*, fibroblast growth factor receptor; HRQL, health-related quality of life; IV, intravenous; OS, overall survival; PD-(L)1, programmed death-ligand 1; PFS, progression-free survival; UC, urothelial carcinoma. **Notes:** [a] Comparators listed are specific to Cohort 1 of the THOR trial. [b] Bolded outcomes represent those directly used in the economic model. **Source:** THOR clinical study report.[76]	

B.2.3. Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1. THOR

B.2.3.1.1. Study design

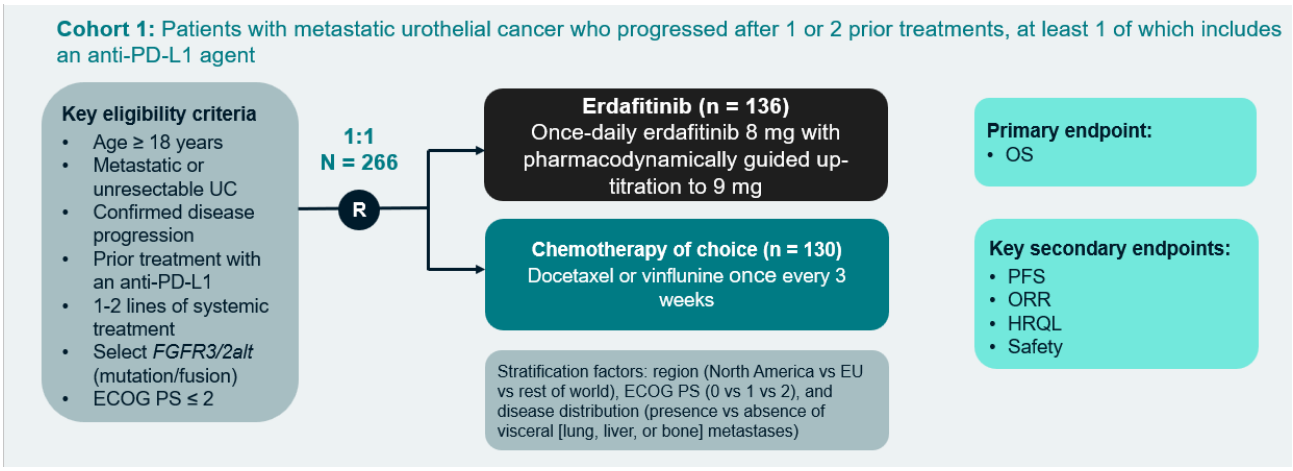
THOR is an ongoing global, Phase III, randomised, open-label, multicentre, confirmatory registrational trial evaluating erdafitinib in patients with advanced UC and susceptible *FGFR* alterations who had progressed on or after one or two prior treatments.[5, 76] The THOR trial consists of two cohorts:

- Cohort 1: erdafitinib versus chemotherapy (docetaxel or vinflunine) in patients who had progressed on or after one or two prior treatments, one of which being an anti-PD-(L)1 agent.
- Cohort 2: erdafitinib versus pembrolizumab in patients who had progressed on or after one prior treatment not containing an anti-PD-(L)1 agent.[78]

Aligning with the decision problem and marketing authorisation presented in Section B.1.1, this submission will focus on Cohort 1 only.

A schematic of the trial design for Cohort 1 is presented in Figure 3.

Figure 3: THOR trial design, Cohort 1



Key: alt, alterations; ECOG PS, Eastern Cooperative Oncology Group performance status; FGFR, fibroblast growth factor receptor; HRQL, health-related quality of life; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed death-ligand 1; PFS, progression-free survival; UC, urothelial carcinoma.
Source: THOR clinical study report[76]; THOR ASCO oral presentation.[16]

The trial consists of three phases: screening, treatment and follow-up. The screening phase comprised molecular and full-study screening. The key inclusion and exclusion criteria applied at the time of screening are presented in Table 5.

Molecular screening was conducted to evaluate patients for molecular eligibility, determined by central laboratory screening or local historical test results (from tissue or blood) performed at a Clinical Laboratory Improvement Amendments certified or regional equivalent laboratory using the following methods: local next-generation sequencing, direct digital counting methods, or the Qiagen *therascreen*® FGFR Rotor-Gene Q reverse transcription polymerase chain reaction test. At least one of the following fusions was required: *FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3_V1, FGFR3-TACC3_V3, FGFR3-BAIAP2L1;* or one of the following *FGFR3* mutations: R248C, S249C, G370C, Y373C.

In Cohort 1, patients were then randomly assigned at a 1:1 ratio to either:

- Treatment Group 1: 8 mg erdafitinib once daily for 21 days in a 21-day cycle (with pharmacodynamically guided up-titration to 9 mg)

- Treatment Group 2: chemotherapy (320 mg/m^2 vinflunine administered as a 20-minute IV infusion, or 75 mg/m^2 docetaxel administered as a 1-hour IV infusion, once every 3 weeks)

The choice of the type of chemotherapy (i.e. vinflunine or docetaxel) was made at site level by the investigator prior to the enrolment of patients.

Stratified factors at randomisation within each cohort were as follows:

- Region (North America versus EU versus rest of world)
- ECOG PS (0 or 1 versus 2)
- Disease distribution (presence versus absence of visceral metastases: lung, liver, or bone)

In the treatment phase, patients continued to receive treatment until disease progression, intolerable toxicity, withdrawal of consent or a decision taken by the investigator to discontinue treatment. The post-treatment follow-up phase extended from the end-of-treatment visit until the patient died, withdrew consent, was lost to follow-up, or the end of study, whichever came first.

Table 5 presents an overview of the methodology of the THOR trial.

Table 5: Summary of the THOR trial methodology

Trial name	**THOR**
Trial design	Phase III, randomised, open-label, multicentre trial
Location	121 sites in 23 countries, including: Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, France, Germany, Greece, Hungary, Israel, Italy, Japan, Netherlands, Russia, the Republic of Korea, Spain, Taiwan, Turkey, the UK and the US
Key eligibility criteria for patients	**Inclusion criteria:** • Histological demonstration of transitional cell carcinoma of the urothelium • Metastatic or surgically unresectable UC • Documented progression of disease, defined as any progression that requires a change in treatment prior to randomisation • Prior treatment with an anti-PD-(L)1 agent as monotherapy or as combination therapy; no more than two prior lines of systemic treatment. Prior treatment with an anti-PD-(L)1 agent could have

Trial name	THOR
	been given as neoadjuvant, adjuvant, or in the metastatic line of treatment as frontline or maintenance therapy • Patients must meet appropriate molecular eligibility criteria, as determined by central laboratory screening or by local historical test results. Tumours must have at least one of the following fusions: *FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1*; or one of the following *FGFR3* mutations: R248C, S249C, G370C, Y373C • ECOG PS Grade 0, 1, or 2 **Exclusion criteria:** • Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 30 days prior to randomisation • Active malignancies (that is, requiring treatment change in the last 24 months). The only allowed exceptions are UC, skin cancer treated within the last 24 months that is considered completely cured, localised prostate cancer with a Gleason score of 6 (treated within the last 24 months or untreated and under surveillance) and localised prostate cancer with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence • Symptomatic CNS metastases • Received prior FGFR inhibitor treatment • Known allergies, hypersensitivity or intolerance to erdafitinib or its excipients • Corneal or retinal abnormality likely to increase the risk of eye toxicity. • History of uncontrolled cardiovascular disease • Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions • History of severe hypersensitivity reaction to either docetaxel, or to other drugs formulated with polyoxyethylated castor oil, or to vinflunine or other vinca alkaloids. The full eligibility criteria can be found in Appendix M.
Settings and locations where the data were collected	A total of 266 patients were enrolled and treated at one of the 121 trial sites.
Trial drugs	**Intervention** • Erdafitinib (8 mg oral tablet administered once daily for 21 days in a 21-day cycle) **Comparator** • Vinflunine (320 mg/m^2 as a 20-minute IV infusion every 3 weeks) or

Trial name	THOR
	• Docetaxel (75 mg/m^2 as a 1-hour IV infusion every 3 weeks)
Permitted and disallowed concomitant medication	The following concomitant medications were permitted during the study: • Symptomatic treatment: supportive care, such as antibiotics, analgesics, transfusions, diet, etc., and concomitant medications for the symptomatic treatment of related toxicities (Grade 1–4) could be administered according to the SoC at the site, and the treating physician's discretion, as clinically indicated • Prophylactic medication: appropriate prophylactic antiemetic regimens could be provided if required, in accordance with institutional practice and current ESMO guidelines • Chronic supportive therapies: ongoing bisphosphonates and denosumab or other supportive therapies were permitted • Palliative radiotherapy: localised radiotherapy for symptomatic control was permitted, but should not have included definitive radiation to target lesions The following medications were prohibited during the study: • Concurrent investigational agents • Concurrent antineoplastic agents or hormonal anticancer therapy • For patients receiving erdafitinib: - Medications known to increase serum levels of calcium and serum phosphate levels. • For patients receiving chemotherapy (vinflunine or docetaxel): • Strong inhibitors of the CYP3A4 enzymes For patients receiving vinflunine: – Strong inducers of CYP3A4 enzymes – QT/QTc prolonging drugs
Primary endpoints	• OS, defined as the date of randomisation to the date of the patient's death
Key secondary endpoints	• PFS, assessed per RECIST v1.1 by the investigator, or death, whichever is reported first; defined as duration in days from the date of randomisation to the date of disease progression • ORR, assessed per RECIST v1.1 by the investigator; defined as the proportion of patients who achieved complete response (CR) or partial response (PR) • DOR, defined as duration in days from the date of initial documentation of a response to the date of first documented evidence of progressive disease or death (for responders) • PROs: – Change from baseline in HRQL as assessed by the FACT-BI, EQ-5D-5L questionnaire, and PGIS, and time until urinary bladder cancer symptom deterioration (subset of FACT-BI items) • Safety

Trial name	THOR
Subgroup analyses	• *FGFR* alteration type • PD-(L)1 status • Tumour location • Visceral metastases • Prior therapy • Type of chemotherapy (docetaxel or vinflunine) • Demographic and baseline characteristics (gender, age, race, ethnicity, region, baseline creatine clearance, baseline haemoglobin level, baseline ECOG PS) Please see Appendix E for full list. The subgroup analyses was not powered to assess treatment effect within subgroups.
Key: CNS, central nervous system; CYP3A4, cytochrome P450 3A4; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ESMO, European Society of Medical Oncology; FACT-BI, Functional Assessment of Cancer Therapy – Bladder; *FGFR*, fibroblast growth factor receptor; HRQL, health-related quality of life; IV, intravenous; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed death-ligand 1; PFS, progression-free survival; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome; RECIST, Response Evaluation Criteria In Solid Tumours; SoC, standard of care; UC, urothelial carcinoma. **Source:** Loriot et al. (2023).[5] THOR clinical study report.[76]	

B.2.3.1.2. Outcomes reported

The primary endpoint of the THOR trial was OS, measured from the date of randomisation to the date of the patient's death. The secondary endpoints evaluated PFS, ORR, duration of response (DOR), HRQL, safety and pharmacokinetics of erdafitinib. Safety assessments were based on treatment-emergent AEs (TEAEs), laboratory analyte values, vital sign and physical examination measurements, electrocardiogram data, and ophthalmological examinations reported during the trial.[79]

TEAEs were categorised with the use of the Medical Dictionary for Regulatory Activities Version 24.1, and the severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.[76, 79]

A detailed summary of the trial endpoints, their definitions and censoring rules is presented in Appendix M.

B.2.3.1.3. Baseline demographics and disease characteristics in the THOR study

A summary of the key baseline demographics and disease characteristics for Cohort 1 are presented in

Table 6.

Demographic and baseline characteristics, *FGFR* alterations, and prior systemic anticancer therapy received by patients were generally well balanced between the two treatment arms.[5] Most patients were male (71.4%), white (54.1%), and from Europe (60.9%). The median age at full-study screening was 67.5 years (range: 32, 86 years). Most patients were aged 65 and over. The patient population enrolled in THOR is considered broadly representative of that seen within UK clinical practice, as confirmed by UK clinicians.[26] Further details on the generalisability of the THOR trial are provided in Section B.2.12.2.

In patients with eligible *FGFR* alterations (99.2%, as one patient in each treatment group had a false-positive result), 80.8% had eligible *FGFR* mutations, 16.5% had eligible *FGFR* fusions, and 1.9% had both eligible *FGFR* mutations and fusions.[5] All patients with *FGFR* alterations had at least one *FGFR3* alteration; no patients had *FGFR2* alterations.

Table 6: Baseline demographics and disease characteristics (Cohort 1; ITT population)

Characteristic	Erdafitinib (n = 136)	Chemotherapy (n = 130)
Age, years		
Median (range)	66.0 (32-85)	69.0 (35-86)
< 65 years, n (%)	59 (43.4)	45 (34.6)
65–69 years, n (%)	30 (22.1)	23 (17.7)
70–74 years, n (%)	21 (15.4)	32 (24.6)
≥ 75 years, n (%)	26 (19.1)	30 (23.1)

Characteristic	Erdafitinib (n = 136)	Chemotherapy (n = 130)
Gender, n (%)		
Male	96 (70.6)	94 (72.3)
Female	40 (29.4)	36 (27.7)
Race, n (%)		
Asian	37 (27.2)	40 (30.8)
Black or African American	0	1 (0.8)
White	81 (59.6)	63 (48.5)
Multiple	0	1 (0.8)
Not reported	18 (13.2)	25 (19.2)
Geographic region, n (%)		
North America	8 (5.9)	5 (3.8)
Europe	82 (60.3)	80 (61.5)
Rest of the world	46 (33.8)	45 (34.6)
Primary tumour location, n (%)		
Lower tract	95 (69.9)	82 (63.1)
Bladder	90 (66.2)	74 (56.9)
Urethra	5 (3.7)	8 (6.2)
Prostate	0	0
Upper tract	41 (30.1)	48 (36.9)
Renal Pelvis	19 (14.0)	20 (15.4)
Ureter	22 (16.2)	28 (21.5)
Baseline ECOG PS, n (%)		
0	63 (46.3)	51 (39.2)
1	61 (44.9)	66 (50.8)
2	12 (8.8)	13 (10.0)
Disease distribution at study entry, n (%)		
Presence of visceral metastases[a]	101 (74.3)	97 (74.6)
Lung	71 (52.2)	67 (51.5)
Liver	31 (22.8)	38 (29.2)
Bone	36 (26.5)	39 (30.0)
Absence of visceral metastases (lung, liver, or bone)	35 (25.7)	33 (25.4)
PD-(L)1 status, n (%)		
N	96	79
CPS ≥ 1	38 (39.6)	38 (48.1)
CPS < 1	58 (60.4)	41 (51.9)
PD-(L)1 status, n (%)		
N	96	79
CPS ≥ 10	7 (7.3)	11 (13.9)

Characteristic	Erdafitinib (n = 136)	Chemotherapy (n = 130)
CPS < 10	89 (92.7)	68 (86.1)
FGFR3 alterations, n (%)		
n	135	129
Mutations	108 (79.4)	107 (82.3)
Fusions	25 (18.4)	19 (14.6)
Mutations and fusions	2 (1.5)	3 (2.3)

Key: CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; eCRF, electronic case report form; FGFR, fibroblast growth factor receptor; ITT, intention-to-treat; PD-(L)1, programmed death-ligand 1.
Notes: Percentages are based on the number of patients in a specified group with non-missing values for the relevant parameter. [a] Number and percentages for lung, liver, and bone are based on patients marked with 'Yes' in the eCRF question 'Are there currently any metastatic disease sites involving liver, lung, and/or bone?'
Source: Loriot et al. (2023).[5] THOR clinical study report.[76]

Table 7 summarises the prior therapy received by patients. One-third (33.1%) of patients in the erdafitinib group and one-quarter (25.4%) in the chemotherapy group received one line of prior systemic therapy.[76] Most of the patients in both treatment groups (66.2% in the erdafitinib group and 74.6% in the chemotherapy group) received two lines of prior systemic therapy. More than half of patients in both treatment groups (55.9% in the erdafitinib group and 58.5% in the chemotherapy group) received an anti-PD-(L)1 therapy as a single agent in the 2L setting.[76]

Although prior treatment with chemotherapy was not required per the protocol, most patients received at least one prior chemotherapy (90.4% in the erdafitinib group and 87.7% in the chemotherapy group).[76] Almost all of these patients received platinum-based chemotherapy (89.7% in the erdafitinib group and 85.4% in the chemotherapy group). This is line with the current UK clinical practice as per the NICE treatment guidelines and supported by UK clinical experts through the UK oncologist perspective review by Jones et al. (as discussed in Section B.1.3.5.2) and advisory boards.[25, 26]

Table 7: Summary of prior anticancer therapy received (Cohort 1, ITT population)

Patients receiving prior therapy, n (%)	Erdafitinib (n = 136)	Chemotherapy (n = 130)
One line of prior systemic therapy	45 (33.1)	33 (25.4)
Chemotherapy + anti-PD-(L)1	32 (23.5)	14 (10.8)
Anti-PD-(L)1 (+ other)	11 (8.1)	16 (12.3)
Chemotherapy	1 (0.7)	2 (1.5)
Chemotherapy + Anti-PD-(L)1 + other	1 (0.7)	1 (0.8)
Two lines of prior systemic therapy	90 (66.2)	97 (74.6)
First line of therapy		
Chemotherapy	77 (56.6)	76 (58.5)
Chemotherapy + anti-PD-(L)1	6 (4.4)	10 (7.7)
Other	7 (5.1)	11 (8.5)
Second line of therapy		
Anti-PD-(L)1	76 (55.9)	76 (58.5)
Chemotherapy	10 (7.4)	14 (10.8)
Other	4 (2.9)	7 (5.4)

Key: 2L, second line; ITT, intention-to-treat; PD-(L)1, programmed death-ligand 1.
Notes: Percentages are based on the number of patients in the analysis set of the corresponding treatment group. The symbol '+' = indicates medications that are part of the same line of therapy, which may have been administered sequentially or concurrently.
Source: THOR clinical study report.[76]

Table 8 shows a summary of key baseline demographics and disease characteristics by chemotherapy. Overall, the characteristics are well balanced, though there are differences between the treatment groups. For example, patients receiving vinflunine were slightly older than those receiving docetaxel and erdafitinib, and most patients receiving vinflunine were from Europe. Additionally, there were distribution imbalances with respect to patients' race in each treatment group; the docetaxel treatment group had fewer white patients compared with the erdafitinib and vinflunine treatment groups, which is not reflective of UK practice.[76]

Table 8: Baseline demographics and disease characteristics by chemotherapy (Cohort 1; ITT population)

Characteristic	Erdafitinib (n = 136)	Docetaxel (n = 82)	Vinflunine (n = 48)
Age, years			
Median	66.0	67.5	71.5
< 65 years, n (%)	59 (43.4)	34 (41.5)	11 (22.9)
65–69 years, n (%)	30 (22.1)	14 (17.1)	9 (18.8)
70–74 years, n (%)	21 (15.4)	19 (23.2)	13 (27.1)
≥ 75 years, n (%)	26 (19.1)	15 (18.3)	15 (31.3)
Gender, n (%)			
Male	96 (70.6)	61 (74.4)	33 (68.8)
Female	40 (29.4)	21 (25.6)	15 (31.3)
Race, n (%)			
Asian	37 (27.2)	40 (48.8)	0
Black or African American	0	0	1 (2.1)
White	81 (59.6)	31 (37.8)	32 (66.7)
Multiple	0	0	1 (2.1)
Not reported	18 (13.2)	11 (13.4)	14 (29.2)
Geographic region, n (%)			
North America	8 (5.9)	5 (6.1)	0
Europe	82 (60.3)	35 (42.7)	45 (93.8)
Rest of the world	46 (33.8)	42 (51.2)	3 (6.3)
Primary tumour location, n (%)			
Lower tract	95 (69.9)	48 (58.5)	34 (70.8)
Bladder	90 (66.2)	43 (52.4)	31 (64.6)
Urethra	5 (3.7)	5 (6.1)	3 (6.3)
Prostate	0	0	0
Upper tract	41 (30.1)	34 (41.5)	14 (29.2)
Renal pelvis	19 (14.0)	15 (18.3)	5 (10.4)
Ureter	22 (16.2)	19 (23.2)	9 (18.8)
Baseline ECOG PS, n (%)			
0	63 (46.3)	36 (43.9)	15 (31.3)
1	61 (44.9)	40 (48.8)	26 (54.2)
2	12 (8.8)	6 (7.3)	7 (14.6)
Disease distribution at study entry, n (%)			
Presence of visceral metastases[a]	101 (74.3)	55 (67.1)	42 (87.5)
Lung	71 (52.2)	41 (50.0)	26 (54.2)
Liver	31 (22.8)	18 (22.0)	20 (41.7)

Characteristic	Erdafitinib (n = 136)	Docetaxel (n = 82)	Vinflunine (n = 48)
Bone	36 (26.5)	18 (22.0)	21 (43.8)
Absence of visceral metastases (lung, liver, or bone)	35 (25.7)	27 (32.9)	6 (12.5)
PD-(L)1 status, n (%)			
N	96	42	37
CPS ≥ 1	38 (39.6)	24 (57.1)	14 (37.8)
CPS < 1	58 (60.4)	18 (42.9)	23 (62.2)
PD-(L)1 status, n (%)			
N	96	42	37
CPS ≥ 10	7 (7.3)	7 (16.7)	4 (10.8)
CPS < 10	89 (92.7)	35 (83.3)	33 (89.2)
Number of prior systemic therapy lines, n (%)			
One	45 (33.1)	25 (30.5)	8 (16.7)
Two	90 (66.2)	57 (69.5)	40 (83.3)
Three	1 (0.7)	0	0

Key: CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; eCRF, electronic case report form; ITT, intention-to-treat; PD-(L)1, programmed death-ligand 1.
Notes: Percentages are based on the number of patients in a specified group with non-missing values for the relevant parameter. [a] Number and percentages for lung, liver, and bone are based on patients marked with 'Yes' in the eCRF question 'Are there currently any metastatic disease sites involving liver, lung, and/or bone?'.
Source: THOR clinical study report.[76]

B.2.3.2. BCL2001

The methodology of the supportive Phase II BCL2001 trial is presented in Appendix N.

B.2.4. Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1. THOR

B.2.4.1.1. Analysis sets

The analysis population sets in the THOR trial are presented and defined in Table 9. In Cohort 1, the intention-to-treat (ITT) analysis set was used to summarise the study population and baseline characteristics, efficacy and patient-reported outcome data.

Of note, as specified in the statistical analysis plan, efficacy analyses using the per protocol population were not conducted, as the protocol population was not < 95% of the ITT population.

Table 9: THOR analysis sets

Analysis set	Definition	Number of patients		
		Erdafitinib	Chemotherapy	Total
Cohort 1 ITT Analysis Set	All randomised patients in Cohort 1. Patients in this population will be analysed according to the treatment to which they are randomised.	136	130	266
Safety	All randomised patients who received at least one dose of the study drug. Safety data will be analysed according to the actual treatment received.	135	112	247

Key: ITT, intention-to-treat.
Source: THOR statistical analysis plan[79]; THOR clinical study report.[76]

B.2.4.1.2. Statistical analyses

A summary of statistical analyses conducted for the THOR trial is presented in

Table 10. This submission presents data from the interim analysis (clinical cut-off date of 15 January 2023).[76] The interim analysis occurred after 155 death events had been observed (at approximately 75% information fraction). The efficacy boundary p-value was predetermined to be 0.019 (two-sided) based on the O'Brien–Fleming alpha-spending function.

After the interim analysis, the independent data monitoring committee made a recommendation to stop cohort 1 due to superiority of erdafitinib over chemotherapy and allowed cross-over of 6 patients in the chemotherapy group to the erdafitinib group. Given the small number of patients who crossed over, no adjustment analyses were performed.

Table 10: Summary of statistical analyses in THOR

Hypothesis objective	Erdafitinib treatment prolongs OS in patients with advanced UC harbouring selected *FGFR* alterations following one or two prior line(s) of systemic therapy, with at least one line containing anti-PD-(L)1, compared with the OS of those treated with chemotherapy (docetaxel or vinflunine)
Statistical analysis	For the primary efficacy analysis, the Kaplan–Meier method was used to estimate the distribution of OS for each treatment group within each cohort. The stratified log-rank test was used to compare survival curves of OS between the two treatment arms. The Type 1 error was controlled at 5% (two-sided) for the primary endpoint. All tests were conducted at a two-sided alpha level of 0.05, and a 95% CI was provided, unless stated otherwise. Secondary endpoints were assessed at the same significance levels as specified for testing the primary endpoint (OS) to protect the overall Type 1 error rate. The testing order of these endpoints was as follows: PFS, ORR, time to urinary bladder cancer symptom deterioration. PFS was analysed the same as OS. ORR was analysed by the Cochran–Mantel–Haenszel chi-squared test. For time to urinary bladder cancer symptom deterioration, the median time to deterioration was estimated using a Kaplan–Meier method. Additionally, HR and associated 95% CIs were estimated by stratified Cox's proportional hazards model with stratification variables. The Kaplan–Meier method was used to estimate the distribution of DOR.
Sample size, power calculation	Approximately 280 patients (approximately 140 patients per arm) were planned to be enrolled in Cohort 1. The final analysis was planned when approximately 208 death events occurred. The study had at least 85% power to detect an HR of 0.65 at a statistical significance level of 5% (two-sided), with one interim analysis for efficacy at an approximately 65% information fraction (approximately 136 deaths) and a final analysis.
Data management, patient withdrawals	A patient who discontinues study treatment continued to participate in the study for follow-up of survival status, subsequent anticancer therapy, EQ-5D-5L questionnaire completion, and resolution of any ongoing drug-related AEs. For patients who discontinue treatment before disease progression, every effort should be made to continue to monitor their disease status according to the Time and Events Schedule. If a patient discontinued treatment, an end-of-treatment visit was conducted 30 (+7) days after the patient's last dose of the study drug. The primary reason for treatment discontinuation was clearly documented in the patient's medical record and recorded in the eCRF. Once a patient discontinued treatment with the study drug, the patient was not permitted to be retreated. When a patient withdrew consent before completing the study, the reason for withdrawal was documented in the eCRF and in the source document. In addition, patients who withdrew consent had to complete and sign a withdrawal of consent form to specify if they agreed to have survival data collected or not. The study drug assigned to the withdrawn patient was not assigned to another patient. Patients were replaced only if the patient withdrew prior to the study drug administration.

Key: AE, adverse event; CI, confidence interval; DOR, duration of response; eCRF, electronic case report form; FGFR, fibroblast growth factor receptor; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed death-ligand 1; PFS, progression-free survival; UC, urothelial carcinoma.
Source: THOR clinical study report.[76] THOR statistical analysis plan.[79] THOR clinical protocol.[80]

B.2.4.1.3. Patient flow

Patient disposition data, which include all randomised patients enrolled in Cohort 1 of the trial, are presented in Appendix D.2. In summary, 266 patients were enrolled in the trial, of which 136 were randomly assigned to receive erdafitinib and 130 to receive chemotherapy. Of these patients, 135 and 112 patients received at least one dose of erdafitinib or chemotherapy, respectively. At the time of clinical cutoff (January 2023), 29 patients in the erdafitinib arm and 10 in the chemotherapy arm were still receiving treatment within the trial. The primary reasons for discontinuation of treatment included disease progression (erdafitinib: n = 81; chemotherapy: n = 62) and AEs (erdafitinib: n = 17; chemotherapy: n = 19). A total of 57 patients in the erdafitinib arm and 37 in the chemotherapy arm were continuing in the trial. The primary reason for discontinuation of the trial was death (erdafitinib n = 77; chemotherapy: n = 78).[76]

B.2.5. Critical appraisal of the relevant clinical effectiveness evidence

The laws and regulatory requirements of all countries that had sites participating in this study were adhered to. THOR was conducted in accordance with current International Council for Harmonisation guidelines on Good Clinical Practice, applicable regulatory and country-specific requirements, and the ethical principles originating from the Declaration of Helsinki.[5, 76]

Data quality checks were applied using manual and electronic verification methods, and an audit trail was maintained to support data query resolution and any data modification. Audits of this study were included as part of the independent quality assessment performed by the sponsor.[5, 76]

The quality assessment of the THOR trial has been conducted using the NICE Single Technology Appraisal (STA) tool.[81] Overall, the THOR study was assessed to

have a low risk of bias.[80] Full results of this assessment are presented in Appendix D.3.

B.2.6. Clinical effectiveness results of the relevant trials

B.2.6.1. THOR

B.2.6.1.1. Primary endpoint: overall survival

Table 11 presents the results for OS for Cohort 1 ITT analysis set of the THOR trial.

Erdafitinib significantly prolonged OS compared with chemotherapy.[5, 76] The median OS was 12.1 months (95% CI: 10.3, 16.4) in the erdafitinib group and 7.8 months (95% CI: 6.5, 11.1) in the chemotherapy group, representing a 36% relative reduction in the risk of death for patients treated with erdafitinib (HR: 0.64; 95% CI: 0.47, 0.88; p = 0.005).[5, 76] The estimated 6-month and 12-month survival rates for the erdafitinib group were 0.85 (95% CI: 0.77, 0.90) and 0.51 (95% CI: 0.41, 0.60), respectively, compared with 0.66 (95% CI: 0.56, 0.74) and 0.38 (95% CI: 0.28, 0.47), respectively, in the chemotherapy group.[5, 76]

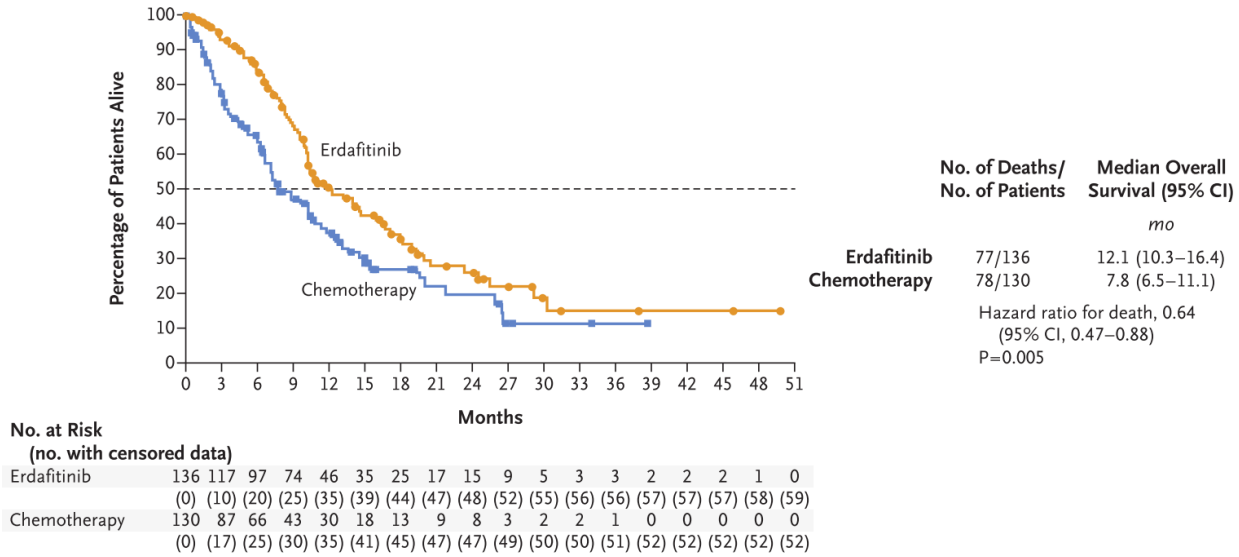
Table 11: Analysis of OS in the THOR trial (Cohort 1 ITT analysis set)

	Erdafitinib (n = 136)	**Chemotherapy (docetaxel or vinflunine; n = 130)**
Number of events (%)	77 (56.6)	78 (60.0)
Median OS, months (95% CI)	12.06 (10.28, 16.36)	7.79 (6.54, 11.07)
OS HR (95% CI)[a]	0.64 (0.47, 0.88)	
p-value[b]	0.005	
6-month survival rate (95% CI)	0.85 (0.77, 0.90)	0.66 (0.56, 0.74)
9-month survival rate (95% CI)	[redacted]	[redacted]
12-month survival rate (95% CI)	0.51 (0.41, 0.60)	0.38 (0.28, 0.47)
24-month survival rate (95% CI)	[redacted]	[redacted]
Key: CI, confidence interval; HR hazard ratio; ITT, intention-to-treat; OS, overall survival.		

	Erdafitinib (n = 136)	Chemotherapy (docetaxel or vinflunine; n = 130)
Notes [a] HR and 95% CI are estimated using a Cox proportional hazards regression model, with treatment as the only explanatory variable. An HR < 1 indicates longer survival time in the erdafitinib arm compared with the chemotherapy (vinflunine or docetaxel) arm. [b] p-value is two-sided and based on a log-rank test. **Source:** Loriot et al. (2023);[5] THOR clinical study report.[76]		

The Kaplan–Meier curve of OS is presented in Figure 4. The curves demonstrate an early and sustained separation, reflecting a persistent OS benefit with erdafitinib compared with chemotherapy.[5]

Figure 4: Kaplan–Meier plot of OS (Cohort 1 ITT analysis set)



Key: CI, confidence interval; ITT, intention-to-treat; mo, months; OS, overall survival.
Notes: Circles and squares indicate censored data in the erdafitinib and chemotherapy groups, respectively.
Source: Loriot et al. (2023).[5]

B.2.6.1.2. Secondary endpoints

B.2.6.1.2.1. Progression-free survival (key secondary endpoint)

Table 12 presents the results for PFS for Cohort 1 ITT analysis set of the THOR trial.

A statistically significant improvement in PFS was observed in the erdafitinib group compared with the chemotherapy group.[5, 76] The median PFS was 5.6 months (95% CI: 4.4, 5.7) in the erdafitinib group and 2.7 months (95% CI: 1.8, 3.7) in the chemotherapy group, representing a 42% relative reduction in the risk of disease progression or death (HR: 0.58; 95% CI: 0.44, 0.78; p = 0.0002).[5, 76] These results represent an approximately two-fold higher PFS for the erdafitinib treatment group versus the chemotherapy treatment group.

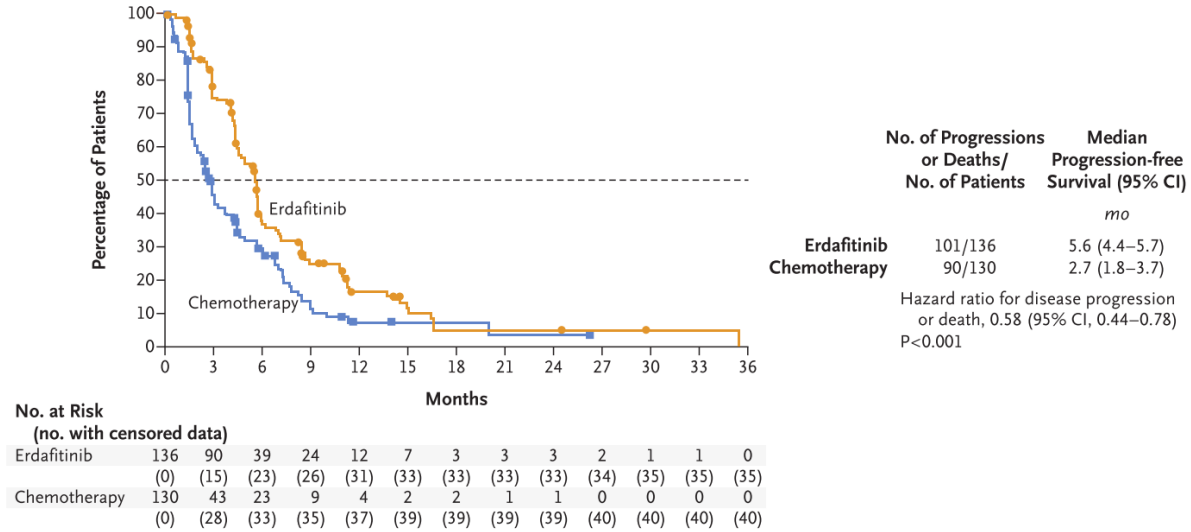
Table 12: Analysis of PFS in the THOR trial (Cohort 1 ITT analysis set)

	Erdafitinib (n = 136)	**Chemotherapy (n = 130)**
Number of events, n (%)	101 (74.3)	90 (69.2)
Median PFS, months (95% CI)	5.55 (4.40, 5.65)	2.73 (1.81, 3.68)
PFS HR (95% CI)[a]	0.58 (0.44, 0.78)	
p-value[b]	0.0002	
6-month survival rate, n (95% CI)	[redacted]	[redacted]
9-month survival rate (95% CI)	[redacted]	[redacted]
12-month survival rate (95% CI)	[redacted]	[redacted]
24-month survival rate (95% CI)	[redacted]	[redacted]

Key: CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.
Notes: [a] HR and 95% CI are estimated using a Cox proportional hazards regression model with treatment as the explanatory variable. An HR < 1 indicates longer survival time in the erdafitinib arm compared with the chemotherapy (vinflunine or docetaxel) arm. [b] p-value is two-sided and is based on a log-rank test.
Source: Loriot et al. 2023[5] and THOR clinical study report.[76]

As presented in Figure 5, the Kaplan–Meier curves for erdafitinib and chemotherapy separate early and remain separated until 16 months, where the curves begin to plateau for both treatment arms and the curves start to overlap, although the numbers at risk are very low in this part of the Kaplan–Meier plot.[5, 76]

Figure 5: Kaplan–Meier plot of PFS (Cohort 1 ITT analysis set)



Key: CI, confidence interval; ITT, intention-to-treat; mo, months; PFS, progression-free survival.
Source: Loriot et al. (2023).[5]

B.2.6.1.2.2. Objective response rate (key secondary endpoint)

The results for ORR per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 by investigator assessment for Cohort 1 ITT analysis set of the THOR trial are presented in Table 13 and Figure 6.

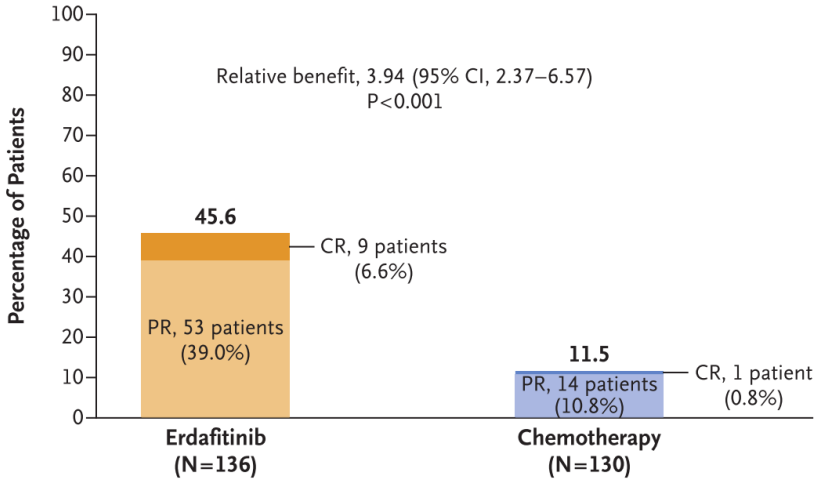
Erdafitinib provides a statistically significant improvement in ORR compared with chemotherapy. [5, 76] The percentage of patients with an ORR according to investigator assessment was higher in the erdafitinib group compared with the chemotherapy group (45.6% versus 11.5%, respectively). The difference in ORR between treatment groups was statistically significant (observed relative risk of 3.94 [95% CI: 2.37, 6.57]; 2-sided $p < 0.001$), based on a 2-sided and multiplicity-adjusted significance level of 0.019. These results represent an approximately four-fold higher probability of achieving an objective response for the erdafitinib treatment group versus the chemotherapy treatment group. [5, 76]

Table 13: Analysis of ORR in the THOR trial (Cohort 1 ITT analysis set)

	Erdafitinib (n = 136)	Chemotherapy (n = 130)
ORR, n (%)	62 (45.6)	15 (11.5)
Relative risk (95% CI)	3.94 (2.37, 6.57)	
p-value[a]	< 0.001	
BOR, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
SD[b]	[redacted]	[redacted]
PD	[redacted]	[redacted]
NE	[redacted]	[redacted]
DCR, n (%)	[redacted]	[redacted]
Relative risk (95% CI)	[redacted]	
p-value[a]	< 0.001	

Key: BOR, best overall response; CI, confidence interval; CR, complete response; DCR, disease control rate; ITT, intention-to-treat; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
Notes: [a] All p-values are two-sided. [b] Minimum duration requirement for SD is 6 weeks from the date of randomisation. SD includes patients with no measurable disease at baseline and their best response was non-CR/non-PD. ORR: relative risk > 1 indicates that the probability of achieving an objective response (PR or CR) is higher on the erdafitinib arm compared with the chemotherapy arm. DCR: relative risk > 1 indicates that the probability of achieving a response of SD or better is higher on the erdafitinib arm compared with the chemotherapy arm.
Source: Loriot et al. (2023);[5] THOR clinical study report.[76]

Figure 6: Graphical representation of ORR of the THOR trial (Cohort 1 ITT analysis set)



Key: CI, confidence interval; CR, complete response; ITT, intention-to-treat; ORR, objective response rate; PR, partial response.
Source: Loriot et al. (2023).[5]

Additionally, 36.8% of patients in the erdafitinib group and 31.5% of patients in the chemotherapy group achieved a best response of stable disease (SD) for at least one disease evaluation period (> 6 weeks), contributing to an overall disease control rate (DCR) (complete response [CR] + partial response [PR] + SD) of 82.4% in the erdafitinib group and 43.1% in the chemotherapy group.[76] The DCR was numerically higher for erdafitinib compared with chemotherapy, with a relative risk of 1.91 (95% CI: 1.55, 2.35).[76]

B.2.6.1.2.3. Duration of response

The results for DOR determined by the investigator are presented in Table **14** and Figure 7. Patients treated with erdafitinib had a numerically shorter DOR compared with patients treated with chemotherapy (HR: 0.85; 95% CI: 0.43, 1.66).[5, 76] The median DOR was 4.9 months (95% CI: 3.8, 7.5) for the erdafitinib arm and 5.6 months (95% CI: 2.1, 6.0) for the chemotherapy arm. [5, 76] Of note, the DOR of the chemotherapy group was evaluated based on a much smaller number of responders (CR + PR; n = 15) compared with the erdafitinib group (n = 62). Analyses of the DOR in patients with a CR were consistent with these results.[5, 76]

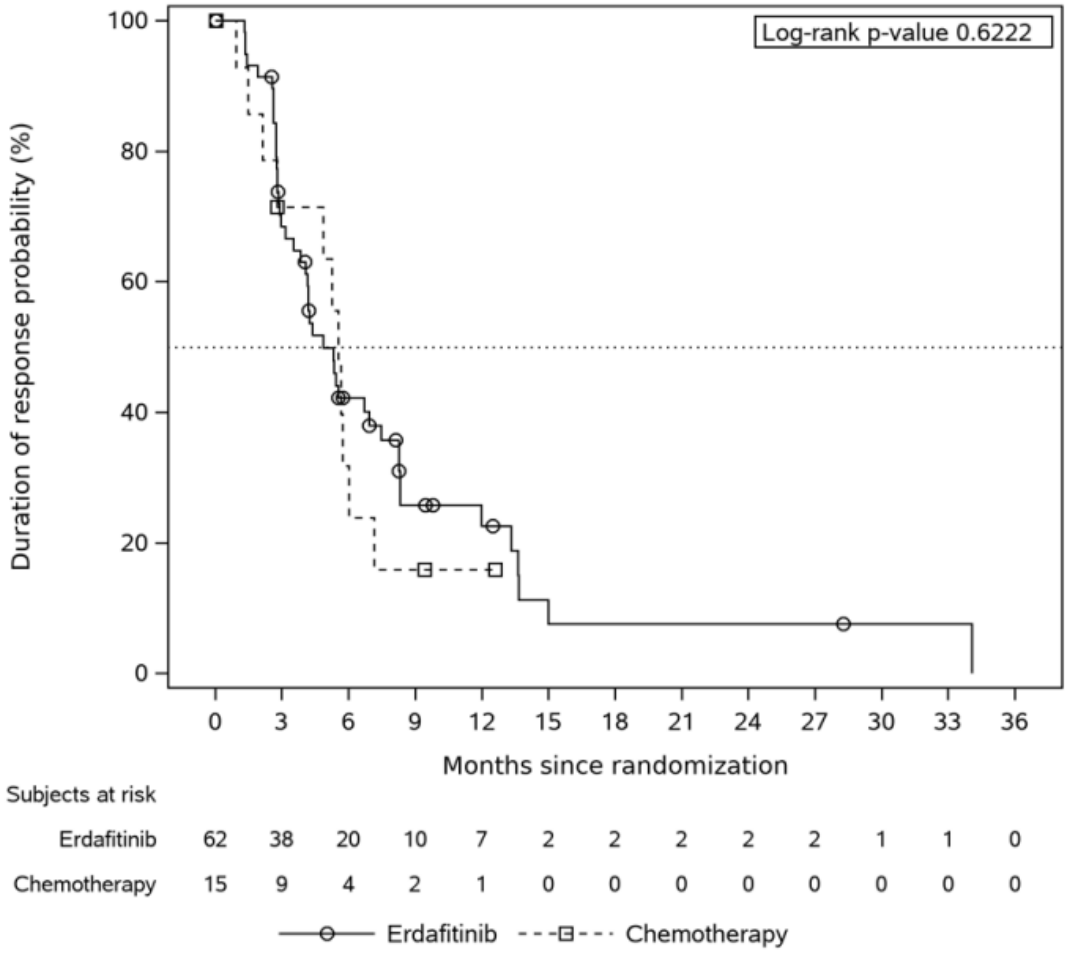
Table 14: Analysis of DOR in the THOR trial (Cohort 1 ITT analysis set)

	Erdafitinib (n = 62)	**Chemotherapy (n = 15)**
DOR		
Number of events, n (%)	[redacted]	[redacted]
Number censored, n (%)	[redacted]	[redacted]
Started subsequent anticancer therapy	[redacted]	[redacted]
No progression until data cut-off	[redacted]	[redacted]
Kaplan–Meier estimates (months)		
25% percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	4.86 (3.84, 7.46)	5.55 (2.14, 6.01)
75% percentile (95% CI)	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
6-month survival rate (95% CI)	[redacted]	[redacted]
9-month survival rate (95% CI)	[redacted]	[redacted]
12-month survival rate (95% CI)	[redacted]	[redacted]
24-month survival rate (95% CI)	[redacted]	[redacted]

	Erdafitinib (n = 62)	Chemotherapy (n = 15)
HR (95% CI)[a]	0.85 (0.43, 1.66)	
p-value[b]	0.6222	

Key: CI, confidence interval; DOR, duration of response; HR, hazard ratio; ITT, intention-to-treat; NE, not evaluable.
Notes: [a] HR and 95% CI are estimated using a Cox proportional hazards regression model with treatment as the explanatory variable. An HR < 1 indicates longer DOR in the erdafitinib arm as compared with the chemotherapy (vinflunine or docetaxel) arm. [b] p-value is two-sided and is based on a log-rank test. + Indicates censored observation.
Source: Loriot et al. (2023);[5] THOR clinical study report.[76]

Figure 7: Kaplan–Meier plot of DOR (Cohort 1; ITT analysis set)



Key: DOR, duration of response; ITT, intention-to-treat.
Source: THOR clinical study report.[76]

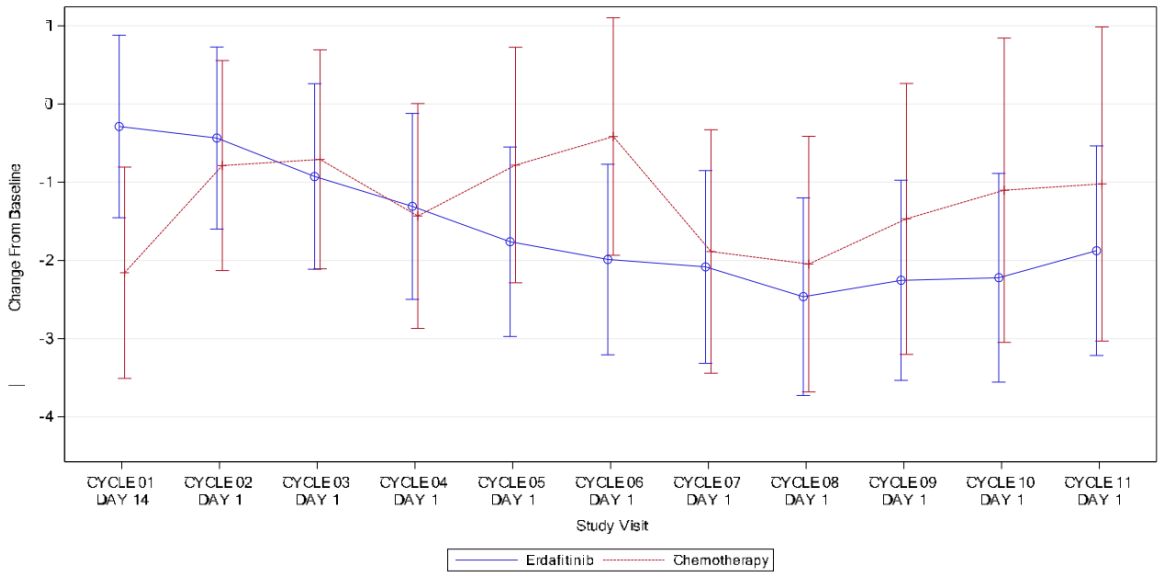
B.2.6.1.2.4. *HRQL PRO compliance*

There was high PRO compliance (>80%) at baseline with FACT-BI, EQ-5D-5L and PGIS assessments and for most treatment cycles through to Cycle 10 for both treatment groups.[76] Compliance rates were more variable at later cycles (Cycle 11 onwards) due to smaller sample sizes, largely caused by disease progression or death, particularly in the chemotherapy group.[76]

Change from baseline over time

Baseline scores for the Functional Assessment of Cancer Therapy – Bladder Cancer (FACT-BI) assessment were similar across treatment groups.[76] Mixed models for repeated measures (MMRM) analyses were conducted to evaluate change from baseline in FACT-BI scores at each scheduled visit through Cycle 11 between the two treatment groups. Results from the FACT-BI assessment (domains and total scores) in Cohort 1 showed that HRQL was maintained on treatment across all five primary domains of physical, social, emotional, functional well-being and total scores. There were few differences in physical well-being domain between treatment groups, as shown in Figure 8.

Figure 8: Change from baseline in FACT-BI scores (physical well-being domain) with erdafitinib and chemotherapy (Cohort 1; ITT analysis set)



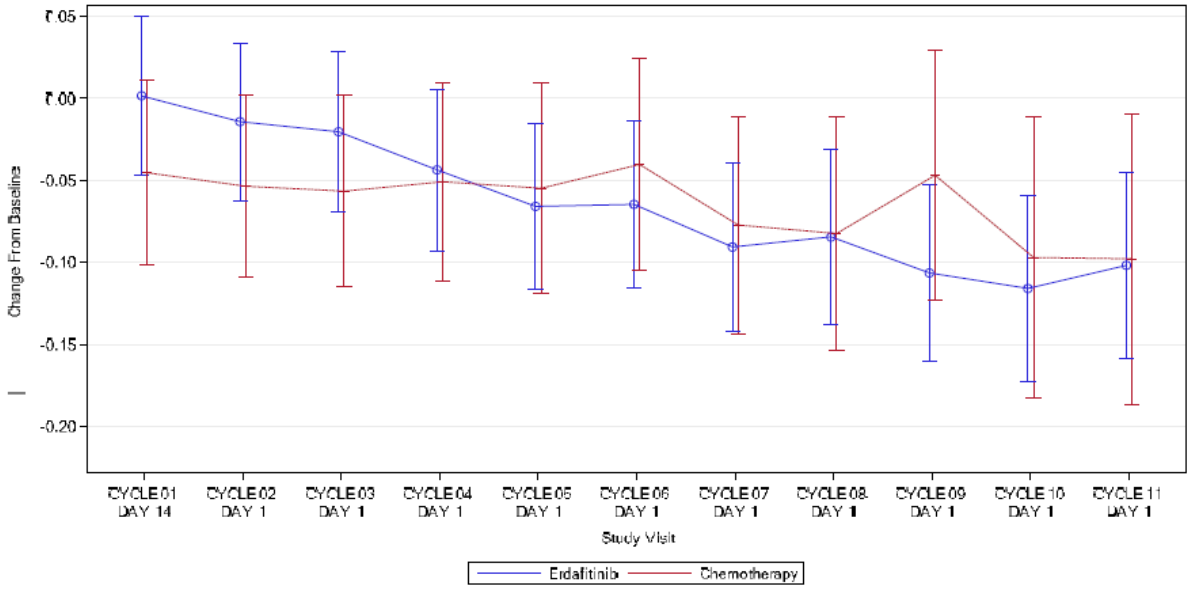
Key: FACT-BI, Functional Assessment of Cancer Therapy – Bladder; ITT, intention-to-treat.

Source: THOR clinical study report.[76]

Baseline scores for the EQ-5D-5L health utility index and Visual Analogue Scale assessment were similar across treatment groups.[76] MMRM analyses of change from baseline to Cycle 11 in EQ-5D-5L health utility index and Visual Analogue Scale assessment showed that general HRQL and overall health status were maintained on treatment. The changes form baseline in EQ-5D-5L health utility index in patients who received erdafitinib and chemotherapy are presented in

Figure 9.

Figure 9: Change from baseline in EQ-5D-5L HUI scores with erdafitinib and chemotherapy (Cohort 1; ITT analysis set)



Key: FACT-BI, Functional Assessment of Cancer Therapy – Bladder; HUI, health utility index; ITT, intention-to-treat.

Source: THOR clinical study report[76]

The PGI-S scale is a single item that was used as an in-trial global anchor to calculate a minimally important difference for urinary bladder cancer symptom score. Further information on the proportion of change from baseline in PGIS score from baseline is presented in the clinical study report. [76]

Time to urinary bladder cancer symptom deterioration

Analysis of time to urinary bladder cancer symptom deterioration (based on the urinary bladder cancer symptoms score from three items (urinary incontinence, frequency and pain on the FACT-BI assessment) showed no statistically significant difference in time to first clinically meaningful urinary symptom deterioration for patients treated with erdafitinib versus chemotherapy (HR: [redacted]), based on a two-sided significance level of 0.019.76 The median time to urinary bladder cancer symptom deterioration was [redacted]

[redacted] in the erdafitinib group and [redacted] in the chemotherapy group. Of note, this endpoint was impacted by heavy and imbalanced censoring in the chemotherapy group, leading to increased variability and wide CIs.[76]

B.2.6.1.3. Subsequent therapies

Table 15 presents a summary of the subsequent therapies used for patients in Cohort 1 ITT analysis set of the THOR trial.

The proportion of patients who received subsequent therapies was similar in both treatment groups (32.4% in the erdafitinib group and 36.9% in the chemotherapy group).[5] The subsequent therapies used include chemotherapy (erdafitinib group: 15.4%; chemotherapy group: 16.2%), and antibody–drug conjugates (ADCs) (erdafitinib group: 16.2%; chemotherapy group: 10.8%). Of these, the most commonly used antibody–drug conjugate was enfortumab vedotin (erdafitinib group: 14.0%; chemotherapy group: 10.0%). Patients also received subsequent immunotherapy, specifically CPIs (erdafitinib group: 6.6%; chemotherapy group: 6.9%), and FGFR inhibitors (erdafitinib group: 2.2%; chemotherapy group: 7.7%). Of these, six patients in the chemotherapy group received erdafitinib.[5]

The subsequent treatment distribution was considered balanced, for subsequent chemotherapy, ADC and CPI's, the use was considered equal. The THOR trial confirmed the insights that were gathered from the UK RW mUC study, demonstrating that only a small proportion of patients receive subsequent active treatment in the 2L+ setting and this was also confirmed by UK clinicians.[20, 25, 26] For further information on rationale for the subsequent treatment costs used in the base case analysis, refer to Section B.3.5.4.1.

Table 15: Subsequent treatments from THOR

Subsequent therapy, n (%)	**Erdafitinib (n = 136)**	**Chemotherapy (n = 130)**
Any subsequent therapy[a]	44 (32.4)	48 (36.9)
Number of subsequent therapy lines		
1	33 (24.3)	40 (30.8)

Subsequent therapy, n (%)	Erdafitinib (n = 136)	Chemotherapy (n = 130)
2	9 (6.6)	8 (6.2)
3	0 (0.0)	0 (0.0)
> 3	2 (1.5)	0 (0.0)
Chemotherapy	21 (15.4)	21 (16.2)
Carboplatin	8 (5.9)	9 (6.9)
Gemcitabine	6 (4.4)	10 (7.7)
Paclitaxel	8 (5.9)	6 (4.6)
Docetaxel	4 (2.9)	2 (1.5)
Vinflunine	4 (2.9)	0
Cisplatin	0	2 (1.5)
Methotrexate	0	2 (1.5)
Pemetrexed	2 (1.5)	0
Doxorubicin	0	1 (0.8)
Vinblastine	0	1 (0.8)
Immunotherapy	9 (6.6)	9 (6.9)
Pembrolizumab	4 (2.9)	4 (3.1)
Atezolizumab	2 (1.5)	2 (1.5)
Tislelizumab	1 (0.7)	2 (1.5)
Nivolumab	1 (0.7)	1 (0.8)
Avelumab	1 (0.7)	0
FGFR inhibitors	3 (2.2)	10 (7.7)
Erdafitinib	0	6 (4.6)
Derazantinib	3 (2.2)	2 (1.5)
Pemigatinib	0	2 (1.5)
Antibody–drug conjugate	22 (16.2)	14 (10.8)
Enfortumab vedotin	19 (14.0)	13 (10.0)
Sacituzumab govitecan	3 (2.2)	0
Disitamab vedotin	0	1 (0.8)
Other systemic therapy	2 (1.5)	1 (0.8)
Sitravatinib	1 (0.7)	1 (0.8)
Lenvatinib	1 (0.7)	0
Investigational systemic therapy	0	3 (2.3)

Key: FGFR, fibroblast growth factor receptor.
Notes: [a] Patients may have received > 1 subsequent therapy.
Source: Loriot et al. (2023);[5] THOR clinical study report.[76]

B.2.6.2. BLC2001

The BLC2001 trial is a Phase II trial of erdafitinib in patients with metastatic or surgically unresectable UC with *FGFR* alterations. It assessed the long-term efficacy and safety of erdafitinib of the selected regimen of once-daily 8 mg erdafitinib with provision for pharmacodynamically guided up-titration to 9 mg/day.[6] The results presented in this section are based on final analysis and focus on the results from the 8 mg daily regimen.[77] As of the cut-off date for the end of final analysis (27 July 2021), all patients had discontinued treatment. The median survival follow-up was 50.3 months for the 8 mg daily regimen.[77]

The investigator-assessed ORR met the primary objective, with the lower bound of the 95% CI >25%.[6] The confirmed ORR by investigator assessment was 39.6% (95% CI: 30.1%, 49.1%) for the primary efficacy population and 39.3% (95% CI: 29.2%, 49.5%) for the chemo-relapsed/refractory population, compared with an ORR of 40.4% (95% CI: 30.7%, 50.1%) and 40.2% (95% CI: 29.9%, 50.5%), respectively, at the primary analysis.[77] In addition, 41% of patients achieved a best response of SD, contributing to an overall DCR (CR + PR + SD) of 80.2% (95% CI: 72.4%, 88%) for the primary efficacy population and of 79.8% (95% CI: 71.4%, 88.1%) for the chemo-relapsed/refractory population.[77] The responses were durable, with a median DOR of 5.98 months (95% CI: 4.24, 7.52) for the primary efficacy population and 5.59 months (95% CI: 4.21, 7.23) for the chemo-relapsed/refractory population.[6, 77]

With a median efficacy follow-up of 48.16 months for the end of main study analysis, median PFS was 5.52 months (95% CI: 4.34, 5.95) for the primary efficacy population. The estimated 6-month, 12-month and 24-month PFS rates were 40%, 21% and 9%, respectively.[77] For the chemo-relapsed/refractory population, the median PFS was 5.50 months (95% CI: 3.98, 5.65), and the estimated 6-month, 12-month and 24-month PFS rates were 36%, 16% and 7%, respectively.[77]

The median OS of the primary efficacy population was 11.30 months (95% CI: 9.69, 15.15 months), and the 12-month and 24-month survival rates were 49% and 30%, respectively.[77] The median OS of the chemo-relapsed/refractory population was

10.58 months (95% CI: 8.97, 14.72 months), and the 12-month survival rate was 46%.[77]

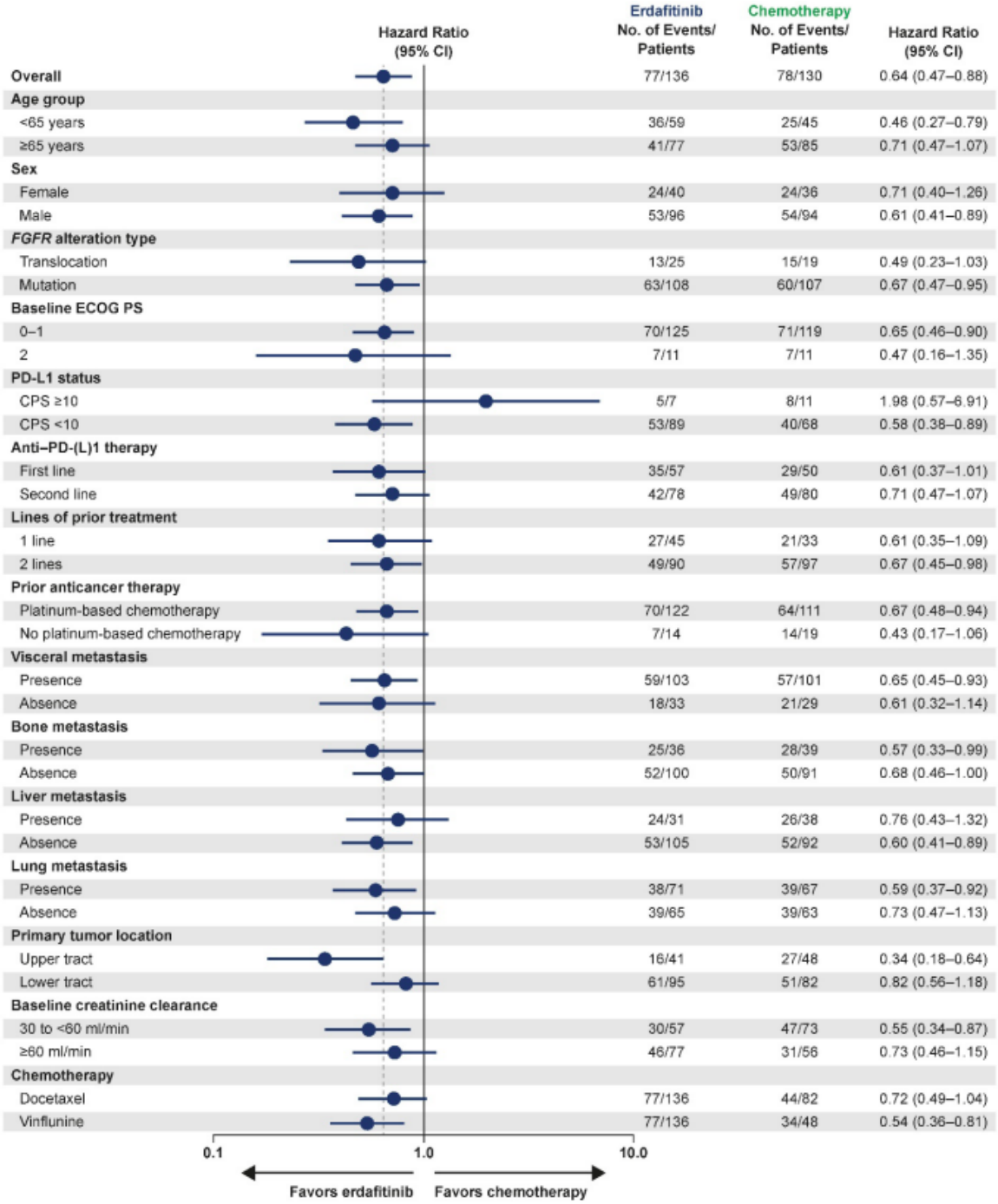
Further details on BLC2001 are presented in Appendix N.

B.2.7. Subgroup analysis

Subgroup analyses of the THOR trial were conducted to assess efficacy consistency across patient populations with different demographics or baseline characteristics.[76] Figure 10 presents the forest plot for OS by subgroups. The OS benefit of erdafitinib was consistently reflected in the results of the subgroup analyses by prior line of therapy, by prior line of anti-PD-(L)1 therapy, by type of prior therapy (i.e. with and without prior platinum-based chemotherapy, as well as with prior cisplatin-based and carboplatin-based chemotherapy), and by type of chemotherapy (docetaxel or vinflunine).

For the key secondary endpoints, PFS and ORR, the clinical benefit of erdafitinib compared with chemotherapy was generally consistent across various prespecified subgroups.[5] Further information on subgroup analyses is presented in Appendix E.

Figure 10: Forest plot of OS hazard ratio by subgroup factors



Key: CI, confidence interval; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; *FGFR*, fibroblast growth factor receptor; OS, overall survival; PD-(L)1, programmed death-ligand 1.
Source: Loriot et al. (2023).[5] Lines of prior treatment, prior anticancer therapy, and chemotherapy were not pre-specified subgroup analysis (for reference see SAP).

As discussed in Section B.1.3.5.2, neither vinflunine nor docetaxel are used in UK clinical practice, although, docetaxel is reimbursed in the UK.[22, 26, 59] The type of chemotherapy was not part of a pre-specified sub-group analyses, a post hoc analysis of OS for erdafitinib compared with the individual chemotherapies was conducted; it found that OS was consistent based on HR, with wide 95% CIs (docetaxel: 0.72 (0.49 – 1.04) and vinflunine: 0.54 (0.36 – 0.81; see Figure 10) and strong overlap with the primary analysis of erdafitinib compared with the full chemotherapy arm. However, as these analyses were defined post hoc, the study was not powered to detect differences between the individual treatment groups.[76]

As outlined in Section B.2.3.1.3, there are some limitations with the vinflunine and docetaxel subgroup analyses, including an imbalance of some baseline patient demographics and disease characteristics. For example, the docetaxel group had fewer white patients compared with the erdafitinib group (38% versus 60%, respectively), which has been demonstrated to be a confounder for OS.[76]

The primary and secondary efficacy results by individual chemotherapy are presented in Table 16. The median OS remains consistent; however, the 95% CIs are wide. This can be attributed to the relatively smaller sample size. Next to that, by individual assessment, the power of randomisation is lost because the chemotherapy arms were defined by physicians' choice. Despite the limited number of patients in each group, it is anticipated that the effectiveness of vinflunine and docetaxel will not significantly differ, as there are minimal distinctions between the two treatments. The HR or RR for OS, PFS and ORR are in close proximity to each other and the 95% CI exhibit significant overlap. However, an adjusted analysis incorporating ECOG PS, haemoglobin levels and race as confounders, comparing erdafitinib with docetaxel resulted in an OS HR of 0.66 (95% CI 0.45-0.96), demonstrating the robustness of the erdafitinib efficacy results.

Table 16: THOR primary and key secondary efficacy results by chemotherapy type

	Erdafitinib (n = 136)	Docetaxel (n = 82)	Vinflunine (n = 48)	Chemotherapy (n = 130)
OS				
Number of events (%)	77 (56.6%)	44 (53.7%)	34 (70.8%)	78 (60.0%)
Median, months (95% CI	12.06 (10.28, 16.36)	8.74 (6.08, 13.60)	7.56 (4.04, 10.35)	7.79 (6.54, 11.07)
HR (95% CI)	-	0.72 (0.49, 1.04)	0.54 (0.36, 0.81)	0.64 (0.47, 0.88)
PFS				
Number of events (%)	101 (74.3%)	52 (63.4%)	38 (79.2%)	90 (69.2%)
Median, months (95% CI)	5.55 (4.40, 5.65)	2.37 (1.51, 3.06)	3.58 (1.64, 5.78)	2.73 (1.81, 3.68)
HR (95% CI)	-	0.54 (0.39, 0.76)	0.64 (0.44, 0.93)	0.58 (0.44, 0.78)
ORR				
CR (%)	9 (6.6%)	1 (1.2%)	0	1 (0.8%)
PR (%)	53 (39.0%)	7 (8.5%)	7 (14.6%)	14 (10.8%)
ORR (CR + PR)	62 (45.6%)	8 (9.8%)	7 (14.6%)	15 (11.5%)
RR, (95% CI)	-	4.67 (2.36, 9.26)	3.13 (1.54, 6.35)	3.94 (2.37, 6.57)

Key: CI, confidence interval; CR, complete response; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RR,relative risk.
Source: THOR clinical study report.[76]

In summary, caution should be exercised when reviewing the primary and secondary efficacy in chemotherapy subgroups. The design of the study did not specifically aim to assess treatment effects in these subgroups, and the number of patients included in each subgroup was limited. Consequently, the individual comparisons within these subgroups cannot be considered informative or suitable for making decisions. As discussed earlier, vinflunine is not reimbursed and docetaxel is used in a very limited capacity, and paclitaxel ± carboplatin is considered the relevant chemotherapy after exposure to anti-PD-(L)1 therapy in England. Therefore, the Johnson & Johnson - initiated RW study conducted in England represents the most reliable evidence available for this submission, as it reflects current clinical practice.[20]

B.2.8. Meta-analysis

No other relevant studies supporting the use of erdafitinib or relevant comparators for the treatment of patients with unresectable or metastatic UC and susceptible *FGFR* alterations who had progressed on or after prior treatment with a PD-(L)1 have been identified for inclusion in a meta-analysis. Therefore, a meta-analysis is not required.

B.2.9. Indirect and mixed treatment comparisons

Paclitaxel ± carboplatin is the relevant comparator in the UK setting. The comparator arm of THOR comprises of global treatment options, including vinflunine and docetaxel. Vinflunine is not reimbursed in the UK, and docetaxel is reimbursed but not recommended in NICE guidelines nor widely used (Section B.1 and B.2). An ITC is required in the absence of head-to-head clinical trial data for erdafitinib versus current practice in the UK. This has been considered following NICE Decision Support Unit (DSU) Technical Support Documents (TSD) 17 and 18.[82, 83]

As described in Section B.2.1, the SLR did not identify any relevant clinical trials demonstrating the safety or efficacy of comparators for erdafitinib in the context of the decision problem for this appraisal (i.e., [redacted]).

B.2.9.1. Base case analysis

Within the context of the limited evidence base for paclitaxel ± carboplatin, Johnson and Johnson initiated a RW study of clinical practice in mUC in England.[20] The methodological approach and data collection underpinning this study are described in Appendix O. The objective of the registry study was to source high-quality data on comparators that reflect UK clinical practice within the context of the decision problem for this appraisal. Linked datasets available through the NCRAS, including the Systemic Anti-Cancer Therapy (SACT) dataset and Hospital Episode Statistics (HES) dataset, were considered. The study cohort reflects the RW population that is likely to receive erdafitinib in UK clinical practice, and the study provides the best

data source. These datasets are mentioned in the NICE RWE framework as useful sources of data for the UK that are widely used by NICE.[84]

The study was designed to focus on the primary and secondary endpoints aligned to the THOR trial (OS and PFS). Since PFS data are not available in the NCRAS datasets, time to next treatment (TTNT) data were collected, as a potential proxy for PFS for paclitaxel ± carboplatin. Conducting this study provided individual patient-level data (IPD) for paclitaxel ± carboplatin, which allowed for more comprehensive ITC approaches to be explored compared with when only aggregate data are available for the comparator arm (commonplace in NICE technology appraisals), as suggested in NICE DSU TSD 17.[83]

Full details of the ITC are given in Appendix P. The ITCs of erdafitinib against paclitaxel ± carboplatin were carried out using individual patient-level data (IPD) from the enrolled erdafitinib arm of THOR (n = 126) and the real-world mUC cohort for participants who received paclitaxel ± carboplatin after prior exposure to PD-(L)1 inhibitors (n = 72). Full details of the methodology for the indirect comparison including a detailed assessment of data suitability that include provenance, quality, and relevance are provided in Appendix P. The following seven patient characteristics were available for the analysis from the UK RW mUC study:

- Number of prior lines of therapy: categorised as 1 line or 2 lines.
- ECOG PS: 0 or 1-2
- Tumour location: upper or lower
- Age group at diagnosis: <65 or ≥65 years of age
- Sex
- Tumour stage at diagnosis: 1-2 or 3-4
- Cisplatin ineligibility

The data sources for the intervention and comparators reflect different settings (clinical trial vs. real-world practice). As such there is heterogeneity between study populations in terms of baseline variables, some of which are prognostic. Unlike THOR, the UK RW mUC study did not restrict inclusion criteria to patients with an

ECOG PS of 0-2. Although ECOG PS is one of the most commonly used clinical trial eligibility criteria, it is not routinely submitted by NHS Trusts to the cancer registry, and therefore a number of patients in the UK RW mUC study have missing values. In the paclitaxel ± carboplatin cohort, ECOG PS was missing for 41 patients (56.9%). In the erdafitinib arm from THOR, tumour stage at diagnosis was missing for 34 patients (27.0%). Imputation of missing values was considered inappropriate, as the missingness criteria of the data was deemed not missing at random. In addition, ECOG PS score determined at diagnosis was reported in the real-world dataset, whereas in the THOR trial it was determined at enrolment.

In order to preserve the sample size, a worst-case scenario approach was used to handle missing data. Specifically, it was assumed that patients with missing ECOG PS scores were assigned values ranging from 1 to 2, and those with missing tumour stage at diagnosis were assigned Stage 3 to 4. This conservative approach was selected as it considers the comparison involving upweighting of the worst patients in terms of erdafitinib treatment, who had poorer ECOG PS and higher tumour stage compared to the patients enrolled in the THOR study (i.e., a conservative scenario which assumes the best characteristics for the comparator and worst for erdafitinib – the base case of this submission). These assumptions may align with clinical practice, as clinicians have indicated that the UK patient population receiving second-line chemotherapy typically have an ECOG PS of 2. Furthermore, a scenario analysis was conducted by restricting the sample size to patients with available ECOG PS scores and tumour stage at diagnosis, resulting in reduced sample sizes in both datasets.

Erdafitinib patients in THOR had more often received 2 prior lines of therapy (66.7% vs 50.0%) and more had ECOG PS of 0 (45.2% vs 29.2%) compared to the UK RW mUC study as shown in Appendix P Table 28. Age at diagnosis, sex, tumour location, stage at diagnosis and the proportion of patients deemed cisplatin eligible were comparable between the two data sets. Baseline characteristics between the erdafitinib trial population and UK RW mUC cohort were balanced using propensity score reweighting with respect to prognostic factors that were available to both datasets. Three statistical approaches, including regression adjustment, the inverse

probability weighting method, and the doubly robust estimator, were employed to analyse the data. These exploratory analyses were conducted as a means to examine the potential variability and uncertainty that may arise from the selection of different analytical methods.

The results of the ITC are summarised in

Table 17, Figure 11 and

Figure **12**, which show the estimates of the effect of erdafitinib relative to paclitaxel ± carboplatin before and after adjustment. Based on the average treatment effect for the control (ATC)-adjusted results, erdafitinib is estimated to reduce the risk of death by 65% (HR: 0.35; 95% CI: 0.23, 0.52) compared with paclitaxel ± carboplatin, with a median OS of 10.6 months (95% CI: 9.5, 16.7) for erdafitinib and 6.5 months (95% CI: 4.9, 7.0) for paclitaxel ± carboplatin. Erdafitinib also likely improves the risk of progressing to next treatment or death (using TTNT) by 67% (HR: 0.33; 95% CI: 0.22, 0.50) in the base case analysis using the ATC method, with a median TTNT of 10.2 months (95% CI: 9.3, 13.9) for erdafitinib and 5.4 months (95% CI: 3.7, 6.8) for paclitaxel ± carboplatin.

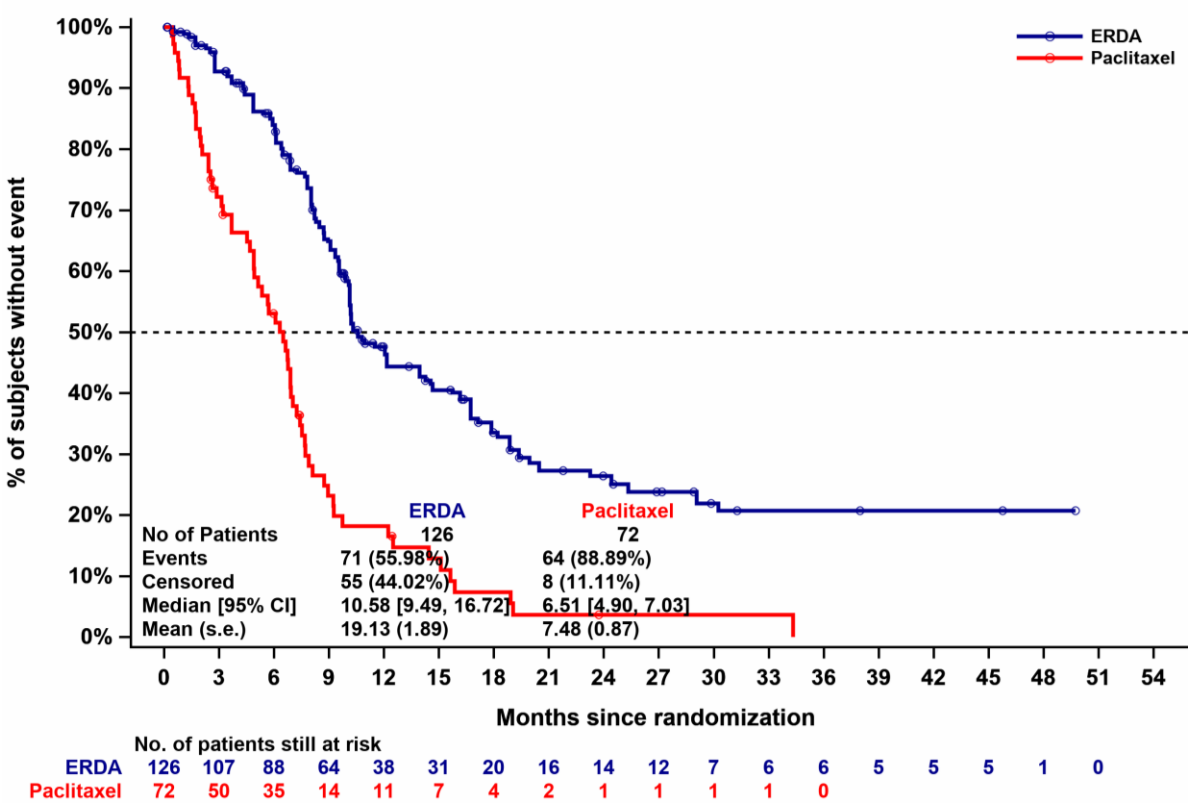
These results show that the unadjusted estimates of the relative effectiveness were consistent across all analyses against erdafitinib, irrespective of the adjustment method used (covariate adjustment or inverse probability of treatment weighting) and irrespective of the weighing approach applied if using inverse probability of treatment weighting. Moreover, the HRs remained consistent when either average treatment effect for the treated (ATT) weights or average treatment effect for the control (ATC) weights were applied. This suggests that there is no significant interaction between the treatment effect and the characteristics of the population under investigation. The observed consistency demonstrates the robustness of the results, with limited uncertainty associated with the choice of methods. Full details of the results, including all relevant exploratory scenario of limiting the analysis to complete cases, are provided in Appendix P.

Table 17: Summary of results of the ITC (THOR and UK RW mUC study)

Comparison	OS HR (95% CI)	p-value	TTNT HR (95% CI)	p-value
Unadjusted comparison	0.33 (0.24–0.47)	<0.0001	0.32 (0.23–0.45)	<0.0001
Adjusted comparisons				
Covariate adjustment	0.37 (0.26–0.54)	<0.0001	0.34 (0.23–0.48)	<0.0001
Weighting				
ATT	0.32 (0.21–0.48)	<0.0001	0.31 (0.20–0.48)	<0.0001
ATC (**base case**)	0.35 (0.23–0.52)	<0.0001	0.33 (0.22–0.50)	<0.0001
ATO	0.36 (0.24–0.52)	<0.0001	0.35 (0.24–0.52)	<0.0001
ATE	0.33 (0.22-0.48)	<0.0001	0.34 (0.23-0.48)	<0.0001

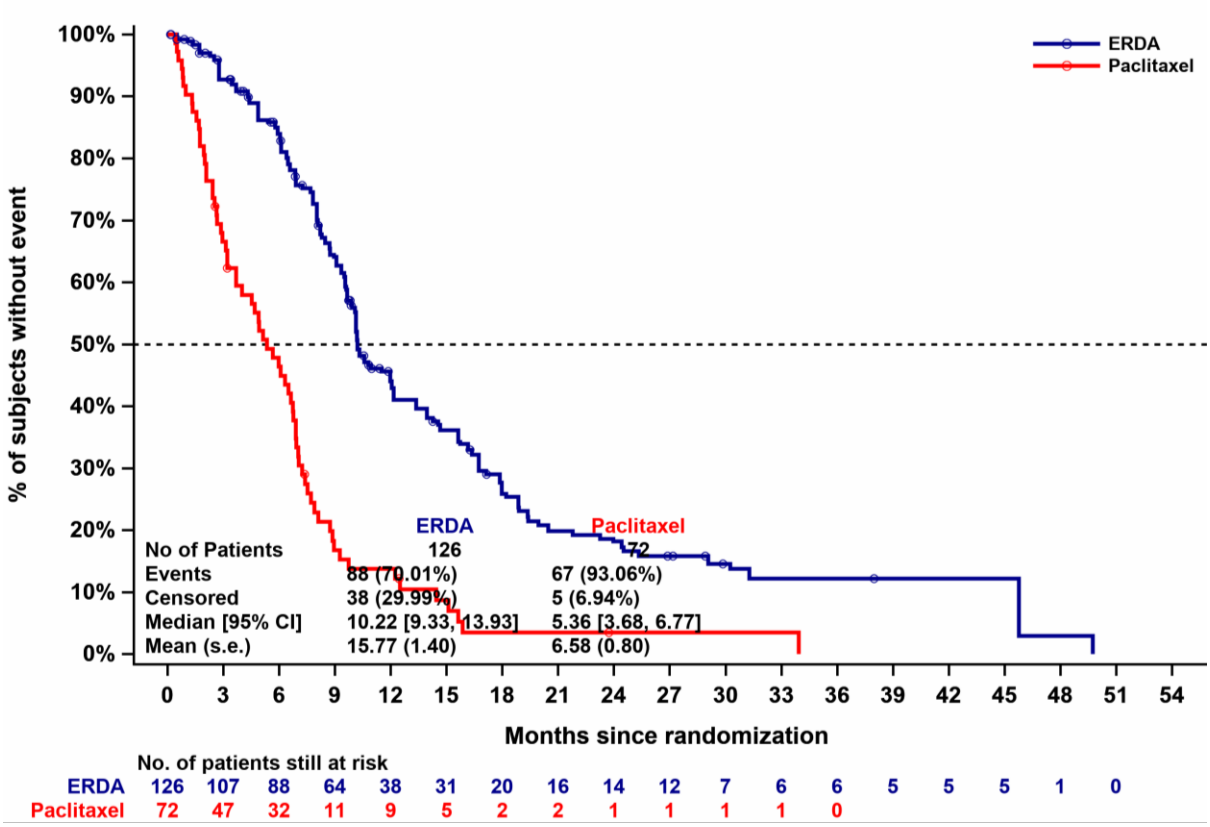
Key: ATE, average treatment effect; ATC, average treatment effect for the control; ATO, average treatment effect for overlap; ATT, average treatment effect for the treated; CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; mUC, metastatic urothelial carcinoma; OS, overall survival; RW, real world; TTNT, time to next treatment.

Figure 11: Kaplan–Meier curve for ATC-adjusted OS comparison for erdafitinib versus paclitaxel



Key: ATC, average treatment effect for the control; ERDA, erdafitinib; OS, overall survival; Paclitaxel, paclitaxel ± carboplatin.

Figure 12: Kaplan–Meier curve for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel



Key: ATC, average treatment effect for the control; ERDA, erdafitinib; Paclitaxel, paclitaxel ± carboplatin; TTNT, time to next treatment.

The impact of adding covariates cumulatively is presented in Appendix P, where covariates did not change the HR from the naïve analysis. The robustness of these findings was consistently observed across all sensitivity analyses conducted. Results remained consistent when the doubly robust approach was used to analyse the data, the HRs for both OS and TTNT were similar to the ATC approach. In a scenario analysis when only complete cases are analysed, hazard ratios remained favourable for erdafitinib (Appendix P). OS HR was 0.22 (95% CI: 0.12, 0.39) which translates to a reduction in risk of death by 78% compared to paclitaxel ± carboplatin.

B.2.9.2. Exploratory analyses

UK clinicians agreed that there was no comparator study identified in the SLR that perfectly matched the erdafitinib target population. UK clinical practice has been based on the modest efficacy of the paclitaxel arm of the PLUTO trial.[25-27, 85] Patients treated with paclitaxel monotherapy in PLUTO had longer survival outcomes than experienced in real-world practice.[85] Importantly, the PLUTO trial population had only been exposed to platinum-based chemotherapy, without any prior exposure to PD-(L)1 inhibitors. The outcomes experienced by these patients are not likely to be generalisable to the population relevant in this appraisal, and they would not be eligible to receive erdafitinib. Nonetheless, we included this broader evidence base to understand the range of uncertainty associated with choice of comparative data (Appendix Q).

Pooled data from THOR (n = 136) and BLC2001 (n = 101) studies for participants with erdafitinib exposure were used to inform the analysis. The trials were pooled to increase the sample size for matching.

An unanchored matched-adjusted indirect comparison (MAIC) using the PLUTO trial data on paclitaxel monotherapy showed consistent results, compared to our base case analysis (Appendix Q). A comparative assessment of the efficacy of erdafitinib versus paclitaxel using the comparator arm in the PLUTO trial yielded a base case OS HR of 0.59 (95% CI: 0.42, 0.85), demonstrating a risk of death reduction of 41% compared to paclitaxel. No significant differences were observed between progression free survival. These results were robust in all sensitivity analyses.

These exploratory analyses represent the upper bounds of relative efficacy between erdafitinib and paclitaxel. These patients had been recently diagnosed with mUC (median time from diagnoses of 15 months) and had only received prior platinum-based treatment, making their treatment less intensive compared to patients in the erdafitinib arm in THOR. As a result, patients receiving paclitaxel monotherapy in the PLUTO trial were expected to have better outcomes than the target patients who would be treated with erdafitinib in a clinical setting. A scenario was explored in the

cost-effectiveness analyses to provide greater certainty on the comparative clinical efficacy of erdafitinib versus paclitaxel.

Acknowledging the limitations and uncertainties associated with comparing trial data with real world evidence and indeed unanchored matched adjusted indirect comparisons between trials of differing patient populations, Johnson and Johnson have also conducted a scenario analysis using the efficacy data from THOR. Whilst THOR did not include a comparator relevant to UK's clinical practice, it is informative to include a randomised comparison in the clinical and economic analyses. To contextualise these results, it is important to note that the patient population in THOR were more heavily pre-treated than the population expected to receive erdafitinib in clinical practice.

This exploratory scenario analysis uses the efficacy data from the THOR comparator arm and assumes costs and adverse event profile that are associated with paclitaxel ± carboplatin treatment.

B.2.9.3. Uncertainties in the indirect and mixed treatment comparisons

The analysis shows that the THOR trial population and the external UK RW mUC cohort did not differ with respect to five variables (i.e., age at diagnosis, sex, tumour location, tumour stage at diagnosis and the proportion of patients deemed cisplatin eligible) included in the analysis before adjustment. After adjustment, the two populations were better matched and provided a more appropriate basis to compare OS and TTNT outcomes between the two populations.

As with any comparisons between randomised controlled trial (RCT) data and RWE, we acknowledge that there are some limitations associated with the analysis. Following the NICE real-world evidence framework, the following areas of risk for bias are more relevant for this analysis:[84]

- Although real-world data were available for patients with similar prior treatments, details on FGFR alterations were not available as the registry cohort includes an untested population. Currently, there are no treatment options available that

specifically target FGFR3 alterations. As a result, diagnostics tests to assess FGFR positivity status are conducted at limited capacity. As described in **Error! R eference source not found.** the UK RW mUC study therefore only has data in an untested population, leading to unknown FGFR status. A MAIC analysis (appendix Q1) was conducted to address this uncertainty. The MAIC revealed that there was no statistically significant difference in OS, PFS and responses between the chemotherapy arms of the THOR trial (vinflunine or docetaxel) and the EV-301 trial (vinflunine, docetaxel, or paclitaxel), with a slight positive trend towards chemotherapy efficacy in the untested EV-301 population. The analysis suggests FGFR3 genetic alterations are not predictive of chemotherapy effectiveness in this population (Appendix Q1). With the MAIC addressing this uncertainty, it can be assumed that the efficacy described in the UK RW mUC study would be comparable, if not conservative, compared to an FGFR3+ population. This analysis showed that there is indirect evidence that suggests that paclitaxel ± carboplatin has a similar efficacy in the untested population or the FGFR3-positive population. Since there is no direct data comparing the efficacy of FGFR3-positive patients to the untested population, Johnson & Johnson assume that the comparator efficacy is similar in both groups.[5, 32]

- There could be residual confounding that is impossible to account for due to the presence of fewer variables, in addition to the unobserved variables, to match with between the datasets in the ITC. However, there is no a priori reason to expect that any presence of potential residual confounding would impact the results in favour of or against erdafitinib. On balance, the analysis can be deemed acceptable as a pragmatic approach.
- The issue of missing ECOG PS scores in the RW cohort, which required resolution in the ITC analysis, was deemed not missing at random (Appendix P). The decisions regarding methodological approach had little impact on the analysis itself as well as the sample size and final results. Two approaches were implemented to explore the potential impact of missingness of ECOG PS scores and both methods showed consistent results.

Despite the above limitations, the UK RW mUC study facilitates a reliable ITC using an evidence base that is highly relevant to the UK setting.

B.2.9.4. Conclusions

The results show that irrespective of the selected method, erdafitinib provides substantial clinical benefit compared with paclitaxel ± carboplatin. Erdafitinib is estimated to reduce the risk of death by 65% compared with paclitaxel ± carboplatin. Erdafitinib also likely reduces the risk of progressing to the next treatment or death (using TTNT) by 67%.

These ITC estimates are supported by the exploratory MAIC, which considers a slightly different evidence base (Appendix Q). The results of the MAIC showed that erdafitinib reduces the risk of death by 41% compared with paclitaxel. As previously described, due to differences in the study populations the results from the MAIC are exploratory and should be viewed with caution.

B.2.10. Adverse reactions

B.2.10.1. THOR

The safety analyses presented in this section are based on 247 patients who received at least one dose of the study drug (135 patients receiving erdafitinib, 112 patients receiving chemotherapy).[5]

In the trial, TEAEs were categorised with the use of the Medical Dictionary for Regulatory Activities Version 24.1; the severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

B.2.10.1.1. Treatment exposure

Table 18 summarises treatment exposure and duration of treatment for both treatment arms. The median duration of exposure was longer for erdafitinib than with chemotherapy (4.8 months versus 1.4 months, respectively).[5, 76]

In the erdafitinib treatment group, 104 (77.0%) patients were up-titrated from 8 mg to 9 mg daily. Of these, 57 (42.2%) of patients maintained the 9mg up-titrated dose or the 8mg starting dose. Sixty-six (48.9%) maintained a dose of 8 mg or more without a dose reduction. [5, 76]

Table 18: Summary of treatment exposure

	Erdafitinib (n = 135)	Chemotherapy (n = 112)
Extent of exposure (days)		
Median	146.0	43.0
Range	(5, 1162)	(1, 820)
Number of chemotherapy cycles		
Median	NA	3.0
Range	NA	(1, 35)
Source: THOR clinical study report.[76]		

B.2.10.1.2. Summary of adverse events

Table 19 presents a summary of all AEs. Almost all patients experienced TEAEs, and the frequency was generally well balanced between the treatment arms (133 patients [98.5%] in the erdafitinib group and 109 patients [97.3%] in the chemotherapy group). [5, 76] In the erdafitinib group, 56 patients (41.5%) experienced serious AEs (SAEs), similar to the chemotherapy group (n = 47; 42.0%).[5, 76] Most patients experienced TEAEs related to the treatment, known as TRAEs (131 patients [97.0%] in the erdafitinib group, and 97 [86.6%] in the chemotherapy group). A total of 45.9% (n=62) of patients in the erdafitinib arm and 46.4% (n=52) of patients in the chemotherapy arm experienced at least one Grade 3–4 TRAE.

The safety profile of erdafitinib differs from that of chemotherapy. However, it is generally well tolerated and managed with dose modifications. Fewer patients (one [0.7%]) in the erdafitinib group experienced TEAEs with an outcome of death considered related to study drug by the investigator compared with the chemotherapy group (six [5.4%] patients). A smaller percentage of patients discontinued treatment as a result of AEs in the erdafitinib group than chemotherapy group: 19 patients (14.1%) versus 20 patients (17.9%), respectively.

Table 19: Summary of AEs in THOR; Cohort 1 safety analysis set

Event, n (%)	Erdafitinib (n = 135)	Chemotherapy (n = 112)
AEs	133 (98.5)	109 (97.3)
TRAEs[a]	131 (97.0)	97 (86.6)
AEs leading to death[b]	6 (4.4)	7 (6.3)
TRAEs[a] leading to death	1 (0.7)	6 (5.4)
SAEs	56 (41.5)	47 (42.0)
Treatment-related SAEs	18 (13.3)	27 (24.1)
AEs leading to discontinuation of study agent	19 (14.1)	20 (17.9)
TRAEs[a] leading to discontinuation of study agent	11 (8.1)	15 (13.4)
AEs leading to dose reduction of study agent	93 (68.9)	27 (24.1)
TRAEs[a] leading to dose reduction of study agent	89 (65.9)	24 (21.4)
AEs leading to dose interruption of study agent	97 (71.9)	35 (31.3)
TRAEs[a] leading to dose interruption of study agent	89 (65.9)	22 (19.6)
Grade 3–4 AEs	85 (63.0)	72 (64.3)
Grade 3–4 TRAEs[a]	62 (45.9)	52 (46.4)
Grade 3–4 SAEs	52 (38.5)	41 (36.6)
Grade 3–4 treatment-related SAEs[a]	16 (11.9)	23 (20.5)
Covid-19 TRAEs	12 (8.9)	5 (4.5)
Covid-19 treatment-related SAEs	1 (0.7)	0 (0.0)

Key: AE, adverse event; SAE, serious adverse event; TRAE, treatment-related adverse event.
Notes: [a] An AE is categorised as related if assessed by the investigator as 'possibly', 'probably', or 'very likely' related to study agent. [b] AEs leading to death are based on whether the AE outcome was fatal.
Source: Loriot et al. (2023);[5] THOR clinical study report.[76]

B.2.10.1.2.1. Treatment-emergent adverse events

Table 20 presents the most frequently reported TEAEs for any grade (≥ 10%) and Grade 3–4 (≥ 2%) for both the erdafitinib and chemotherapy treatment groups. The

frequency of Grade 3–4 TEAEs was generally well balanced between treatment groups; 85 patients (63.0%) receiving erdafitinib and 72 patients (64.3%) receiving chemotherapy experienced at least one Grade 3–4 TEAE. The most frequently reported Grade 3-4 TEAEs (>8%) in the erdafitinib arm were palmar-plantar erythrodysesthesia syndrome (9.6%) and stomatitis (8.1%). In the chemotherapy arm, these were neutropenia (14.3%), leukopenia (8.9%), and anaemia (8.0%).[5, 76]

Table 20: Any grade TEAEs occurring in ≥ 10% of patients in either treatment arm, and corresponding Grade ≥ 3 TEAEs occurring in ≥ 2% of patients

	Erdafitinib (n = 135)		Chemotherapy (n = 112)	
	Any grade	**Grade 3–4**	**Any grade**	**Grade 3–4**
No. of patients, n (%)				
Diarrhoea	84 (62.2)	4 (3.0)	19 (17.0)	3 (2.7)
Stomatitis	65 (48.1)	11 (8.1)	14 (12.5)	2 (1.8)
Constipation	36 (26.7)	-	31 (27.7)	-
Dry mouth	53 (39.3)	-	4 (3.6)	-
Nausea	20 (14.8)	-	27 (24.1)	-
Vomiting	13 (9.6)	2 (1.5)	16 (14.3)	3 (2.7)
Hyperphosphataemia	108 (80.0)	7 (5.2)	-	-
Decreased appetite	36 (26.7)	4 (3.0)	23 (20.5)	3 (2.7)
Hyponatraemia	16 (11.9)	10 (7.4)	4 (3.6)	2 (1.8)
Asthenia	20 (14.8)	2 (1.5)	28 (25.0)	4 (3.6)
Fatigue	20 (14.8)	0	21 (18.8)	4 (3.6)
Pyrexia	20 (14.8)	-	14 (12.5)	-
Oedema peripheral	8 (5.9)	-	13 (11.6)	-
Alopecia	34 (25.2)	-	27 (24.1)	-
Palmar-plantar erythrodysesthesia syndrome	41 (30.4)	13 (9.6)	1 (0.9)	0
Dry skin	31 (23.0)	-	5 (4.5)	-
Onycholysis	31 (23.0)	8 (5.9)	1 (0.9)	0
Onychomadesis	28 (20.7)	-	2 (1.8)	-
Nail discolouration	24 (17.8)	-	2 (1.8)	-
Nail disorder/dystrophy	19 (14.1)	3 (2.2)	2 (1.8)	0
Urinary tract infection	15 (11.1)	6 (4.4)	8 (7.1)	3 (2.7)
Paronychia	16 (11.9)	-	0	-
Anaemia	35 (25.9)	10 (7.4)	36 (32.1)	9 (8.0)
Neutropenia	0	0	22 (19.6)	16 (14.3)

	Erdafitinib (n = 135)		Chemotherapy (n = 112)	
	Any grade	**Grade 3–4**	**Any grade**	**Grade 3–4**
Leukopenia	1 (0.7)	0	15 (13.4)	10 (8.9)
Dysgeusia	37 (27.4)	-	8 (7.1)	-
Alanine aminotransferase increased	37 (27.4)	4 (3.0)	4 (3.6)	1 (0.9)
Weight decreased	30 (22.2)	3 (2.2)	3 (2.7)	0
Aspartate aminotransferase increased	29 (21.5)	3 (2.2)	3 (2.7)	0
Blood creatinine increased	19 (14.1)	-	7 (6.3)	-
Blood alkaline phosphatase increased	14 (10.4)	3 (2.2)	4 (3.6)	1 (0.9)
Arthralgia	14 (10.4)	-	9 (8.0)	-
Dry eye	23 (17.0)	-	2 (1.8)	-
Epistaxis	17 (12.6)	-	3 (2.7)	-
Haematuria	16 (11.9)	3 (2.2)	10 (8.9)	2 (1.8)

Key: TEAE, treatment-emergent adverse event.
Source: THOR clinical study report.[76]

B.2.10.1.2.2. Treatment-related adverse events

Table 21 presents the most frequently reported TRAEs for any grade (≥ 10%) for both erdafitinib and chemotherapy treatment groups. The most frequently reported TRAEs in the erdafitinib group were hyperphosphataemia (78.5%), diarrhoea (54.8%), stomatitis (45.9%) and dry mouth (38.5%), whereas in the chemotherapy group, anaemia (27.7%), alopecia (21.4%) and nausea (19.6%) were the most frequently reported TRAEs. [5, 76]

The frequency of Grade 3–4 TRAEs were generally well balanced between treatment groups; 45.9% of patients receiving erdafitinib and 46.4% of patients receiving chemotherapy experienced at least one Grade 3–4 TRAE. In the erdafitinib arm, the most frequently reported Grade 3–4 TRAEs were palmar-plantar erythrodysesthesia syndrome (9.6%), stomatitis (8.1%) and onycholysis (5.9%). In the chemotherapy arm, the most frequently reported Grade 3–4 TRAEs were neutropenia (13.4%), leukopenia (8.0%) and febrile neutropenia (7.1%).[5, 76]

Table 21: Any grade TRAEs occurring in ≥ 10% of patients in either treatment arm

	Erdafitinib (n = 135)	Chemotherapy (n = 112)
No. of patients, n (%)		
Diarrhoea	74 (54.8)	12 (10.7)
Stomatitis	62 (45.9)	13 (11.6)
Dry mouth	52 (38.5)	3 (2.7)
Nausea	14 (10.4)	22 (19.6)
Constipation	12 (8.9)	21 (18.8)
Vomiting	9 (6.7)	15 (13.4)
Hyperphosphataemia	106 (78.5%)	-
Decreased appetite	28 (20.7)	20 (17.9)
Alopecia	32 (23.7)	24 (21.4)
Palmar-plantar erythrodysesthesia syndrome	41 (30.4)	1 (0.9)
Dry skin	30 (22.2)	4 (3.6)
Onycholysis	31 (23.0)	1 (0.9)
Onychomadesis	27 (20.0)	2 (1.8)
Nail discolouration	24 (17.8)	2 (1.8)
Nail disorder	18 (13.3)	2 (1.8)
Fatigue	18 (13.3)	17 (15.2)
Asthenia	11 (8.1)	21 (18.8)
Anaemia	16 (11.9)	31 (27.7)
Neutropenia	0	21 (18.8)
Leukopenia	0	13 (11.6)
Dysgeusia	34 (25.2)	7 (6.3)
Dry eye	22 (16.3)	2 (1.8)
Alanine aminotransferase increased	29 (21.5)	3 (2.7)
Aspartate aminotransferase increased	25 (18.5)	1 (0.9)
Weight decreased	14 (10.4)	3 (2.7)
Paronychia	16 (11.9)	0 (0.0)
Source: THOR clinical study report.[76]		

B.2.10.1.2.3. Serious adverse events

Table 22 presents the most frequently reported SAEs for both treatment arms (≥ 2%). SAEs were experienced by 56 (41.5%) patients in the erdafitinib group and 47 (42.0%) patients in the chemotherapy group.[5, 76] Of these, 18 (13.3%) patients in

the erdafitinib group and 27 (24.1%) patients in the chemotherapy group had SAEs considered by the investigator to be related to the study drug.[5, 76]

The most frequently reported SAEs (> 3%) in the erdafitinib group were urinary tract infection (4.4%) and haematuria (3.7%). In the chemotherapy group, they were febrile neutropenia (6.3%) and febrile bone marrow aplasia (3.6%).[5, 76]

Table 22: SAEs occurring in ≥ 2% of patients in either treatment arm

Event, n (%)	Erdafitinib (n = 135)	Chemotherapy (n = 112)
Patients with ≥ 1 SAE	56 (41.5)	47 (42.0)
Urinary tract infection	6 (4.4%)	2 (1.8%)
Febrile neutropenia	0	7 (6.3%)
Febrile bone marrow aplasia	0	4 (3.6%)
Neutropenia	0	3 (2.7%)
Pyrexia	2 (1.5%)	3 (2.7%)
Haematuria	5 (3.7%)	1 (0.9%)
Acute kidney injury	3 (2.2%)	0
Hyponatraemia	3 (2.2%)	1 (0.9%)

Key: AE, adverse event; SAE, serious adverse event.
Notes: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event. AEs are coded using the Medical Dictionary for Regulatory Activities Version 24.1.
Source: THOR clinical study report.[76]

B.2.10.1.2.4. Adverse events of interest

Adverse events of clinical importance include those that are class effects of FGFR inhibitors, specifically eye (other than central serous retinopathy), nail, skin and gastrointestinal disorders and hyperphosphataemia.[76]

In the erdafitinib group, the Grade 3–4 AEs related to the former are as follows: eye disorders excluding central serous retinopathy (n = 3; 2.2%), nail disorders (n = 15, 11.1%), skin disorders (n = 16; 11.9%), gastrointestinal disorders (n=12; 8.9%) and hyperphosphataemia (n=8; 5.9%).[76]

Central serous retinopathy is an adverse event of special interest and a known class effect of FGFR inhibitors. Twenty-three patients (17%) experienced this event.

Central serous retinopathy events were manageable with dose modifications.[76] In patients with any grade central serous retinopathy, 70% of the events were resolved by the clinical cutoff date; of the ongoing events, 71% were Grade 1. No patients experienced blindness (a Grade 4 event) due to central serous retinopathy.[76]

Full details on AEs of interest and central serous retinopathy events are available in Appendix F.

Hyperphosphataemia is a common drug-induced toxicity for FGFR-targeted agents due to renal tubular FGFR inhibition. Therefore, UK clinicians pointed out labelling hyperphosphataemia as an adverse event could be considered misleading as it is an intended event.[26] This serves as a pharmacodynamic marker of erdafitinib activity. In the THOR trial, the erdafitinib dose was personalised and either up-titrated to 9 mg or maintained at 8 mg considering phosphate level measured on Cycle 1 Day 14.

Hyperphosphataemia was well-managed by dose modification and treatment with phosphate binders; 27 (20.0%) patients in the erdafitinib group received the phosphate binder sevelamer.[76]

As shown in Table 23, 108 (80.0%) patients in the erdafitinib group experienced TEAEs of hyperphosphataemia.[76] Most events of hyperphosphataemia in the erdafitinib group were Grade 1 or 2 (101 patients [74.8%]), while eight patients (5.9%) experienced a Grade 3 or 4 event of hyperphosphataemia. No patients had serious TEAEs of hyperphosphataemia. Events of hyperphosphataemia leading to dose reduction and leading to dose interruption were reported for six patients (4.4%) and 10 patients (7.4%) in the erdafitinib group, respectively. No patients discontinued erdafitinib due to hyperphosphataemia. The median time to first onset of events of hyperphosphataemia in the erdafitinib group was 15.0 days for any grade event and 35.0 days for Grade 3 or 4 events. The incidence of hyperphosphataemia was highest during the first month of exposure. As of the clinical cutoff, the majority of events were resolved; 16 patients had ongoing events, of which all were Grade 1.[76]

Table 23: Hyperphosphataemia by severity, seriousness, action taken, time to onset, and resolution: Cohort 1

Event n (%)	Erdafitinib (n = 135)
Overall Incidence	
Hyperphosphataemia	[redacted]
Maximum severity	
Grade 1–2:	[redacted]
Grade 3:	[redacted]
Grade 4:	[redacted]
Serious events	[redacted]
Dose modification	
Reduction	[redacted]
Interruption	[redacted]
Discontinuation	[redacted]
Median time to first onset (days)	
Any grade	[redacted]
Grade 3:	[redacted]
Time to first onset by treatment interval	
≤ 1 month: > 1–2 months: > 2–3 months: > 3–6 months: > 6 months:	[redacted]
Resolution at data cutoff	
Resolved	[redacted]
Unresolved	[redacted]
Grade 1	[redacted]
Grade 2	[redacted]
Grade 3	[redacted]
Grade 4	[redacted]
Source: THOR clinical study report[76]	

B.2.10.1.2.5. Adverse events leading to treatment discontinuation

A lower number of patients had TRAEs leading to treatment discontinuation in the erdafitinib group (n = 11; 8.1%) compared with the chemotherapy group (n = 15; 13.4%).[5] The most frequent TEAEs (by system organ class) leading to discontinuation of erdafitinib were general disorders and administration site conditions (n=4), infections and infestations (n = 4), eye disorders (n = 3), and skin and subcutaneous tissue disorders (n = 3). The most frequent TRAEs leading to discontinuation of chemotherapy were blood and lymphatic system disorders (n = 5), general disorders and administration site conditions (n=3), infections and infestations (n = 3), nervous system disorders (n = 3), and gastrointestinal disorders (n = 3).[76]

Full details on AEs leading to treatment discontinuation is available in Appendix F.

B.2.10.1.3. Deaths

Table 24 presents a summary of all deaths in the THOR trial. As of the clinical cut-off for the analysis, 77 patients (56.6%) in the erdafitinib treatment group and 78 patients (60.0%) in the chemotherapy treatment group had died during the study.[5] The primary reason for death in both treatment groups was progression of disease; this was the case for [redacted] and [redacted] of patients in the erdafitinib and chemotherapy groups, respectively.[76]

Table 24: Summary of deaths (Cohort 1 ITT analysis set)

	Erdafitinib (n = 136)	**Chemotherapy (n = 130)**
No. of patients, n (%)		
Deaths during study	[redacted]	[redacted]
Primary reason for death		
Progressive disease	[redacted]	[redacted]
AE	[redacted]	[redacted]
Related to study agent	[redacted]	[redacted]
Not related to study agent	[redacted]	[redacted]
Relationship unknown	[redacted]	[redacted]
Covid-19 related	[redacted]	[redacted]

	Erdafitinib (n = 136)	Chemotherapy (n = 130)
Other	[redacted]	[redacted]
Cause unknown	[redacted]	[redacted]
Deaths within 30 days of last dose	[redacted]	[redacted]
AE	[redacted]	[redacted]
Related to study agent	[redacted]	[redacted]
Not related to study agent	[redacted]	[redacted]
Relationship unknown	[redacted]	[redacted]
Covid-19 related	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Other	[redacted]	[redacted]

Key: AE, adverse event; ITT, intention-to-treat.
Notes: Related includes deaths that were very likely, probably, or possibly related to study agent. Relationship unknown includes doubtful, unknown or missing relationship to study agent.
Source: THOR clinical study report.[76]

Table 25 summarises the TRAEs leading to death. In the erdafitinib group, eight (5.9%) patients died due to an AE; the event was considered to be related to erdafitinib for one (0.7%) patient.[5] In the chemotherapy group, 10 (7.7%) patients died due to an AE; the event was considered to be related to the study drug (docetaxel or vinflunine) in six of those patients (4.6%).[76]

Table 25: Treatment-related TEAEs leading to death

	Erdafitinib (n = 135)	Chemotherapy (n = 112)
No. of patients, n (%)		
Patients with one or more TAEs leading to death	[redacted]	[redacted]
Febrile bone marrow aplasia	[redacted]	[redacted]
Febrile neutropenia	[redacted]	[redacted]
Septic shock	[redacted]	[redacted]
Atypical pneumonia	[redacted]	[redacted]
Sudden death	[redacted]	[redacted]

Key: AE, adverse event; TEAE, treatment-emergent adverse event.

Notes: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event. AEs are coded using the Medical Dictionary for Regulatory Activities Version 24.1.

Source: THOR clinical study report.[76]

B.2.10.2. BLC2001

A summary of safety data from BLC2001 is provided in Appendix N. These data were consistent with those observed during the THOR trial, and the known safety profile of erdafitinib.[6]

B.2.11. Ongoing studies

The THOR trial is currently ongoing, and the estimated trial completion date is September 2024.[86]

B.2.12. Interpretation of clinical effectiveness and safety evidence

B.2.12.1. Principal findings of the clinical evidence base

There is a clear unmet need for additional, novel treatment options with proven effectiveness for adults with unresectable or metastatic *FGFR*-altered UC in the 2L setting. There is a need for non-invasive therapies that improve survival and maintain HRQL while having a manageable safety profile.

The THOR trial provides pivotal evidence to support the role of erdafitinib for the treatment of patients with *FGFR* alterations in mUC after PD-(L)1 therapy.[5] In the trial, erdafitinib significantly prolonged OS compared with chemotherapy (median OS of 12.1 versus 7.8 months; HR: 0.64; 95% CI: 0.47, 0.88; p-value = 0.005), which represents a 36% reduction in the relative risk of death.[5, 76] Treatment with erdafitinib also provided significantly longer PFS and a greater ORR versus chemotherapy. Subgroup analyses supported the superiority of OS, PFS and ORR for erdafitinib over chemotherapy in all clinically relevant subgroups.[5]

Additionally, erdafitinib with dose modifications had a manageable tolerability profile compared with that of chemotherapy.[76] Observed TRAEs were mostly of low severity and generally not life threatening. There were fewer TEAEs considered related to erdafitinib that had an outcome of death, were serious, or led to treatment discontinuation in the erdafitinib group compared with the chemotherapy group.[76] Importantly, patients receiving erdafitinib experienced no clinically meaningful change from baseline in their HRQL.[5]

The effectiveness and safety profile of erdafitinib demonstrated by the confirmatory registrational THOR trial was consistent with the prior BLC2001 trial.[6, 77] For patients treated with the erdafitinib 8mg daily regimen in BLC2001, median OS was 13.8 months and ORR was 40%. The median time to response was 1.4 months, and the response was sustained. The median DOR was 5.6 months, and around 30% of these responses were maintained for more than 12 months. Similarly to the evidence demonstrated in the THOR trial, in BLC2001 erdafitinib was generally well tolerated and AEs could be managed by supportive care and dose modification.[6, 77]

The chemotherapies in the comparator arm (docetaxel and vinflunine) of THOR are not representative of clinical practice in England and Wales. Vinflunine is not reimbursed in England and Wales, and although docetaxel is reimbursed, it is not recommended in NICE guidance and is rarely used. As discussed in Section B.2.7, results from the subgroup analyses of either individual chemotherapy group should be interpreted with caution, and the individual comparisons within these subgroups cannot be considered informative or suitable for making decisions, because the trial

was not adequately designed to evaluate differences between erdafitinib and individual chemotherapy groups. Additionally, there were imbalances in baseline and disease characteristics, as well as limited patient numbers in the subgroups.

Johnson & Johnson initiated a UK RW mUC study using several linked datasets available through the NCRAS (as discussed in Section B.2.9), designed to retrospectively track the treatment pathway and health outcomes of patients with mUC using routine healthcare data.[20] This RW study provides the best available and appropriate data to enable comparisons of erdafitinib with the most relevant comparators that are currently being used in clinical practice in England and Wales.

The UK RW mUC study indicates that in patients who have previously received anti-PD-(L)1 treatment, the most common treatment options are treatment with paclitaxel ± carboplatin, and in some cases, retreatment with platinum-based chemotherapy or a PD-(L)1 inhibitor if disease progression occurred ≥ 12 months.[20] However, clinical experts and NICE guideline NG2 do not recommend this approach as there is no evidence to support rechallenge. Treatment with docetaxel is very limited in clinical practice in England. In the UK RW mUC study, there were only four (2.0%) patients who received treatment with docetaxel at 2L or beyond following on progression from anti-PD-(L)1 inhibitors.[20]

An ITC was conducted to compare the efficacy of erdafitinib with paclitaxel ± carboplatin after exposure to a PD-(L)1 inhibitor. The UK RW mUC study reflects the RW population that is likely to receive erdafitinib in UK clinical practice and provides the most accurate representation of RW treatment and health outcomes data for patients treated for mUC in England. The ITC results demonstrate that, irrespective of the selected method, erdafitinib provides substantial clinical benefit compared with paclitaxel ± carboplatin. Overall survival in this analysis was defined as the time from treatment initiation to the time of death or censoring to match the RW data. Erdafitinib is estimated to reduce the relative risk of death by 65% (HR: 0.35; 95% CI: 0.23, 0.52) compared with paclitaxel ± carboplatin, with a median OS of 10.6 months (95% CI: 9.5, 16.7) for erdafitinib and 6.5 months (95% CI: 4.9, 7.0) for paclitaxel ± carboplatin (Appendix P).

Erdafitinib also likely reduces the relative risk of progression to next treatment or death (using TTNT) by 67% (HR: 0.33; 95% CI: 0.22, 0.50) in the base case analysis using the ATC method, with a median TTNT of 10.2 months (95% CI: 9.3, 13.9) for erdafitinib and 5.4 months (95% CI: 3.7, 6.8) for paclitaxel ± carboplatin.

B.2.12.2. Strengths and limitations of the clinical evidence base

The population outlined in THOR aligns with the population outlined in the decision problem presented in the submission: [redacted].

The THOR trial is a high-quality, randomised trial that adheres to a series of predefined steps to avoid any potential bias. The open-label design of the study may have influenced the interpretation of some efficacy endpoints determined by the investigator – although, since the primary endpoint was OS, this potential bias would not impact the primary study endpoint. However, post hoc analyses showed that this had minimal impact on the primary analysis.

The primary efficacy outcomes, PFS and OS, are well established trial endpoints that are of most relevance to patients, carers and healthcare professionals in the UK. HRQL endpoints also allow further assessment of the impact of mUC on patients and allow formal utility analyses to support economic modelling.

THOR was designed as a truly global clinical trial to investigate the efficacy and safety of erdafitinib across many country populations. THOR was conducted at 121 study sites in 23 countries across Asia, Europe, North America, South America, and Australia, including a number of patients who were enrolled in the study in the UK (n = [redacted] in nine different sites).[76, 86] Due to the broad and global scale of THOR, it is unlikely for every aspect of the trial to match settings in any single country, including the UK. However, a comparison of baseline characteristics for patients in THOR and those in UK RW mUC study showed that patients in general were comparable, without any major differences in the age ranges of the patients in the two studies.

Any differences have been thoroughly addressed in the ITC comparing THOR and the UK RW mUC with all possible confounders available (Appendix P).

A broad range of patients were enrolled into the THOR trial in terms of histology, prior therapies, tumour location and disease status at trial entry. Baseline patient demographics and disease characteristics, *FGFR* alterations, and prior systemic anticancer therapy were generally well balanced between the two arms of the trial. However, limitations exist when assessing the disease characteristics and patient demographics at baseline:

- No patients with *FGFR2* alterations were enrolled in the trial; therefore, it is not possible to evaluate the efficacy of erdafitinib in patients with these alterations
- Clinicians have stated that there is an underrepresentation of people of black or African descent, and an overrepresentation of Asian people in the trial. Most patients included in Cohort 1 were white (54.1%) and from Europe (60.9%). Only 4.9% of patients were enrolled in North America, and only one patient was black or African American
- Most patients had ECOG PS 0–1, which is not reflective of the UK population receiving 2L chemotherapy, who tend to have ECOG PS 2

The RW study is the most reflective of current clinical practice in England and provides efficacy data for the relevant comparator of interest, paclitaxel ± carboplatin. However, there are some limitations to the study, such as missing ECOG PS scores and few baseline characteristics available for analysis. Furthermore, most patients in THOR were receiving 3L treatment, whereas most patients in the RW study were receiving 2L treatment. To counteract this imbalance, the analyses were adjusted.

B.3. Cost-effectiveness

B.3.1. Published cost-effectiveness studies

To inform model conceptualisation, an SLR of existing economic evidence in mUC, including previously published economic models, was conducted on 10 April 2024.

Preliminary searches were unable to identify any publications reporting specifically on patients with unresectable or metastatic urothelial cancer treated with one line of prior anti-PD-(L)1 therapy. Therefore, the SLR took a broader perspective than that outlined by the anticipated marketing authorisation for erdafitinib, focusing on publications reporting cost-effectiveness analyses in patients treated with at least one line of prior systemic therapy.

A total of 16 studies reported economic evaluations for patients treated with one prior line of systemic therapy. Fifteen of these studies were cost-effectiveness analyses, while one study presents a cost–consequence analysis for erdafitinib, pembrolizumab, atezolizumab, nivolumab and durvalumab in a Brazilian population. Full details of the economic evaluation SLR can be found in Appendix G.

To support the findings from the SLR, a review of previous NICE HTA submissions was conducted in March 2023, focusing on appraisals published in the last 5 years. At the time of writing this submission, there were no published NICE appraisals that focused on a cohort previously treated with a PD-(L)1 inhibitor; therefore, the review focused on the most recent and relevant TAs in UC where patients had received prior platinum-based chemotherapy population.

There were seven TAs identified in this wider population. Table 26 presents a comparison of the decision problem, model structure, comparators, sources of utilities and costs. These informed the design and development of the de novo model used for this submission.

Table 26: Summary list of published cost-effectiveness studies identified in the NICE HTA review

Study	TA525[58]	TA530[65]	TA692 (TA519)[57]	TA674[87]	TA739[69]	TA788[24]	TA797[88]
Year	June 2018	July 2018	April 2021	February 2021	October 2021	May 2022	June 2022
Indication	Locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy	Locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy	Locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy	Untreated PD-(L)1-positive, locally advanced or metastatic urothelial cancer when cisplatin is unsuitable	Untreated PD-(L)1-positive advanced urothelial cancer when cisplatin is unsuitable	Locally advanced or metastatic urothelial cancer after platinum-based chemotherapy	Previously treated locally advanced or metastatic urothelial cancer
Intervention	Atezolizumab	Nivolumab	Pembrolizumab	Pembrolizumab	Atezolizumab with carboplatin plus gemcitabine	Avelumab	Enfortumab vedotin
Comparators	• Chemotherapy (paclitaxel or docetaxel)	• Chemotherapy (paclitaxel or docetaxel)	• Carboplatin plus gemcitabine • Atezolizumab • Best supportive care	• Carboplatin plus gemcitabine	• Carboplatin plus gemcitabine	• BSC (watchful waiting/no active treatment)	• Chemotherapy (paclitaxel or docetaxel) • BSC
Model structure	Three-state partitioned survival model	Three-state partitioned survival model	Three-state partitioned survival model	NR (appraisal terminated)	Three-state partitioned survival model	Three-state partitioned survival model	NR (appraisal terminated after final scope)
Time horizon	20 years	Lifetime	35 years (lifetime)		20-years	25 years (lifetime)	
Treatment waning effect	No	No	No		Scenario analyses	No	

Study	TA525[58]	TA530[65]	TA692 (TA519)[57]	TA674[87]	TA739[69]	TA788[24]	TA797[88]
Source of utilities	Utility values from Australian PBAC appraisal of vinflunine	Pivotal trial, and external data for AEs	Pivotal trial data (KEYNOTE-052)		Pivotal trial data (IMvigor130 trial)	Pivotal trial, and external data for AEs	
Source of costs	NCC for the NHS, literature and expert opinion	NCC for the NHS, literature and expert opinion	NCC for the NHS, literature and expert opinion		NCC for the NHS, literature and expert opinion	NCC for the NHS, published literature and expert opinion	
Discount of 3.5% on utilities and costs	Yes	Yes	Yes		Yes	Yes	
Decision modifier(s)*	Met EoL criteria	Met EoL criteria	Met EoL criteria		Met EoL criteria	Met EoL criteria	
NHS PSS perspective	Yes	Yes	Yes		Yes	Yes	
RDI applied	NR	NR	No		NR	Yes	

Key: AE, adverse event; BSC, best supportive care; EoL, end of life; HTA, health technology assessment; NCC, National Cost Collection; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; NR, not reported; PBAC, Pharmaceutical Benefits Advisory Committee; PD-(L)1, programmed death-ligand 1; PSS, Personal Social Services; TA, technology appraisal.

Note: *Past appraisals were under the previous NICE guidance.[89]

B.3.2. Economic analysis

A de novo model was developed to evaluate the cost-effectiveness of erdafitinib against relevant comparators in the indicated population, as detailed below.

B.3.2.1. Patient population

The economic analysis addresses the patient population directly in line with the marketing authorisation and decision problem for erdafitinib:

[redacted]

The modelled population is reflected by Cohort 1 of the THOR trial population (Section B.1.1); please refer to Section B.2.9, Section B.3.3.1 and Appendix D regarding population-adjustment approach required to facilitate comparative analysis for this appraisal.

B.3.2.2. Model structure

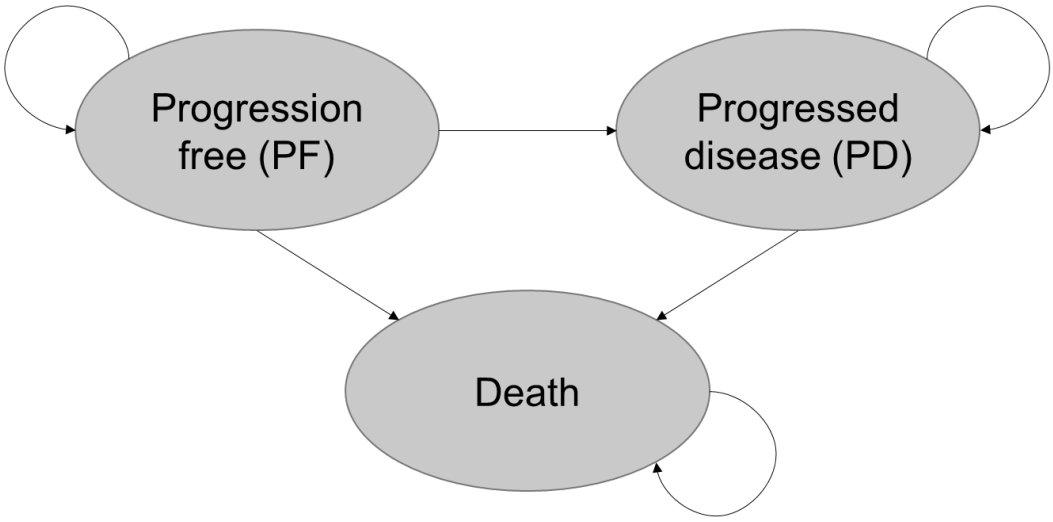
The economic model follows a partitioned survival modelling approach, where state membership is defined by disease status (progression-free [PF] versus progressed disease [PD]) and mortality status. This structure is acceptable to model the relevant outcomes for this decision problem. Previous NICE TAs in UC have also been based on a standard three-state partitioned survival structure (Figure 13).

Importantly, the partitioned survival modelling approach facilitates direct use of clinical trial evidence available from THOR[76]– including the primary endpoint of OS and secondary endpoint of PFS. The cohort model structure accurately captures survival and HRQL implications for patients and cost and resource use implications relevant to the NHS perspective, in line with the NICE reference case.[90]

Figure 13 illustrates the health states and possible transitions in each model treatment arm. The health states capture disease progression status (PF or PD) and treatment status (on or off treatment). Treatment-dependent costs and health

outcomes associated with each arm are captured within each mutually exclusive heath state.

Figure 13: Economic model structure



Patients with mUC who have previously received at least one line of therapy containing a PD-1 or PD-(L)1 inhibitor enter the model in the PF state and are assumed to be on treatment. In each model cycle, those in the PF state can either remain in that state or move into the PD or death state. Those in the PD state can remain in that state or move into the death state. Death is included as an absorbing health state.

Additionally, the following adjustments are applied to maintain logical consistency in the patient flow of the model:

- The mortality risk at each model cycle is bound by age-matched general population predictions, sourced from the latest available Office for National Statistics Life Tables.[91]
- A limit is built into the model to ensure that PFS cannot exceed OS. The limit is applied to the per-cycle hazard of progression/death and hazard of death; if the hazard of death exceeds that of progression/death, the maximum hazard is assumed.

A 7-day (1-week) cycle length is considered sufficiently short to reflect dosing regimens and accurately capture differences in key clinical and cost outcomes. Given the short cycle length, a half-cycle correction is not necessary.

Table 27 summarises key features of the economic analysis.

Table 27: Features of the economic analysis

Factor	Current evaluation	
	Chosen values	**Justification**
Indication	[redacted]	In alignment with the marketing authorisation for erdafitinib
Intervention	Erdafitinib	In alignment with the marketing authorisation for erdafitinib
Comparator	Paclitaxel ± carboplatin	In alignment with the decision problem
Model structure	Three-state partitioned survival model	Appropriately captures the disease and objectives of the analysis. Following the key endpoints from THOR (OS, PFS)
Time horizon	40 years	Sufficiently long to capture health and cost outcomes over patient lifetime, consistent with NICE reference case[90]
Cycle length	7 days (half-cycle correction not applied)	Consistent with previous NICE appraisals (Table) and sufficiently short to capture key clinical outcomes and dosing regimens.
Treatment waning effect?	Not explored	It is anticipated that the range of survival models considered within the cost-effectiveness model reflects difference in treatment effects over time, therefore treatment waning is not required.
Decision modifier(s)	Severity modifier of x1.7	See Section B.3.6
Source of utilities	Pivotal THOR trial, and external data for AEs	In line with NICE guidance and reference case[90]
Source of AE incidence	Literature values used for paclitaxel ± carboplatin and observed data from THOR used for erdafitinib	Adverse events were not available for the comparator and therefore previously published
Source of costs	NCC for the NHS, published literature and expert opinion	In line with NICE guidance and reference case[90]

Factor	Current evaluation	
	Chosen values	Justification
Dose skipping	In the base case, the number of doses skipped is assumed to be 17.07%, based on the THOR safety population.	Dose skipping is captured in the model by applying a proportional reduction to the number of doses received.
Key: AE, adverse event; *FGFR*, fibroblast growth factor receptor; NCC, National Cost Collection; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival.		

B.3.2.3. Intervention technology and comparators

B.3.2.3.1. Intervention

Erdafitinib is implemented in the analysis according to the anticipated MHRA marketing authorisation described in Section B.1.2, and THOR trial (please see Section B.2.3 for further information about erdafitinib and the clinical trial protocol).

The dose and administration schedule for erdafitinib follows details obtained from the SmPC for erdafitinib, which is consistent with the administration of erdafitinib in the THOR trial (see below).[76] Treatment with erdafitinib should continue until disease progression, withdrawal or unacceptable toxicity.

- Erdafitinib is administered at a dose of 8 mg/kg, once daily for 21 days (3 weeks).[76]

B.3.2.3.2. Comparators

As described previously, the most relevant comparator to include in the cost-effectiveness model is paclitaxel ± carboplatin (Section B.2). This is implemented in the model as a basket of paclitaxel as a monotherapy and paclitaxel in combination with carboplatin, weighted 3:1, respectively, in line with NCRAS estimates. This is based on consensus from a UK advisory board, including six clinicians, and confirmed by the results from the UK RW mUC study conducted by Johnson and Johnson Innovative Medicine.[20, 25]

The dose and administration for paclitaxel ± carboplatin is based on the SmPC (UC indication) and confirmed by clinical experts:

- Paclitaxel is administered at a dose of 80 mg/m^2 as a 1-hour IV infusion, in 250 ml sodium chloride on Days 1, 8 and 15 every 28 days until progression, withdrawal, or intolerable toxicity[92]
- When paclitaxel is administered in combination with carboplatin every 3 weeks, paclitaxel is dosed at 175 mg/m² over a period of 3 hours, alongside carboplatin, which is dosed to a targeted area under the curve (AUC) of 6 mg/ml as a 30-minute IV infusion over 30 minutes every 3 weeks in 500 ml glucose 5%.[93]

In this document we have focused on the main comparator, paclitaxel ± carboplatin.

B.3.3. Clinical parameters and variables

B.3.3.1. Overview of clinical data sources and outcomes in the economic model

B.3.3.1.1. Patient population characteristics

The patient population relevant to the decision problem is generally reflected by the THOR trial population.[76] Due to the requirement of an ITC, outlined in Section B.2.9, the modelled population for the cost-effectiveness analysis is based on the THOR population which has been adjusted to reflect a real-world patient population in the UK. This ensures consistency and comparability with the UK RW mUC study population that is used to represent clinical outcomes for paclitaxel ± carboplatin (Section B.2.9 and Section B.3.3.2).[20] As previously described, the base case approach uses the ATC-adjusted dataset.

The population characteristics used in the model are presented in Table 28. These were deemed generalisable and representative of the UK setting by UK-based clinicians.[25]

Table 28: Patient population characteristics used in the model (THOR ATC-adjusted data)

Population characteristic	Mean	Standard deviation	Sample size
Age at model start	66.5	10.39	126
Average patient weight (kg)	75.0	20.59	126
Average body surface area (m²)	1.85	0.261	125
Average creatinine clearance (mL/min)	64.0	24.14	126
Proportion male	73.7%	N/A	126
Key: ATC, average treatment effect of the control.			

B.3.3.1.2. Summary of clinical data sources

Table 29 presents an overview of the data sources associated with the key clinical outcomes in the model (OS, PFS, time to treatment discontinuation, time to next treatment, AEs and utility values). Clinical data inputs used to model outcomes in the erdafitinib arm are based on the THOR trial data which has been adjusted to the UK RW mUC study (Section B.2.9).[20] The clinical outcomes associated with paclitaxel ± carboplatin are estimated based on the ITC using the UK RW mUC study (see Section B.2.9 and Appendix P for further details).

Further details are presented in Section B.3.3.2.

Table 29: Overview of data sources informing the economic model (base case)

Model input	Data source	Justification	Reference in submission
Baseline characteristics			
Median age (years)	THOR, adjusted to UK RW mUC study population[20, 76]	Appropriately reflects the modelled population for this decision problem; validated by clinical experts.	Section B 3.2.1
Proportion male (%)			
Average body surface area (m^2)			
Average patient weight (kg)			
FGFR3+ prevalence (%)	THOR[76]		
Erdafitinib			
OS	THOR, adjusted to UK RW mUC study population[20, 76]	Most appropriate source of clinical evidence for erdafitinib that is consistent with the comparative analysis for paclitaxel ± carboplatin in the UK	Section B 2.6.1 Section B.2.9 Section B 2.10.1 Section B 3.3.4-3.3.6 Section B 3.4.4
TTNT*			
PFS			
TTD			
AEs			
Paclitaxel ± carboplatin			
OS	UK RW mUC study[20]	Most appropriate source of clinical data for paclitaxel ± carboplatin, reflective of the UK population (in the absence of direct head-to-head evidence)	Section B.3.3.2.2
TTNT*			Section B.3.3.2.3
PFS	Assumption: ratio of TTNT and PFS for erdafitinib applied to derive the extrapolation for paclitaxel ± carboplatin PFS		Section B.3.3.2.4
TTD	Assumption: Equivalent to PFS		Section B.3.3.2.5
AEs	PLUTO trial[92]		Section B.3.4.4
Other clinical parameters			
Utility values for health states	Analysis based on THOR[76]	Following NICE reference case	Section B 3.4.5

Key: AEs, adverse events; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation; TTNT, time to next treatment

Notes: *, TTNT is included in the model for the purpose of approximating PFS

B.3.3.2. Methods and inputs

Given the need to model outcomes over a lifetime horizon, it was necessary to extrapolate survival outcomes beyond the data collection periods in THOR and the UK RW mUC study.[20] We adopt conventional methods of parametric survival modelling as outlined in NICE DSU TSD14 in extrapolating the survival estimates beyond the observed Kaplan Meier curves.[94]

B.3.3.2.1. Time-to-event analysis

In order to accommodate the indirect comparison of treatment relative to appropriate treatment in the UK we use the THOR ATC-adjusted dataset provided by the ITC analysis which is matched to the UK RW mUC study data. [20, 82, 83] The resulting analysis therefore provides two IPD datasets that are based on a consistent patient population defined by the baseline characteristics identified through RWE.

Following guidance from NICE DSU TSD 14,[94] time-to-event analyses were performed on IPD available from the ITC (ATC-adjusted data from THOR and the UK RW mUC population; Section B.2.9). This is relevant to OS, TTNT (which is used to determine PFS health state occupancy), and TTD.

Standard parametric models were separately fitted to the Kaplan-Meier curves for each treatment arm. This approach was conducted in line with TSD14[95] which recommends parametric modelling as the primary approach to extrapolating time to event data, then separately fitted models were chosen so as not to rely on the proportional hazards assumption. In Appendix R, we show that the proportional hazards assumption fails to hold. The seven standard distributions were included: exponential, Weibull, gamma, generalised gamma, Gompertz, log-logistic and log-normal.

Assessment of the best-fitting curves for use in the base case and scenario analyses was based on the following criteria:

- Statistical goodness-of-fit based on the Akaike information criterion (AIC) and the Bayesian information criteria (BIC) for each arm
- Visual inspection to assess the fit of the extrapolation to the Kaplan–Meier curve

- Visual inspection for plausibility of the underlying hazard functions (Appendix R)
- Clinical plausibility of survival estimates, based on estimates of survival after 3, 5 and 10 years derived from a structured approach to clinical expert validation

B.3.3.2.2. Overall survival

B.3.3.2.2.1. Erdafitinib

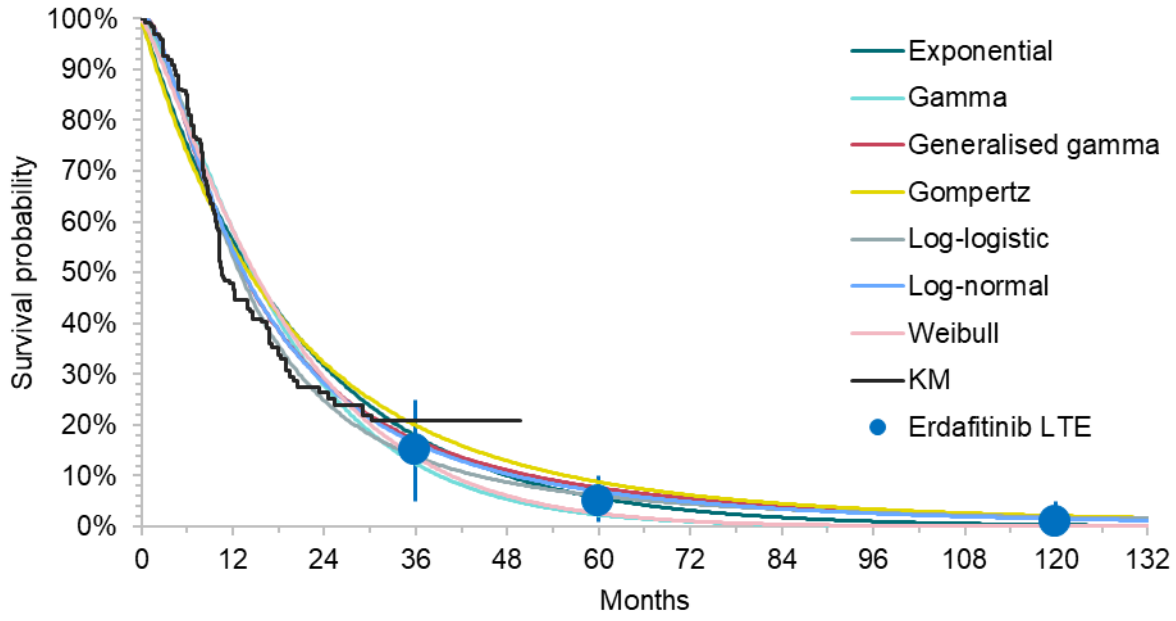
Extrapolation of OS for erdafitinib was performed using analysis weights obtained using the ATC-adjusted patient-level data from the THOR trial. The long-term OS extrapolations for erdafitinib were obtained from fitting standard parametric distributions to observed data and are presented in

Figure 14. The goodness of fit for each distribution and long-term predictions are presented in Table 30. Differences across AIC and BIC statistics were generally small, though the log-logistic, log-normal and generalised gamma extrapolations provided the best statistical fits (lowest AIC and BIC) to the observed THOR OS data.

Figure 14 shows the extrapolated curves and, in-line with closeness of goodness of fit statistics and maturity of the data, show fairly small differences in modelled survival over time.

To inform the validity of the survival projections, Johnson & Johnson sought advice from UK-based clinicians with expertise in treatment and management of mUC patients in the NHS using the Sheffield Elicitation Framework (SHELF).[25] The results of the feedback were that the most likely 3-year survival probability estimate is 15% (lower plausible value of 5% and higher plausible value of 25%), 5-year survival is 5% (1% - 10%), and a 1% (0% - 5%) survival probability at 10 years for patients with mUC receiving erdafitinib. Based on the feedback, the log-logistic and log-normal provided plausible likely estimates of long-term survival probability. The base case used the log-logistic as it had a better statistical fit compared to the log-normal, a hazard function that closely resembled the observed hazard (Appendix R) and it produced slightly more conservative predictions. Scenario analyses that considered the plausible lower and upper limits of the KOL predictions used the gamma and Gompertz distributions, respectively.

Figure 14: Erdafitinib OS KM data and fitted parametric survival models



Key: KM, Kaplan–Meier; LTE, long-term estimates; OS, overall survival.

Table 30: Comparison of long-term erdafitinib OS survival and goodness-of-fit statistics

Model	3-year	5-year	10-year	AIC	BIC
Exponential	17.8%	5.7%	0.3%	571.6	574.4
Weibull	13.7%	2.6%	0.0%	570.2	575.9
Gompertz	19.9%	8.8%	2.1%	573.1	578.8
Log-normal	[redacted]	[redacted]	[redacted]	557.2	562.9
Log-logistic	[redacted]	[redacted]	[redacted]	554.8	560.5
Gamma	12.4%	2.3%	0.0%	567.0	572.6
Generalised gamma	17.1%	7.7%	1.9%	559.1	567.6
Advisory board consensus	15% (5 – 25%)	5% (1 – 10%)	1% (0 – 5%)		

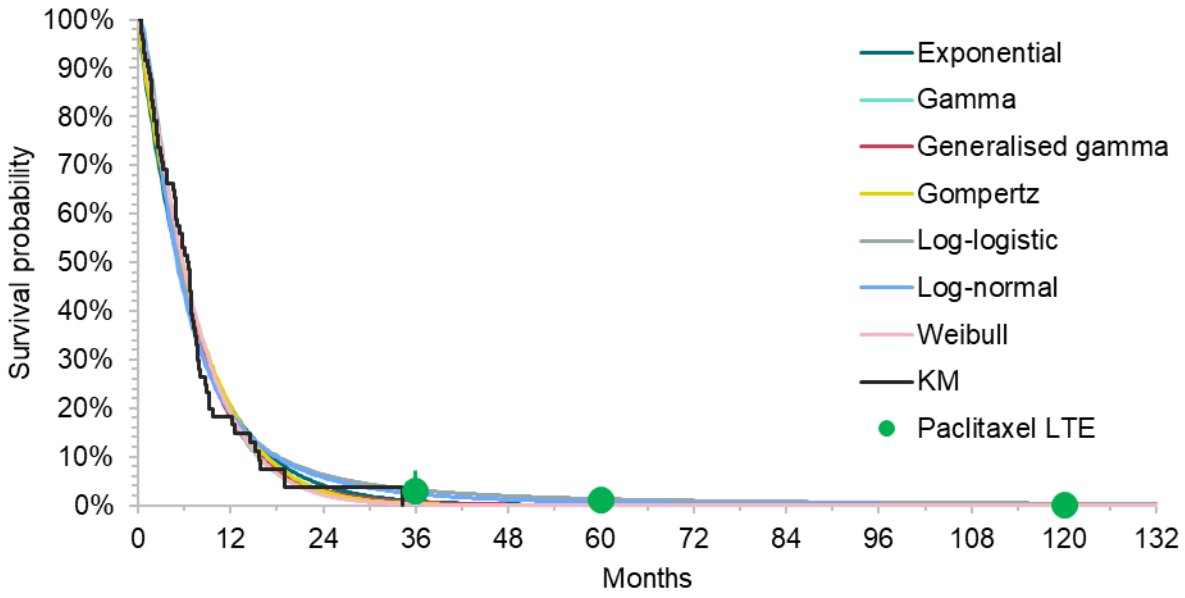
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

B.3.3.2.2.2. Paclitaxel ± carboplatin

OS for patients treated with paclitaxel ± carboplatin was informed by survival models fitted to the original UK RW mUC cohort data.[20] THOR data was weighted to the UK RW mUC cohort data. The fitted models were extrapolated beyond the observed

follow-up period of the cohort study and predicted long-term survival (Figure 15). All model extrapolations had similar statistical fits and long-term survival outcomes (Table 31). The gamma distribution provides the best fit although all models are very similar. To determine the appropriate curve for the base case, stronger emphasis was given to the clinical plausibility of extrapolations. Among these extrapolations, the log-logistic curve has a hazard function that closely resembled the observed hazard (Appendix R) and closely aligned with the most likely estimates provided by clinical experts. The choice of log-logistic is also consistent with the model used for OS with erdafitinib and is conservative as the long-tail marginally increases the likelihood of longer survival.

Figure 15: Paclitaxel ± carboplatin OS KM data and fitted parametric survival models



Key: KM, Kaplan–Meier; LTE, long-term estimates; OS, overall survival

Table 31: Comparison of long-term paclitaxel ± carboplatin OS survival

Model	3-year	5-year	10-year	AIC	BIC
Exponential	0.8%	0.0%	0.0%	388.3	390.6
Weibull	0.2%	0.0%	0.0%	386.6	391.2
Gompertz	0.3%	0.0%	0.0%	389.6	394.2
Log-normal	2.3%	0.6%	0.1%	387.9	392.4
Log-logistic	[redacted]	[redacted]	[redacted]	387.8	392.4
Gamma	0.3%	0.0%	0.0%	385.6	390.1
Generalised gamma	0.6%	0.0%	0.0%	386.9	393.7
Advisory board consensus	3% (0 – 7%)	1% (0 – 3%)	0% (0 – 1%)		

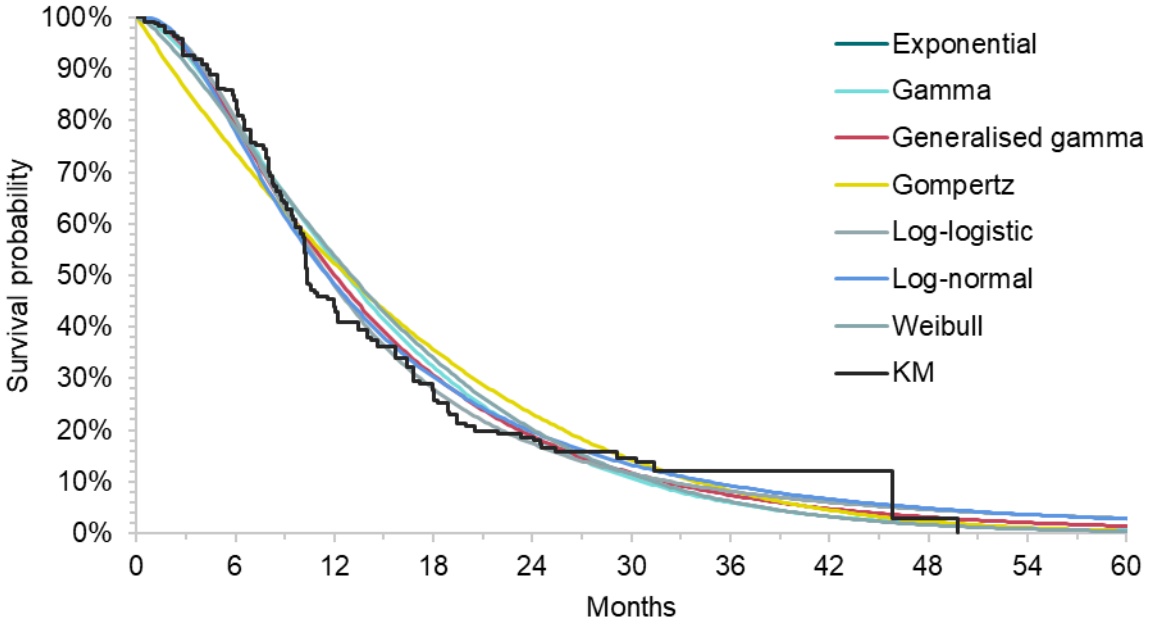
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; OS, overall survival.

B.3.3.2.3. Time to next treatment

B.3.3.2.3.1. Erdafitinib

The long-term TTNT extrapolations for erdafitinib were obtained from fitting standard parametric distributions to ATC-adjusted patient-level data from the THOR trial. The same ITC adjustment approach as for OS was followed in the case of TTNT, to match the THOR trial population to the UK RW mUC population.[20] For modelling TTNT, the same candidate distributions were used as for OS (Figure 16). Given the maturity of the data, visual inspection and AIC/BIC statistics were used to inform model choice. Assessment of the statistical fits showed only small differences between models (Table 32), with the log-logistic considered to be the most appropriate distribution.

Figure 16: Erdafitinib TTNT and fitted parametric survival models



Key: KM, Kaplan–Meier; TTNT, time to next treatment

Table 32: Erdafitinib TTNT – AIC and BIC estimates

Model	3-year	5-year	10-year	AIC	BIC
Exponential	11.6%	2.8%	0.1%	674.9	677.8
Gamma	6.0%	0.5%	0.0%	658.7	664.4
Generalised gamma	7.3%	1.4%	0.0%	657.8	666.4
Gompertz	8.3%	0.4%	0.0%	672.8	678.5
Log-Logistic	[redacted]	[redacted]	[redacted]	653.8	659.5
Log-Normal	9.3%	2.7%	0.3%	658.0	663.7
Weibull	6.2%	0.4%	0.0%	662.9	668.6

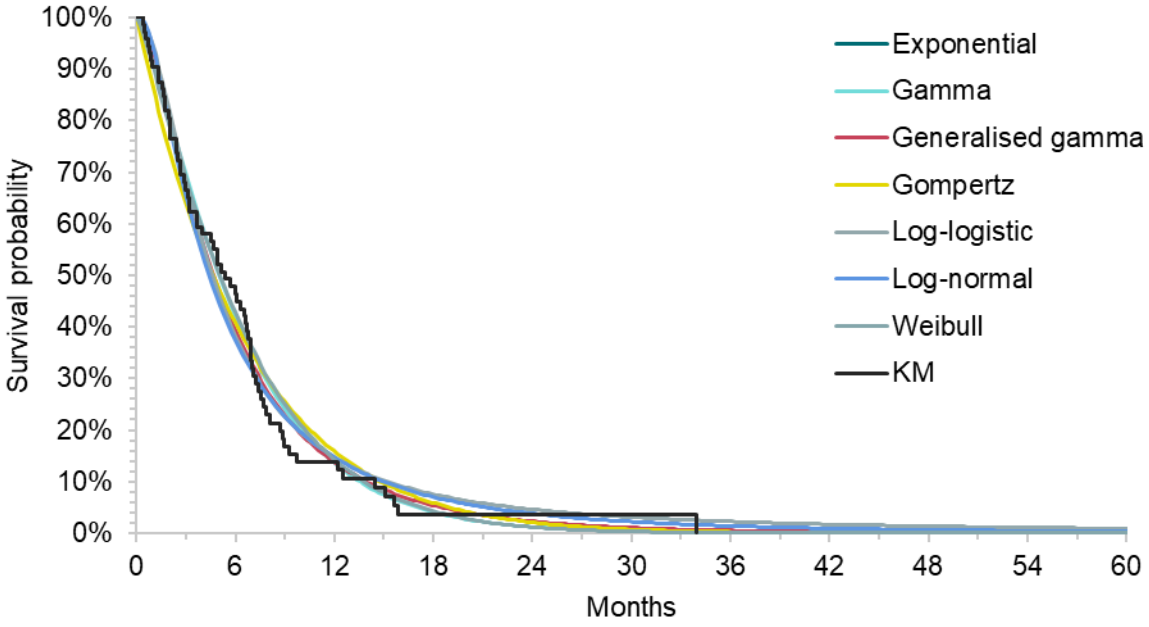
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTNT, time to next treatment.

B.3.3.2.3.2. Paclitaxel ± carboplatin

TTNT for patients treated with paclitaxel ± carboplatin was informed by survival models fitted to the original UK RW mUC cohort data (Figure 17).[20] A summary of the parametric goodness of fit are presented in Table 33. All models were very close

to each other, however based on AIC and BIC statistics, the curve that matches very closely to the data is the log-normal. Given the maturity of the data, the choice of a model to predict long-term probabilities has a limited impact.

Figure 17: Paclitaxel ± carboplatin TTNT and fitted parametric survival models



Key: KM, Kaplan–Meier; TTNT, time to next treatment.

Table 33: Paclitaxel ± carboplatin TTNT - AIC and BIC estimates

Model	3-year	5-year	10-year	AIC	BIC
Exponential	0.4%	0.0%	0.0%	387.4	389.6
Gamma	0.1%	0.0%	0.0%	384.4	388.9
Generalised gamma	0.5%	0.0%	0.0%	384.3	391.1
Gompertz	0.2%	0.0%	0.0%	389.2	393.8
Log-Logistic	2.2%	0.9%	0.2%	384.3	388.9
Log-Normal	[redacted]	[redacted]	[redacted]	383.8	388.3
Weibull	0.1%	0.0%	0.0%	386.0	390.6

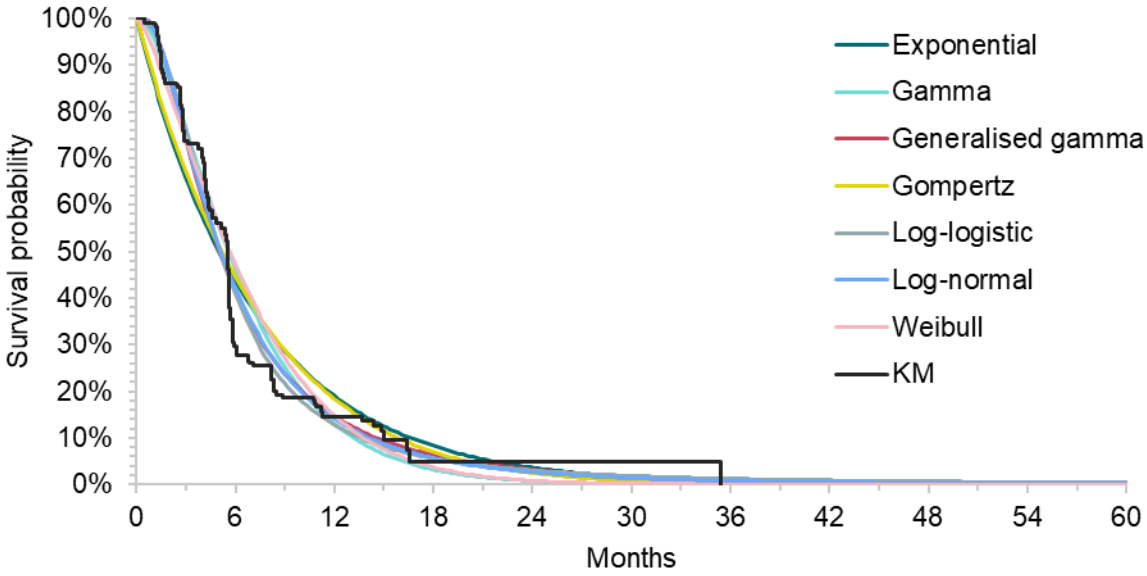
Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; TTNT, Time to next treatment.

B.3.3.2.4. Progression-free survival

B.3.3.2.4.1. Erdafitinib

For erdafitinib, the seven parametric models fitted to the ATC-adjusted patient-level data from the THOR trial were exponential, gamma, generalised gamma, Gompertz, log-logistic, log-normal and Weibull (Figure 18). The PFS data was mature such that no clinical validation was sought. Based on AIC and BIC statistics and visual assessment, the log-logistic and log-normal extrapolations provided the best fitting curves (Table 34). Log-logistic was chosen as it had the smallest AIC and BIC estimates.

Figure 18: Erdafitinib PFS and fitted parametric survival models



Key: KM, Kaplan–Meier; PFS, progression-free survival.

Table 34: Erdafitinib PFS – AIC and BIC estimates

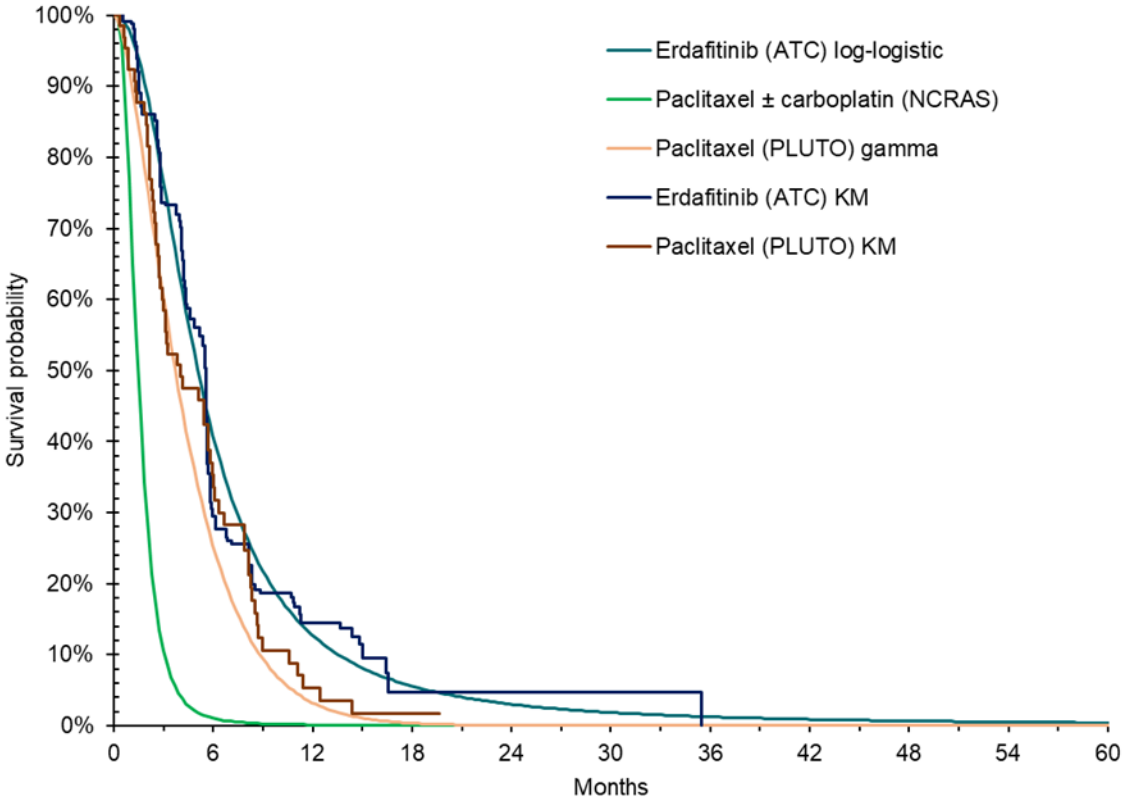
Model	3-year	5-year	10-year	AIC	BIC
Exponential	0.7%	0.0%	0.0%	559.6	562.4
Gamma	0.0%	0.0%	0.0%	541.1	546.8
Generalised gamma	1.1%	0.2%	0.0%	531.7	540.3
Gompertz	0.2%	0.0%	0.0%	561.0	566.7
Log-Logistic	[redacted]	[redacted]	[redacted]	528.0	533.7
Log-Normal	0.7%	0.1%	0.0%	530.0	535.7
Weibull	0.0%	0.0%	0.0%	548.6	554.3

Key: AIC, Akaike information criterion; BIC, Bayesian information criterion; PFS, progression-free survival.

B.3.3.2.4.2. Paclitaxel ± carboplatin

TTNT curves for both erdafitinib and paclitaxel ± carboplatin were close to the OS curves. This led to the conclusion that TTNT alone may not serve as a suitable proxy for PFS in this context. Therefore, a simplifying assumption using the ratio of PFS to TTNT per cycle for erdafitinib was used to derive a PFS extrapolation for paclitaxel ± carboplatin was implemented (Figure 19). The median PFS from the derived curve is about 1.5 months. This was a conservative assumption as using data from alternative sources or methods slightly reduced the incremental cost-effectiveness ratio (ICER). An alternative approach was to set PFS equal to that of paclitaxel from PLUTO trial which was evaluated as a scenario, with a median PFS of 4.1 months.[92]

Figure 19: Paclitaxel ± carboplatin PFS and fitted parametric survival models



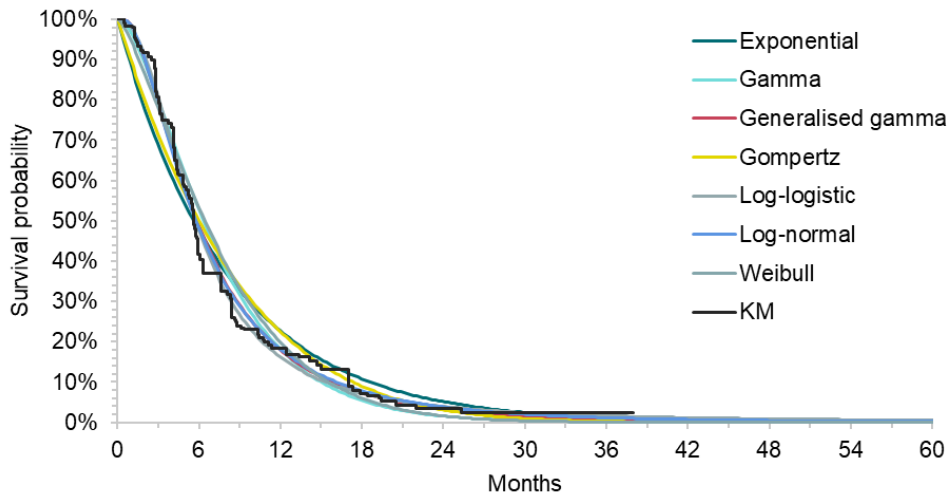
Key: KM, Kaplan–Meier; PFS, progression-free survival. ATC, average treatment effect for the control; NCRAS, National Cancer Registration and Analysis Service. The green curve is the base case PFS curve for paclitaxel ± carboplatin and a scenario will be based on the orange curve

B.3.3.2.5. Time to treatment discontinuation

B.3.3.2.5.1. Erdafitinib

Time to treatment discontinuation for erdafitinib was extrapolated from the ATC-adjusted patient-level data from the THOR trial.[76] Visual assessment of model fits to the observed TTD data shows relatively good fits for all models (Figure 20). The statistical fits show log-logistic and generalised gamma with better statistical fits (Table 35). The log-logistic was used in the base case as it had the best statistical fit.

Figure 20: Erdafitinib TTD and fitted parametric survival models



Key: KM, Kaplan–Meier; TTD, time to discontinuation.

Table 35: Erdafitinib TTD – AIC and BIC estimates

Model	3-year	5-year	10-year	AIC	BIC
Exponential	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Gompertz	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-Logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Log-Normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weibull (AFT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Key: AFT, accelerated failure time; AIC, Akaike information criterion; BIC, Bayesian information criterion; TTD, time to discontinuation.

B.3.3.2.5.2. Paclitaxel ± carboplatin

Although TTD is available from the THOR trial (outlined in Section B.3.3.2.5.1), it is not available from the UK RW mUC study.[20] Therefore, a simplifying assumption was made that TTD for paclitaxel ± carboplatin would be equivalent to the generated PFS (Section 3.3.2.3.2). It is expected that these assumptions are reasonable considering the lack of TTD data. However, they may lead to an underestimation of treatment discontinuations in the model. Considering, the minimal impact of subsequent

treatments on the model's results (as described in Section B.3.5.4.1), it is expected that a potential underestimation of treatment discontinuations would not have any significant impact on the results.

B.3.3.3. Summary of OS, TTNT, PFS and TTD - base case settings

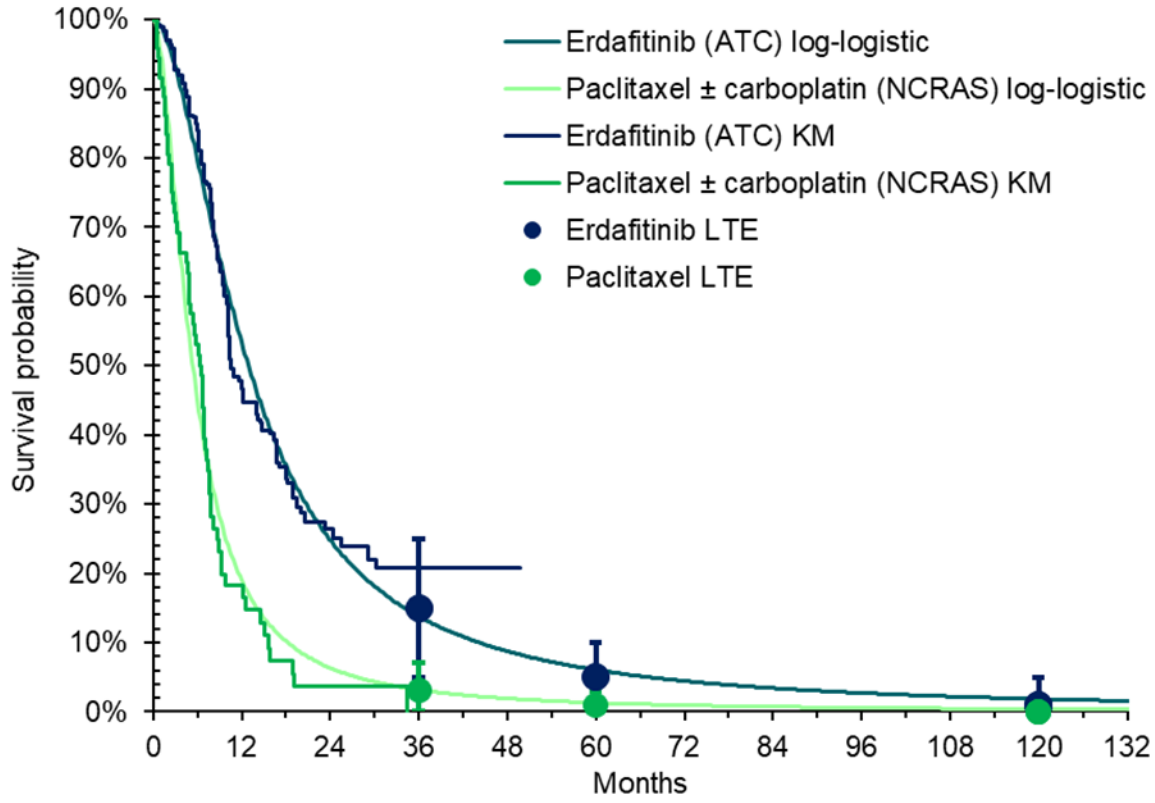
Table 36 provides a summary of the base case survival modelling assumptions included in the economic analysis. An overlay of the base case curves for OS (Figure 21), TTNT (Figure 22), PFS (Figure 23) and TTD (Figure 24) are provided in Sections B.3.3.2.2, B.3.3.2.3, B.3.3.2.4 and B.3.3.2.5, respectively.

Table 36: Base case model assumptions

Event	Erdafitinib	Paclitaxel ± carboplatin
Overall survival	Log-logistic	Log-Logistic
Time to next treatment	Log-logistic	Log-Normal
Progression-free survival	Log-logistic	Assumption based on observed ratio of PFS to TTNT in treatment arm
Time to treatment discontinuation	Log-logistic	Assumed to be similar to PFS curve.
Rationale	OS curve selection was based best fitting AIC & BIC with good visual fit and clinical validity. TTNT, PFS and TTD model selection was based on best fitting AIC and BIC statistics with good visual fit.	OS model choice was mainly driven by clinical validity. TTNT model selection was based on best fitting AIC & BIC with good visual fit. Determination of PFS and TTD was based on plausible assumptions where data was unavailable.

In most cases the data are fully mature and therefore the impact of using parametric survival modelling is simply to smooth a Kaplan–Meier curve and provide a longer tail over time. The exception is OS with erdafitinib where the RCT data end with approximately 20% of the survival times censored.

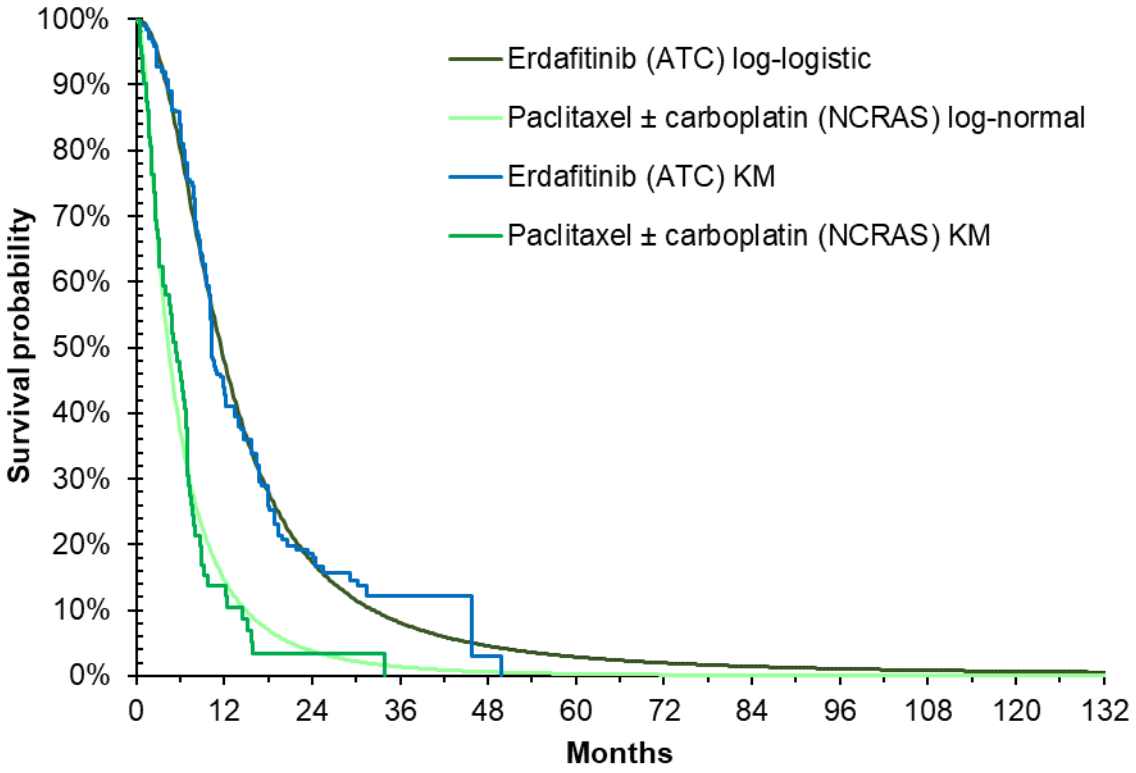
Figure 21: Overlay of OS KM and extrapolated curves in the base case (erdafitinib and paclitaxel ± carboplatin)



Key: ATC, average treatment effect for the control; KM, Kaplan Meier; LTE, long-term estimates; NCRAS, National Cancer Registration and Analysis Service; OS, overall survival.

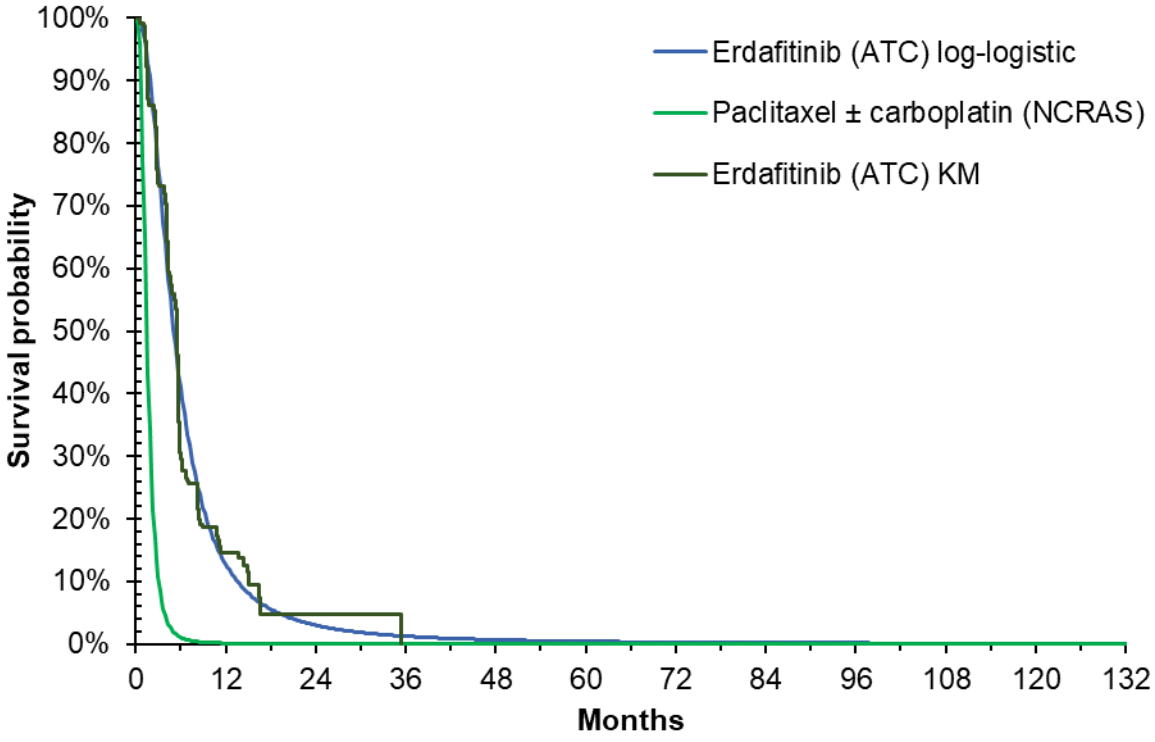
Figure 21 shows that the base case assumption of the log-logistic parametric survival model is somewhat conservative relative to the observed Kaplan–Meier which plateaus at around 20%.

Figure 22: Overlay of TTNT KM and extrapolated curves in the base case (erdafitinib and paclitaxel ± carboplatin)



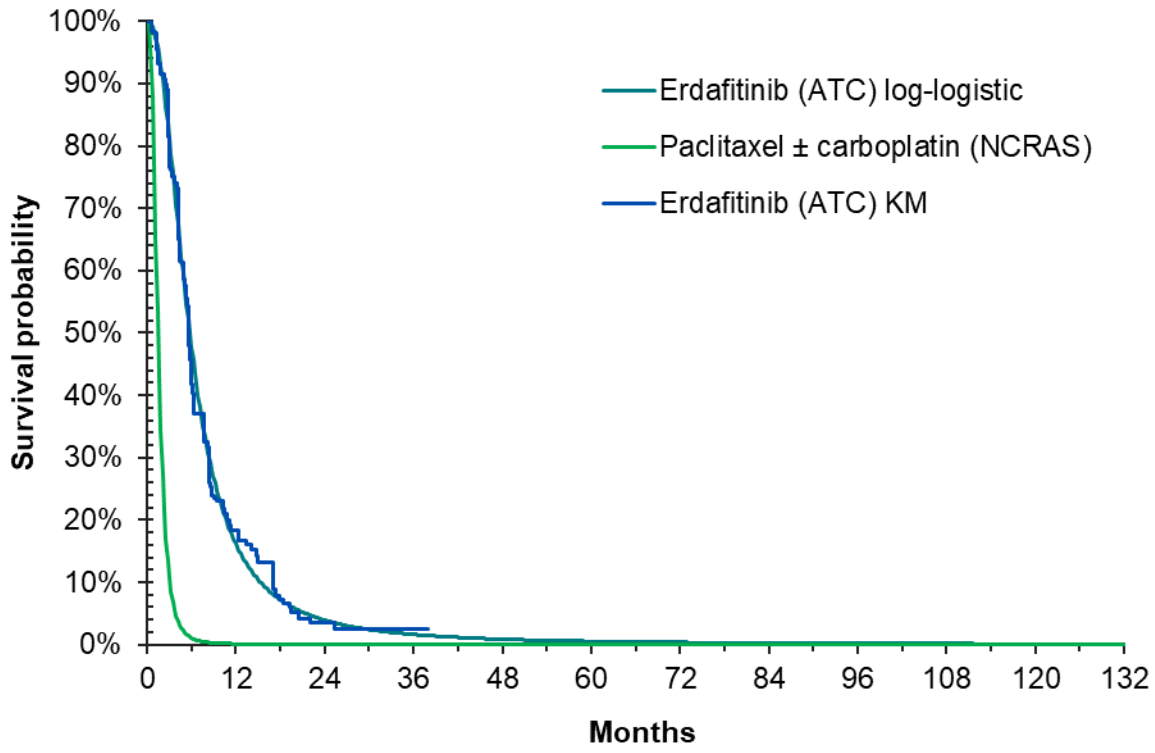
Key: ATC, average treatment effect for the control; KM, Kaplan Meier; NCRAS, National Cancer Registration and Analysis Service.

Figure 23: Overlay of PFS KM and extrapolated curves in the base case (erdafitinib) and assumed curve for paclitaxel ± carboplatin



Key: ATC, average treatment effect for the control; NCRAS, National Cancer Registration and Analysis Service; KM, Kaplan Meier

Figure 24: Overlay of TTD KM and extrapolated curves in the base case for erdafitinib and assumed curve for paclitaxel ± carboplatin



Key: ATC, average treatment effect for the control; NCRAS, National Cancer Registration and Analysis Service; KM, Kaplan Meier

In all non-OS cases the maturity of the data means that the parametric model and choice of parametric model has little impact other than to smooth the survival curve.

B.3.3.3.1. Structural Sensitivity Analysis

Potential bias resulting from key structural assumptions was explored through deterministic scenario analyses. Survival distributions for extrapolation of long-term costs and outcomes aligned with either the lower or higher plausible estimates from clinicians for both erdafitinib and paclitaxel ± carboplatin are explored.

B.3.4. Measurement and valuation of health effects

B.3.4.1. Health-related quality-of-life data from clinical trials

EQ-5D-5L data were collected in the THOR clinical trial. In line with NICE guidelines, the EQ-5D-5L data were mapped to EQ-5D-3L using the UK value set before conducting statistical analysis.[86]

Two approaches were tested to derive health state utility values from the trial data. In the first approach, estimates were derived separately for the PF and PD health states without any additional covariates. This is used in the base case analysis and is a standard approach that is widely accepted to be appropriate for HTAs including in mUC. In the alternative approach, multivariable regression models with additional covariates were explored. In addition, the impact of implementing utilities over time using previously published values was assessed.[57]

In the base-case approach, utilities were estimated with linear mixed models for repeated measures (MMRMs) using pooled data from both treatment arms (Table 37). The PF health state utility was based on the area under the curve (AUC) of mean utility estimates for each treatment cycle among patients remaining PF in that cycle. PD state utility was estimated from questionnaires of patients who were known to have progressed (i.e., excluding questionnaires after censoring) using a single MMRM that accounted for correlations between EQ-5D measurements from the same patient. Compound symmetry covariance structure was selected as resulting in the lowest AIC. These analyses were conducted in SAS.

Table 37 presents the base-case UK health state utility values used in the model for PF and PD health states.

Table 37: Health state utilities (base case)

Health state	Mean utility value	Standard error
Progression-free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]

In the second alternative approach, health state utilities were estimated within a single multivariable regression model with additional covariates. Several mixed-effects regression models were considered, each with a different combination of the following variables:

- Health state (PF, PD)
- Treatment (erdafitinib, docetaxel or vinflunine)
- Grade 3–5 AE occurrence (Yes, No)
- Age, sex, race, body mass index, PD-(L)1 status (combined positive score 10% cut-off), metastasis status as initial diagnosis, baseline ECOG PS, and number of prior lines of therapy

All the models also included a random intercept for patients to adjust for the correlation between multiple observations from the same patient. It is assumed that the observations for a single patient will be distributed around the mean for that patient. These analyses were conducted in R using the 'nlme' package.

A series of analyses were conducted to identify the best fitting models. Simple univariate models were initially fitted separately for each covariate identified as being potentially relevant. This identified only three univariate models: health state, Grade 3–5 AE occurrence, and baseline ECOG PS. These models provided an improved fit to the data, compared to a model with random intercept alone and were carried forward to a stepwise model selection, which considered models with multiple covariates. Despite the treatment univariate model not satisfying this cut-off, it was also carried forward as a variable of particular interest and was required to specify a model that could produce treatment-specific utility estimates.

Backward stepwise variable selection by AIC was used to determine which of the baseline variables were included in the final regression model for use in the economic model. Stepwise variable selection is a parsimonious approach to the inclusion of covariates and was chosen to avoid making models unnecessarily complex without statistical gain. The AIC and BIC scores of this model were compared against models that had covariates removed. Where the AIC score was

lower, further variables were removed. The process continued until the model providing the lowest AIC value was identified. Subsequently, the model that considered progression and AEs was considered the best-fitting model and was used in a scenario analysis (Model 1, Table 38 and Table 39).

Table 38: Utility model results (UK)

Covariate	Coefficient	SE	p-value	AIC (rank)	BIC (rank)
Model 1 – Progression and adverse events					
Intercept	0.786	0.018	-	-1530.23 (1)	-1491.06 (1)
Progression status	-0.105	0.010	< 0.001		
Grade 3-5 AE increment	-0.069	0.013	< 0.001		
Baseline ECOG1	-0.120	0.025	< 0.001		
Baseline ECOG2	-0.395	0.047	< 0.001		
Model 2 – Progression only					
Intercept	0.780	0.018	-	[redacted]	[redacted]
Progression status	[redacted]	0.010	< 0.001		
Baseline ECOG1	[redacted]	0.026	< 0.001		
Baseline ECOG2	[redacted]	0.047	< 0.001		
Model 3 – Progression, adverse events, and treatment					
Intercept	0.782	0.020	-	-1516.56 (2)	-1466.21 (3)
Progression status	-0.105	0.010	< 0.001		
Docetaxel increment	0.019	0.029	0.510		
Vinflunine increment	-0.006	0.034	0.859		
Grade 3-5 AE increment	-0.069	0.013	< 0.001		
Baseline ECOG1	-0.119	0.025	< 0.001		
Baseline ECOG2	-0.393	0.047	< 0.001		
Model 4 – Progression and treatment					
Intercept	0.776	0.020	-	-1496.19 (4)	-1451.44 (4)
Progression status	-0.108	0.010	< 0.001		
Docetaxel increment	0.020	0.029	0.503		
Vinflunine increment	-0.007	0.034	0.850		
Baseline ECOG1	-0.121	0.026	< 0.001		
Baseline ECOG2	-0.399	0.047	< 0.001		

Key: AE, adverse event; AIC, Akaike information criterion; BIC, Bayesian information criterion; ECOG, Eastern Cooperative Oncology Group; SE, standard error.

Table 39: Alternative utility inputs (scenario)

Utility input	Value
Health state	
Progression-free	[redacted]
Progressed	[redacted]
Key: ECOG PS, Eastern Cooperative Oncology Group performance status. **Note:** *Weighted average of ECOG 1–2 coefficients applied to the intercept.	

The cost-effectiveness model also includes functionality to explore time-to-death utilities (Table 40), which were informed by literature and considered patient utility at ≥ 360 days, 180–359 days, 90–179 days, 30–89 days, and 0–29 days to death.[57] This assumes that utility values are affected by patients' proximity to death, and measures utility values accordingly. This allows for a more detailed utility measurement over the duration of the trial period and over the patients' lifetime, compared with analyses purely based on progression status approach (which only distinguishes utility values before and after the point of confirmed progression status). The impact of using these utility values over progression-based utilities was investigated within the scenario analyses.

Table 40: Time to death utilities (scenario)

Time to death (days)	Mean utility value	Standard error
≥ 360	0.778	0.013
180–359	0.693	0.013
90–179	0.590	0.016
30–89	0.451	0.024
0–29	0.325	0.056

As per the NICE reference case, health state utilities were also adjusted within the model to account for the age-matched general population, using a utility multiplier derived from Hernández Alava.[96] This is a standard and necessary approach, given that the data collected in the THOR trial are unlikely to capture the age-related decline in HRQL over longer time periods.

The utility values explored in the cost-effectiveness analysis are presented in Table 41. The utility values derived from THOR were similar to those in TA522. However, they were lower than those in TA788. This difference in values could be attributed to variances in the patients' fitness level. In TA788, patients were still undergoing first-line treatment and subsequently received maintenance therapy. On the other hand, in our trial, patients received erdafitinib as either a second or third-line treatment.

Table 41: Comparison of base case health state utility values from THOR and in previous NICE technology appraisals

Technology appraisal	Health state	Input
Base case (THOR)[76]	Progression-free	[redacted]
	Progressed disease	[redacted]
TA522 (TA692) (pembrolizumab vs chemotherapy – pooled)[97]	Progression-free	0.678
	Progressed disease	0.641
TA739 (atezolizumab vs platinum-based chemotherapy – pooled)[69]	Progression-free	0.632
	Progressed disease	0.611
TA788 (avelumab)[24]	Progression-free	0.772
	Progressed disease	0.698

B.3.4.2. Mapping

As described in Section B.3.4.1, EQ-5D-5L® data were collected in the THOR clinical trial.[86] In line with NICE guidelines, the EQ-5D-5L data were mapped to EQ-5D-3L using the UK value set before conducting statistical analysis.[98]

B.3.4.3. Health-related quality-of-life studies

Appendix H provides details of the SLR for identifying HRQL studies published since 2000 through multiple iterations of SLR updates. The most recent SLR update was performed on 10 April 2024, retrieving up to date evidence available since the previous SLR performed in May 2023. The searches were conducted for the broader population of patients treated with at least one line of prior systemic therapy, to ensure identification of all potentially relevant evidence for utility values.

A total of 14 relevant publications reporting HRQL data or utility values were identified. These included five RCTs, five HTA submissions, and four observational studies.

Five studies reported utility data relevant to the patient population with UC. These have been summarised in Table 42 (please refer to Appendix H for full details). Given the differences in the populations, and the relatively broad range of utility values identified across the study populations, we did not consider the utility estimates identified from the SLR to be informative for the cost-effectiveness model. The THOR-based estimates outlined in Section B.3.4.1 remain the most relevant sources of utility values for the model.

Table 42: Key characteristics and results of included health-related quality of life studies

Author and year of publication	Country/Study setting	Treatments (cohort size)	Method of elicitation	Timepoints when measurements were made	HRQL or Utility/Disutility findings
CADTH 2022[99]	Canada/HTA report with cost-effectiveness analysis results	Treatment: • Enfortumab vedotin (NR) Comparator: • Chemotherapy (NR)	EQ-5D-5L	NR	Utilities: • Pre-progression: 0.795 • Progressive disease: 0.697
PBAC 2022Pharmaceutical Benefits Advisory Committee (PBAC) [100]	Australia/HTA report with cost-effectiveness analysis results	Treatment: • Enfortumab vedotin (NR) Comparator: • Chemotherapy (NR)	EQ-5D-5L	NR	Utilities PFS • Enfortumab vedotin: 0.74 • Chemotherapy: 0.71 Progressive disease: • Enfortumab vedotin: 0.61 • Chemotherapy: 0.61
Wu 2022[101]	US/Cost-effectiveness analysis	Treatment: • Enfortumab vedotin (NR) Comparator • Chemotherapy (NR)	Utility and disutility values	NR	Utilities: • PFS: 0.60 • Progressive disease: 0.52 Disutilities: • AEs Grade 1–2: 0.01 • AEs Grade ≥ 3: 0.28
Lin 2023[102]	US/Cost-effectiveness analysis	Treatment: • Avelumab + BSC (NR) Comparator: • BSC (NR)	Utility and disutility values	NR	Utilities: • PFS: 0.72 • Progressive disease: 0.60 Disutilities: • Anaemia: 0.12 • Asthenia: 0.07

Author and year of publication	Country/Study setting	Treatments (cohort size)	Method of elicitation	Timepoints when measurements were made	HRQL or Utility/Disutility findings
					• Backpain: 0.07 • Fatigue: 0.10 • UTI: 0.10 • Vomiting: 0.05 • Haematuria: 0.09
Xie 2022[103]	US, China/ Cost-effectiveness analysis	Treatment: • Avelumab + BSC (NR) Comparator • BSC (NR)	Utility values	NR	Utilities: PFS: • US: 0.84 • China: 0.84 Progressive disease: • US: 0.80 • China: 0.80
Key: AE, adverse event; BSC, best supportive care; GHS, global health status; HTA, health technology assessment; IQWiG, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NR, not reported; PBAC, Pharmaceutical Benefits Advisory Committee; PFS, progression-free survival; QoL, quality of life; RCT, randomised control trial; TTD, time-to-treatment discontinuation.					

B.3.4.4. Adverse reactions

The impact of AEs on HRQL is incorporated into the economic model. The occurrence of AEs associated with erdafitinib are based on the THOR trial.[76] AEs associated with paclitaxel ± carboplatin are informed by the PLUTO trial.[92] PLUTO only considered patients receiving paclitaxel monotherapy; therefore, it is assumed that the safety profile associated with paclitaxel is similar to that of paclitaxel in combination with carboplatin. In reality, it is possible that this assumption reflects a conservative view of AEs associated with platinum-containing doublet chemotherapy. However, as AEs were not a key driver of results, the absence of AE data for the combination and only 25% of the patients were on combination treatment, this assumption was deemed appropriate.

Treatment-specific Grade 3+ AEs with incidence of greater than 5% of patients in the erdafitinib arm of THOR and/or paclitaxel arm from PLUTO were included. These are expected to have the greatest impact on patients' HRQL and NHS resource use (Table 43). The QALY losses associated with AEs were calculated by multiplying the utility decrement by the duration of the AE. They were then multiplied by the proportion of patients experiencing the AE with each treatment to obtain treatment-specific AE-related QALY losses.

Duration of AEs was informed by the THOR trial and is summarised in Table 44**Error! Reference source not found.**. For each patient experiencing a particular Grade ≥ 3 AE, the total cumulative time spent with that AE was calculated by summing the durations of distinct occurrences of the same even type; for occurrences with missing end dates, duration was assumed equal to the mean of complete observations. The mean time for each AE was then obtained by averaging the times across all patients who experienced that AE. This value was calculated by multiplying the proportion who experience each AE (Table 44) by the total number of patients in each arm (135 erdafitinib patients, 64 paclitaxel patients).

The decrement associated with each AE is based on values sourced from the wider literature (Table 44). The QALY losses associated with AEs were calculated by multiplying the utility decrement by the duration of the AE. They were then multiplied

by the proportion of patients experiencing the AE with each treatment to obtain treatment-specific AE-related QALY losses.

Table 43: Incidence of adverse events used in the model

Adverse event	Erdafitinib (THOR)[76]	Paclitaxel (PLUTO)[92]
Palmar-plantar erythrodysesthesia syndrome	[redacted]	0.00%
Stomatitis	[redacted]	0.00%
Anaemia	[redacted]	0.00%
Hyponatraemia	[redacted]	0.00%
Onycholysis	[redacted]	0.00%
Hyperphosphataemia	[redacted]	0.00%
Hypophosphataemia	[redacted]	9.38%
Neutropenia	[redacted]	9.38%
Fatigue	[redacted]	7.81%

Table 44: Adverse event disutilities and duration information

Grade 3–4 adverse event	Disutility	Duration (days)	Data source: Disutility	Data source: Duration
Palmar-plantar erythrodysesthesia syndrome	-0.040	[redacted]	Assumed equal to stomatitis (following TA780[104])	THOR[76]
Stomatitis	-0.040	[redacted]	TA498[105]	
Anaemia	-0.090 (0.02)	[redacted]	Beusterien et al. (2010)[106]	
Hyponatraemia	-0.115	[redacted]	Lloyd et al. (2006) - Assumed equivalent to fatigue[107]	
Onycholysis	-0.032 (0.012)	[redacted]	Nafees et al. (2009) - Assumed equivalent to skin reactions[108]	
Hyperphosphataemia	-0.115	[redacted]	Nafees et al. (2009)[108] Assumed equivalent to fatigue[107]	
Neutropenia	-0.090 (0.015)	[redacted]	Nafees et al. (2009)[108]	
Fatigue	-0.073 (0.018)	[redacted]	Nafees et al. (2009)[108]	

Grade 3–4 adverse event	Disutility	Duration (days)	Data source: Disutility	Data source: Duration
Key: TA, technology appraisal.				

B.3.4.5. Health-related quality-of-life data used in the cost-effectiveness analysis

A summary of the utility values used in the cost-effectiveness analysis is provided in Table 45Table 45, including details of the relevant scenarios.

Table 45: Summary of utility values for cost-effectiveness analysis

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
Base case				
Progression-free health state	[redacted]	[redacted]		Best-fitting utility model, validated with KOLs and previous NICE TAs
Progressed disease health state	[redacted]	[redacted]		
Decrement due to AEs	Per AE			
Scenarios				
Alternative utility values from multivariable regression model	[redacted]			Assuming different utility values as they are close to prior atezolizumab appraisal (TA739)
Alternative utility values based on time to death	Time to death ≥ 360 days: 0.778 180 – 359 days: 0.693 90 – 179 days: 0.590 30 – 89 days: 0.451			To explore the impact of time to death utilities over progression-based utilities

State	Utility value: mean (standard error)	95% confidence interval	Reference in submission (section and page number)	Justification
	0 – 29 days: 0.325			

B.3.5. Cost and healthcare resource use identification, measurement and valuation

The following cost categories are incorporated in the economic model, as described in this section:

- Drug acquisition costs
- Drug administration costs
- Health state resource use costs (e.g.,
- ongoing monitoring and follow-up)
- AE costs
- Cost of *FGFR* testing and ophthalmology assessments
- Subsequent treatment costs
- End-of-life care costs

B.3.5.1. Intervention and comparators' costs and resource use

An SLR was conducted to identify costs and HCRU studies relevant to the decision problem. A series of SLR updates have been conducted, with the earliest SLR being conducted in 2018. The most recent SLR update was conducted on 10 April 2024, retrieving up to date evidence available since the previous SLR performed on 18 May 2023. Full details of the SLR can be found in Appendix I.

A total of 22 studies were retrieved that reported costs and HCRU data in patients with locally advanced, surgically unresectable or metastatic urothelial cancer beyond the first line of systemic therapy. Eight of these studies were in the US, three each in Canada and Germany, and two each in Italy and Austria. One study included both US and Canada populations.

B.3.5.1.1. Acquisition costs

Treatment costs are calculated based on the recommended dosing regimen for each drug across the modelled treatment duration detailed in Section B.3.3.2. Due to the maturity of the data, by the end of the observed period, almost all patients had discontinued treatment in the erdafitinib arm of THOR (Section B.3.3.2.5) and patients would have completed treatment with chemotherapy in the paclitaxel ± carboplatin arm.

List prices of drugs for paclitaxel ± carboplatin have been sourced from the Drugs and pharmaceutical electronic market information tool (Table 46).[109] As previously described, erdafitinib is implemented in the economic model according to the THOR trial protocol.[76, 110, 111] This follows the appropriate dosing regimens outlined in Table 47.

Table 46: List prices of intervention and comparator drugs

Drug name	Drug form	Quantity per unit (mg)	Units in packet	Price per pack
Erdafitinib	Tablet	Per physician prescription	28, 56 or 84 units per pack, dependent on physician prescription. Dose per patient varies per patient as this is based on the amount of erdafitinib prescribed per 28 days.	£12,750.00
Paclitaxel	6 mg/ml (vial)	30 mg	1	£3.88
Paclitaxel	6 mg/ml (vial)	100 mg	1	£9.13
Paclitaxel	6 mg/ml (vial)	150 mg	1	£16.92
Paclitaxel	6 mg/ml (vial)	300 mg	1	£24.43
Carboplatin	10 mg/ml (vial)	15 ml	1	£20.22
Carboplatin	10 mg/ml (vial)	45 ml	1	£48.09
Carboplatin	10 mg/ml (vial)	5 ml	1	£9.28
Carboplatin	10 mg/ml (vial)	60 ml	1	£71.44

Table 47: Dosing information

Comparators	Dosing	Details	Reference
Erdafitinib	8 mg	8 mg daily for 21 days administered orally*	THOR CSR, 2021[76]
Paclitaxel	80 mg/kg	80 mg/m² as 1-hour intravenous infusion in 250 ml sodium chloride on days 1, 8 and 15 every 28 days	PLUTO trial[92]
Paclitaxel ± carboplatin	175mg/kg	175 mg/m² administered over a period of 3 hours every 3 weeks	Bellmunt et al., 2017[93]
	6 AUC	Dosed to a targeted area under the concentration-time curve (area under the curve) [AUC] = 6 mg/mL · minute over 30 minutes. The dose of carboplatin calculated by the Calvert formula: mg = targeted AUC × (GFR + 25). GFR assumed to be the estimated creatinine clearance.	Vaughn et al., 1998[112]

Key: AUC, area under the curve; CSR, clinical study report; GFR, glomerular filtration rate; SmPC, Summary of Product Characteristics.
Notes: * Treatment may be up-titrated to 9 mg, maintained at 8 mg, or withheld, based on phosphate levels as measured on Cycle 1, Day 14.

Erdafitinib is prescribed and distributed in packs of tablets (28-day packs). The cost per cycle is calculated using the drug administration details and TTD to determine whether a new pack is required. If so, a full new drug packet is costed upfront to all patients on treatment regardless of whether all of it is used.

Paclitaxel and carboplatin are both stored and administrated intravenously, using treatment vials. The distribution of patients receiving monotherapy or combination therapy is costed directly based on data from the NCRAS paclitaxel ± carboplatin cohort:

- Paclitaxel (75%)

- Paclitaxel ± carboplatin (25%)

For erdafitinib, relative dose intensity was not applied using a proportional evaluation of the calculated dose. Instead, the model applied an overall dose modifier for erdafitinib based on the proportion of doses that were skipped in the THOR safety population (17.07%, based on a mean duration of exposure of 206.8 days and a sample size of N = 135). This was done in order to more accurately capture where patients have missed doses, which was not uncommon due to phosphate level monitoring.

In the base case analysis, the model assumes that there will be no wastage in clinical practice (i.e., there is no tablet splitting or vial sharing).

B.3.5.1.2. Administration costs

In addition to the drug acquisition costs, the cost of administration was also included. Administration costs were applied dependent on whether the drug was administered intravenously, as a simple, complex, or subsequent procedure, or orally (Table 48).

For IV drugs, it was assumed that patients would receive treatment in a hospital setting at each administration. For oral therapies (erdafitinib) a single one-off cost is applied. The administration costs per treatment are presented in Table 48, and the costs applied per therapy arm after inflation are displayed in Table 49.

Table 48: Administration types and associated unit costs per administration

Treatment	Administration cost (2021/22)	Inflated cost (2022/23)	Reference
Intravenous (simple)	£286.71	£306.87	SB12Z - Deliver Simple Parenteral Chemotherapy at First Attendance, Total HRGs National Schedule of NHS Costs - Year 2021/22[113]
Intravenous (complex)	£353.64	£378.50	SB13Z - Deliver more Complex Parenteral Chemotherapy at First Attendance, Total HRGs National Schedule of NHS Costs - Year 2021/22[113]
Intravenous (subsequent)	£368.44	£394.35	SB15Z - Deliver Subsequent Elements of a Chemotherapy Cycle, Total HRGs National Schedule of NHS Costs - Year 2021/22[113]
Oral	£216.90	£232.15	SB11Z - Deliver Exclusively Oral Chemotherapy National schedule of NHS costs - Year 2021/22 [113] One-off cost, in line with TA855[114]
Key: HRGs, Healthcare Resource Groups; NHS, National health service.			

Table 49: Total administration costs applied per arm (inflated to 2022/23)

Regimen	Administration cost	Every X model cycles	Oral administration cost (one-off)
Erdafitinib	£0	3.0	£232
Paclitaxel	£307	1.0	£0
Paclitaxel + carboplatin	£378	3.0	£0

B.3.5.2. Health-state unit costs and resource use

Costs associated with ongoing disease management, monitoring and patient follow-up are included in the economic model. The most appropriate HCRU inputs to consider were derived from discussions with clinicians as part of a steering committee meeting conducted by Johnson and Johnson Innovative Medicine.[25]

Healthcare resources were included that were specific to each health state (i.e., PF or PD) and treatment arm. Costs were applied to each resource and accrued according to the time spent in each health state.

In line with the NICE reference case, the relevant unit costs were sourced from either the Personal Social Services Research Unit (PSSRU) 2023 or the NHS reference cost documentation and reflect 2020–2021 prices (Table 50Table 50).[90, 113, 115] Healthcare use frequencies were based on clinician's estimates, previous technology appraisals and the UK RW mUC study – the latter two validated by clinicians during the Johnson and Johnson Innovative Medicine-conducted advisory board (Table 51).[25] For each type of resource, frequency of use was multiplied by the associated cost to calculate the per-cycle cost. This informs an aggregate cost of monitoring associated with each health state, which have been inflated to 2022/2023 prices (Table 52).

Table 50: HCRU unit costs

Resource use	Unit cost (2021/22)	Inflated cost (2022/2023)	Source
GP visit	£55.00	£55.00	PSSRU 2023; cost for GP appointment (10 minutes with direct care staff costs and with qualification costs)[116]
District nurse	£53.00	£53.00	PSSRU 2023; cost of band 5 nurses time per hour[116]
A&E visit	£157.00	£168.04	NHS reference costs - VB08Z Emergency medicine, category 2 investigation with category 1 treatment[113]
Outpatient visit	£197.00	£210.85	NHS reference costs - LB15E minor bladder procedures, 19 years and over (Outpatient procedures) [113]
Inpatient visit	£523.00	£251.52	NHS reference costs - LB15E minor bladder procedures, 19 years and over (Day case)[113]
Blood transfusion	£2.96	£3.17	NHS Reference Cost, DAPS05 (full blood count)[113]
Blood test	£2.39	£2.56	NHS Reference costs 2020-21; HRG code DAPS 03 - Integrated blood services[113]

CT scan	£165.76	£177.41	NHS reference costs 2020-21; HRG code RD27Z - CT scan of more than 3 areas[113]
Radiotherapy	£790.00	£845.54	NHS reference costs 2020-21; HRG code SC45Z - Preparation for Simple Radiotherapy with Imaging and Dosimetry[113]
Interventional radiology	£194.00	£207.64	NHS reference costs 2020-21; Total outpatient attendance, Interventional radiology service (811) Total cost[113]
Key: A&E, accident and emergency; CT, computed tomography; GP, general practitioner; HCRU, healthcare resource use; NHS, National Health Service; PSSRU, Personal Social Services Research Unit.			

Table 51: HCRU by health state and treatment

Cost component		Paclitaxel ± carboplatin	Source	Erdafitinib	Source
Pre-progression					
Investigations and tests	Blood test	3 every 28 days	Expert opinion[25]	No tests	Expert opinion[25]
	CT scan	At least 1 per 3 months	Expert opinion[25]	No scans	Expert opinion[25]
Treatments and procedures	Blood transfusions	1-2 per month for 20-30% patients	Expert opinion[25]	None	Expert opinion[25]
Primary care	GP visits	At least 4-6 per year	Expert opinion[25]	At least 4-6 per year	Expert opinion[25]
	Community nurse visits	4 per month	TA272 and expert opinion[25, 59]	4 per month	TA272 and expert opinion[25, 59]
Secondary care	A&E visits	2 per year	Johnson & Johnson RWE[20]	2 per year	Johnson & Johnson RWE[20]
	Outpatient visits	3 per month	Expert opinion[25]	1.5 per month	Expert opinion[25]
	Inpatient visits	4 per year	Johnson & Johnson RWE[20]	4 per year	Assumed to be similar to chemotherapy
Post-progression					
Investigations and tests	Blood test	1 per 6 weeks	Expert opinion[25]	No tests	Expert opinion[25]
	CT scan	No scans as on best supportive care	Expert opinion[25]	No scans	Expert opinion[25]
Treatments and procedures	Blood transfusions	None	Expert opinion[25]	None	Expert opinion[25]
	Palliative radiotherapy	Once for 9.3% of patients	TA530 (originally from CheckMate 275)[65]	Once for 9.3% of patients	TA530 (originally from CheckMate 275)[58]
	Interventional radiology	Once for 3.3% of patients	TA530 (originally from CheckMate 275)[58]	Once for 3.3% of patients	TA530 (originally from CheckMate 275)[58]
Primary care	GP visits	2 per month	Expert opinion[25]	2 per month	Expert opinion[25]
	Community nurse visits	4 per month	TA272 and Expert opinion[25, 59]	4 per month	TA272 and Expert opinion[25, 59]

Cost component		Paclitaxel ± carboplatin	Source	Erdafitinib	Source
Secondary care	A&E visits	2 per year	Johnson & Johnson RWE[20]	2 per year	Assumed to be similar to chemotherapy
	Outpatient visits	1 per month	Expert opinion[25]	1 per month	Expert opinion[25]
	Inpatient visits	4 per year	Johnson & Johnson RWE[20]	4 per year	Assumed to be similar to chemotherapy
Key: CT, computed tomography; GP, general practitioner; HCRU, healthcare resource use; RWE, real-world evidence.					

With the hospitalisations, clinicians mentioned that it would be useful to distinguish between SACT complications and complications of their cancer. We assumed 50% will be complications of cancer with the cost of SACT complications covered by AE costs.

Table 52: HCRU costs per cycle per health state (inflated to 2022/2023)

Health state	Treatment	Cost per cycle
Progression-free	Erdafitinib	£[redacted]
	Paclitaxel ± carboplatin	£[redacted]
Progressed	Erdafitinib	£[redacted]
	Paclitaxel ± carboplatin	£[redacted]

B.3.5.3. Adverse reaction unit costs and resource use

The list of AEs and frequency of occurrence is described in Section B.3.4.4.

AE unit costs are presented in Table 53, and have been informed by previous NICE submissions and NHS reference costs.[113] AE unit costs are multiplied by the per-cycle probability of each AE occurring based on the received treatment, to indicate the total per-cycle cost.

Table 53: Adverse event costs

Adverse event	Unit cost	Cost (inflated to 2022/23 prices)	Source
Palmar-plantar erythrodysesthesia syndrome	£599.88	£642.05	NHS reference costs 2021/22 – Non-elective inpatient – short stay[117]
Stomatitis	£958.38	£1,025.75	NHS reference costs 2021/22 – Non-elective inpatient – short stay[117]
Anaemia	£808.02	£864.82	NHS reference costs 2021/22 – SA01G-K – Total HRG's – Weighted average of Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia – NES[117]
Hyponatraemia	£2.96	£3.17	NHS reference costs 2021/22 – DAPS05 – DAPS – Haematology[113]
Onycholysis	£499.58	£534.70	NHS reference costs 2021/22 – JD07E-K – Total HRGs – Weighted average of Skin Disorders without Interventions – NES[113]
Hyperphosphataemia	£2.96	£3.17	NHS reference costs 2021/22 - DAPS05 - DAPS – Haematology. Assumed to be the cost of a blood test
Neutropenia	£833.70	£892.31	NHS Reference costs 2021/22 – WJ11Z – Other Disorders of Immunity – HRGs – NES[113]

Adverse event	Unit cost	Cost (inflated to 2022/23 prices)	Source
Leukopenia	£362.22	£428.18	TA522[97]
Febrile neutropenia	£2,641.80	£3,188.10	TA522[97]
Fatigue	£1,010.38	£1,081.41	NHS reference costs 2021/22 – WH52A – NELS (Follow TA788[24])
Decreased neutrophil count	£905.99	£969.68	Assumed the same as neutropenia[117]
Key: DAPS, Directly Accessed Pathology Services; DSU, Decision Support Unit; HRGs, Healthcare Resource Groups; NES, Non-elective short stay; NEL, non-elective long stay; NICE, National Institute for Health and Care Excellence; TA, technology appraisal.			

B.3.5.4. Miscellaneous unit costs and resource use

B.3.5.4.1. Subsequent treatment costs

As described in Section B.1.3.2 and Section B.1.3.5, a substantial proportion of patients will not be eligible for chemotherapy in the 2L+ setting due to poor performance score, or will choose not to have chemotherapy due to the associated AEs.[26]

In further lines of treatment for advanced disease, for example in the 3L and beyond, there would be an increasing proportion of patients receiving palliative care and very few patients receiving subsequent anticancer treatment in clinical practice.[27] In the UK RW mUC study data, 19 out of 3,942 (0.5%) patients received 4L treatment. Additionally, there is no evidence to suggest that this would be different for patients who progress on erdafitinib or paclitaxel ± carboplatin, which suggests that any impact on the incremental results would be minimal.[20]

The shares of different chemotherapy regimens among those who receive subsequent therapy are assumed to be closely aligned for the erdafitinib and paclitaxel ± carboplatin arms in the model. For chemotherapies, carboplatin/cisplatin + gemcitabine, paclitaxel, paclitaxel + carboplatin, and docetaxel, and aggregated both cisplatin + gemcitabine and carboplatin + gemcitabine as “carboplatin + gemcitabine” were considered in the model. The only notable difference is that

patients progressing on paclitaxel ± carboplatin are unlikely to receive a paclitaxel or docetaxel regimen as subsequent treatment; therefore, all chemotherapy was counted under carboplatin + gemcitabine for these patients. Although there is no clinical support or rationale, there is some re-treatment with PD-(L)1 after chemotherapy and erdafitinib. To reflect UK clinical practice and available treatments, the subsequent treatment distribution is based on the chemotherapy distribution of treatments after exposure to PD-(L)1 inhibitors, as observed in the UK RW mUC study (Table 54).[20] In addition to considering the allocation of subsequent treatments, the attrition rate from THOR was considered to adjust for the number of patients undergoing subsequent therapy. In THOR, there were 106 and 102 patients with a TTD event in the erdafitinib and chemotherapy arms, respectively. As a result, 21 (19.8%) and nine (8.5%) patients subsequently received chemotherapy and immunotherapy, respectively, after erdafitinib. Similarly, 21 (20.6%) and nine (8.8%) in the chemotherapy arm subsequently received chemotherapy and immunotherapy.[76]

Table 54: Distribution of patients on chemotherapy in the UK RW mUC study

	Carboplatin + gemcitabine	Paclitaxel	Paclitaxel + carboplatin	Docetaxel
N	61	54	18	4
Frequency	44.5%	39.4%	13.1%	2.9%
Proportion of all subsequent treatments†	8.8%	7.8%	2.6%	0.6%

Key: mUC, metastatic urothelial carcinoma; RW, real world.
Notes: †Multiplied by 19.8% (proportion of patients who received subsequent chemotherapy in THOR)
Source: UK RW mUC Study.[20]

As a result, Table 55 presents the proportion of patients who received each subsequent treatment. The distribution of subsequent treatments broadly reflects approved treatments in the UK and has been validated by clinical experts.[26]

Table 55: Distribution of subsequent treatments

	Erdafitinib (THOR safety population)	Paclitaxel ± carboplatin (NCRAS)	Mean treatment duration, months
	% received	% received	
Carboplatin + gemcitabine	8.82%	20.59%	3.4
Paclitaxel	7.81%	0.0%	1.9
Paclitaxel + carboplatin	2.60%	0.0%	3.4
Docetaxel	0.58%	0.0%	3.8
Atezolizumab	8.49%	8.82%	4.8
Key: NCRAS, National Cancer Registration and Analysis Service.			

Subsequent treatments following progression and cessation of initial treatment are included in the model and are applied once at the point of progression as a simplifying assumption. These are assumed to affect costs only, and they do not factor in any adjustments to efficacy, as the impact of subsequent treatment is assumed to be implicitly included in the modelled OS estimates.

The proportion of patients receiving the cost of subsequent treatments in each cycle is estimated in the model as the proportion of patients who transition out of the pre-progression health state in each model cycle without dying. This is estimated from THOR using the proportion of PFS events that were deaths for the full population (not treatment arm specific). The inverse of this proportion was applied to the proportion of patients leaving the PF health state in each cycle to estimate the proportion of patients whose PFS events were progression (i.e., the proportion of patients leaving the PFS health state who transition into the PD health state).

This probability is assumed constant over time, and it is assumed this can be applied to all treatment arms. A limitation of this approach is that the cost of subsequent treatment is likely to be overestimated for treatments that can be given beyond progression. This is because the cost is applied at the point of progression, which may be earlier than it would be incurred in practice if the initial treatment is allowed to continue beyond progression. However, the impact of this on cost-effectiveness results is likely to be minor, as treatment beyond progression is expected to be only

for a brief period and so any difference in discount rate applied to the cost is expected to be minimal.

A breakdown of full acquisition costs can be found in (Appendix K). This translates to monthly costs associated with each treatment arm.

Table 56: Subsequent treatment costs (other than first-line treatments)

Treatment	Acquisition cost (per month)	Administration cost (per month)
Erdafitinib	£[redacted]	£[redacted]
Paclitaxel ± carboplatin	£[redacted]	£[redacted]

B.3.5.4.2. FGFR testing costs

FGFR testing costs were included in the base case analyses of the model. Based on guidance from the National Genomic Test Directory (GTD),[118] it was identified that the best way to cost the identification process of patients with mUC who are eligible for erdafitinib was to consider the cost of adding a mutation test (*FGFR3*) onto a next generation sequencing (NGS) panel assessment. This was evaluated to be the standard cost of adding a mutation test onto an NGS panel of £34.00 (inflated to £37.33),[118] and was applied under the assumption that all patients who receive erdafitinib are tested for *FGFR*. Subsequently, this cost was divided by the expected prevalence of *FGFR3+* to ensure that both positive and negative results had testing costs captured. This resulted in an active cost of £224.85 based on 16.6% of patients attaining a positive *FGFR* test.[76] This cost is applied as a one-off cost. This approach aligned with guidance from the NHS England, which was reported in past TAs.[119-121]

B.3.5.4.3. Ophthalmology testing costs

Erdafitinib is associated with potential ophthalmology complications. Trials identified that erdafitinib causes a slightly elevated risk of eye conditions such as central serous retinopathy and retinal pigment epithelial detachment, which can cause a visual field defect. To ensure that this is detected as soon as possible, and that subsequent regimen adjustments could be made, testing is recommended. A single

ophthalmology consultation was costed as £166.64 in line with the 2021–22 NHS reference costs,[113] and subsequently inflated to £178.35 (2022/2023). Patients are assumed to require monthly ophthalmological examinations during the first 4 months of treatment and every 3 months afterwards.

B.3.5.4.4. End of life costs

A one-off end-of-life cost was applied to patients at the point of dying to reflect the cost of terminal care. An average per-patient cost was calculated based on the different types of care associated with the end of a patient's life. To account for the fact that some patients may not require all forms of end-of-life care resource use, the related costs were multiplied by the frequency of visits where necessary. The relevant costs and frequencies are presented in Table 57 and Table 58 and were informed by Bardsley and Georghiou (2014) and PSSRU costs.[116, 122] These produced a total cost of £8,769.55 per patient, which is in line with values used in other appraisals when accounting for inflation.[24, 57, 65]

Table 57: Practitioners needed for end-of-life care

	Mean	Standard deviation	Sample size	Source
Number of GP consultations	11.4	6.2	1,836	Bardsley and Georghiou (2014); final year cancer diagnosis GP visits[122]
District nurse time (hours)	7.53	19.57	929	Bardsley and Georghiou (2014); number of hours of nursing per person in final 90 days[122]

Table 58: Social and hospital end-of-life care

	Cost	Standard deviation	Price year	Source	Sample size	Active cost (inflated)
Local authority funded social care	£444.00	£1,484.00	2013/14	Bardsley and Georghiou (2014): Nuffield Trust Report, Table 3[122]	19,934	£542.80
Hospital care	£5,890.00	£5,264.00	2013/14	Bardsley and Georghiou (2014): Nuffield Trust Report, Table 4[122]	485,847	£7,200.66

B.3.6. Severity

Based on the QALY shortfall calculator published by Schneider et al.[123], erdafitinib meets the criteria for the application of a QALY modifier reflecting the severity of locally advanced or metastatic UC in patients who have received prior treatment with an anti-PD-(L)1 agent. It was concluded that the most appropriate severity modifier is x1.7 indicating that the application of the severity modifier should be considered for this appraisal. The main features of the QALY shortfall analysis are summarised in Table 59, and the shortfall calculations in Table 60.

Previous appraisals in mUC support the likelihood that a modifier would be needed, as all TAs that were considered in the HTA review (Section B.3.1) qualified for an end-of-life modifier to be applied. It should be noted that previous appraisals were assessed under the 2013 NICE guidance which considered an end-of-life modifier instead of the current framework which uses a severity modifier.[89, 90]

The QALY shortfall analysis uses baseline characteristics and OS extrapolations of the paclitaxel ± carboplatin cohort in the UK RW mUC cohort study as these are most representative of the population in UK clinical practice.

Based on a starting age of [redacted] and female distribution of [redacted]% the expected QALYs for a health individual are 10.17. The discounted QALYs in the paclitaxel ± carboplatin arm following extrapolation are 0.47. Therefore, the absolute QALY shortfall is 9.70. The proportional QALY shortfall is 95.38%.

Table 59: Summary features of QALY shortfall analysis

Factor	Value (reference to appropriate table or figure in submission)	Reference to section in submission
Sex distribution* (% female)	[redacted]%	Table (Section B.3.3.1.1.)
Starting age* (years)	[redacted]	Table (Section B.3.3.1.1.)
Expected QALYs in target cohort	[redacted]	Cost-effectiveness analysis calculations (B.3.9.1.)
Utility: progression free	[redacted]	Table 36 (Section B.3.4.1.)
Utility: progressed disease	[redacted]	Table 36 (Section B.3.4.1.)
Undiscounted life years: progression free	[redacted]	Economic model output
Undiscounted life years: progressed disease	[redacted]	Economic model output

Key: QALYs, quality-adjusted life-years; ATC, average treatment effect for the control
Note: *Sex distribution and starting age rounded to 0 decimal places per the requirements of the published QALY shortfall tool.

Table 60: QALY shortfall calculation

Expected remaining QALYs for the general population	Total QALYs that people living with a condition would be expected to have with current treatment	Absolute QALY shortfall	Proportional QALY shortfall	QALY weight
[redacted]	[redacted]	9.70	95.38%	1.7

Key: QALYs, quality-adjusted life-years.

Total remaining discounted QALYs for patients treated with paclitaxel ± carboplatin were taken from log-logistic OS extrapolation (and inputted into the QALY shortfall tool to two decimal places). For completeness, all seven available parametric curves used for estimating lifetime paclitaxel ± carboplatin QALYs were tested within the QALY shortfall calculations.

Scenario analysis results from the QALY shortfall calculator are presented in Table 61. The published QALY shortfall tool outlines five methodologies for estimating the general population quality-adjusted life years remaining, outlined below.

- Reference Case:[123]
    - Scoring algorithm: EQ-5D-3L value set from the 1993 MVH study
    - Health state profiles: EQ-5D-3L from the Health Survey for England 2014
    - Model: ALDVMM by Hernandez Alava, et al. 2022
- Alternative A:
    - Scoring algorithm: EQ-5D-5L to 3L mapping by Hernandez Alava, et al. 2020

    - Health state profiles: Health Survey for England 2017 and 2018 (pooled)
    - Model: empirical means / no interpolation
- Alternative B:
    - Scoring algorithm: EQ-5D-5L to 3L mapping by van Hout et al. 2012
    - Health state profiles: Health Survey for England 2017 and 2018 (pooled)
    - Model: empirical means / no interpolation
- Alternative C:
    - Scoring algorithm: EQ-5D-3L value set from the 1993 MVH study
    - Health state profiles: EQ-5D-3L from the 1993 MVH study by Kind et al., 1999
    - Model: empirical means / no interpolation
- Alternative D:
    - Scoring algorithm: EQ-5D-3L value set from the 1993 MVH study
    - Health state profiles: Health Survey for England 2012 + 2014 (pooled)
    - Model: empirical means / no interpolation

For each of the methods, all seven available parametric curves for paclitaxel ± carboplatin OS were tested to estimate the proportional QALY shortfall.

In 35 out of 35 (100%) scenarios tested (Table 61), the criteria for the x1.7 severity modifier was met, based on a proportional shortfall above 95.0%. Therefore, within the context of this appraisal, the criteria for applying the x1.7 modifier are met.

Table 61: QALY shortfall scenarios

Parametric Model	Paclitaxel ± carboplatin QALYs (discounted)	Proportional QALY shortfall scenarios				
		Reference Case	A	B	C	D
Exponential	[redacted]	96.11%	96.04%	96.06%	95.98%	96.13%
Gamma	[redacted]	96.17%	96.11%	96.12%	96.05%	96.20%
Generalised Gamma	[redacted]	96.14%	96.08%	96.09%	96.02%	96.17%
Gompertz	[redacted]	96.15%	96.09%	96.10%	96.03%	96.18%
Log-logistic	[redacted]	**95.38%**	95.30%	95.32%	95.24%	95.41%
Log-normal	[redacted]	95.80%	95.73%	95.74%	95.67%	95.83%
Weibull	[redacted]	96.17%	96.10%	96.12%	96.04%	96.19%

Key: QALYs, quality-adjusted life years

Note: A proportional QALY shortfall greater than 95.0% indicates a x1.7 severity modifier. The value in bold indicates the base case analysis.

B.3.7. Uncertainty

We aim to present an analysis that is as robust as technically feasible with the data available. Nevertheless, some uncertainties remain and are due to limitations in the available data. Johnson & Johnson has undertaken various efforts to present accurate and relevant data. The THOR study, although designed as a randomized controlled clinical trial, did not include comparators that align with UK clinical practice. On the other hand, the RW UK mUC study, which does reflect clinical practice in the UK, is limited by its retrospective design and has been conducted in a population that has not been tested for FGFR3. Lastly, the exploratory work on

PLUTO, although being a UK-based trial, focused on a different line of treatment than what is being evaluated in this current appraisal. These uncertainties are discussed below. In addition, the impact of these uncertainties is further explored through sensitivity analyses where possible, as discussed in Section B.3.10.

One uncertainty within the model is the choice of comparator, which resulted from the key clinical trial (THOR) only including comparators that were not relevant to the UK.[76] Despite the limitations mentioned, Johnson & Johnson considers the THOR study to still hold value. The study's design and randomization process are acknowledged as providing important insights. As a result, the ITT population from the THOR study has been included as one of our scenarios. Subsequently, Johnson and Johnson Innovative Medicine conducted a UK RW mUC study to identify which would be the most relevant comparator.[20] This identified paclitaxel ± carboplatin to be the most commonly used comparator. Paclitaxel ± carboplatin is intended to provide a representative perspective, which is supported by UK RW mUC study and multiple validations with clinicians.[20, 25, 26]

Since THOR did not provide UK specific relevant evidence for the comparator group, the study effectively had elements of being perceived as a single-arm study. Therefore, in light of providing the most appropriate data forward, the UK RW mUC study was conducted to generate efficacy information based on RWE from NCRAS.[20] This was implemented using an ITC, as discussed in Section B.3.3.2.1. This informed the relative efficacy of the paclitaxel ± carboplatin arm which was identified as the only relevant comparator in England and Wales (Section B.1.1). However, there are inevitable uncertainties associated with this form of analysis such as losing the power of randomisation in our THOR trial and population differences which are accounted for through the ATC-adjusted matching exercise, which qualifies the RWE data as appropriate to inform relative efficacy.[20]

As described in **Error! Reference source not found.** the UK RW mUC study was c onducted in an untested population, leading to unknown FGFR status. A MAIC analysis (Appendix Q1) was conducted to address this uncertainty. The MAIC revealed that there was no statistically significant difference in OS, PFS and

responses between the chemotherapy arms of the THOR trial (vinflunine or docetaxel) and the EV301 trial (vinflunine, docetaxel, or paclitaxel), with a slight positive trend towards chemotherapy efficacy in the untested EV-301 population. With the MAIC addressing this uncertainty, it can be assumed that the efficacy described in the UK RW mUC study would be comparable, if not conservative, compared to an FGFR3+ population. This is supported by a real-world study, where FGFR status did not influence PFS from time of mUC diagnosis or among 224 stratified patients receiving either chemotherapy or chemotherapy + ICI.[124]

To assess the validity of the efficacy results produced by the ITC, an alternative secondary approach was considered using PLUTO data.[92] An MAIC using PLUTO was conducted to inform the paclitaxel arm, based on the paclitaxel arm of the PLUTO trial (Appendix Q). Although Johnson & Johnson acknowledges that the PLUTO trial was performed in a less treated and therefore different patient population than the population in this submission, the MAIC produced similar efficacy outcomes to the ITC results and is discussed in Appendix Q. This alignment between different data sources provides greater confidence to the validity of the results.

B.3.8. Summary of base-case analysis inputs and assumptions

B.3.8.1. Summary of base-case analysis inputs

A tabular summary of the variables applied in the economic model, their base case values and the uncertainty distribution and magnitude assumed for each variable, is provided in appendix R.

B.3.8.2. Assumptions

Key assumptions of the economic analysis are summarised in Table 62. The approach to modelling has been designed to make the best use of the available data to inform the decision problem. In the absence of data, assumptions are designed to minimise potential bias in the analysis. These two statements are illustrated by the likely direction of bias and justification for analysis assumptions, summarised in Table 62.

Table 62: Summary of assumptions of the economic analysis

Subject	Base-case assumption	Justification	Reference to section
Perspective	NHS and PSS	NICE reference case[90]	
Discounting	3.5% per annum for both costs and effects	NICE reference case[90]	
Time horizon	40 years	The time horizon was considered long enough to capture the long-term clinical and economic impacts of mUC.	B.3.2.2
Model cycle length	1 week (7 days)	A cycle length of 1 week was considered sufficient to capture the high rate of progression of mUC	B.3.2.2
Modelling approach	Three-state parametric survival model	A three-state parametric survival model closely models PFS and OS trial data and is commonly used in oncology models, as reported in the NICE DSU TSD 14 and in prior evaluations of treatments for mUC.[94]	B.3.2.2
Survival projections	OS may not exceed PFS in either treatment arm	As no OS and PFS curve crossing or plateauing of data is observed in the either treatment's KM data, typical assumptions of partitioned survival modelling, along with trends in hazards over trial period that are generalizable over the extrapolation period.	B.3.3.2.1
Extrapolation	TTD, PFS, and OS curves were extrapolated by fitting parametric distributions to the KM curves. Curve selections were	As per NICE guidance.[90] Because the trial duration was insufficiently long to capture the full long-term benefits of intervention and	B.3.3.2.1

Subject	Base-case assumption	Justification	Reference to section
	based on best statistical fit and clinical face validity of predictions	comparators, survival had to be extrapolated beyond the end of trial follow-up. General population mortality includes beyond the end of trial follow-up, with the application on an SMR to maintain the plausibility of parametric extrapolations.	
PFS and TTD discontinuation for paclitaxel ± carboplatin	As PFS and TTD evidence was not available from the ITC it was informed by the observed ratio of PFS to TTNT or TTD to TTNT in the treatment arm.	This approach was identified to be the most statistically robust given the absence of clinical trial data. A full explanation is provided in Section B.3.3.2.1	B.3.3.2.1
TTD	It relies on the assumption that TTD never exceeds PFS and It relies on the assumption that all discontinuation events are aligned with progression events	In order to identify relevant model inputs and utilise the data from the ITC these simplifying assumptions were necessary.	B.3.3.2.5
Utilities	EQ-5D-5L Utilities extracted from THOR were mapped to EQ-5D-3L and statistical analysis applied as reported in Section B.3.4.5.	In line with the NICE reference case[90]	B.3.4.5
HCRU	Costs based on NHS reference costs and PSSRU costs, and frequencies informed by clinicians.	Disease management costs are assumed to be dependent upon disease status (progressed versus progression-free), which is a common assumption in cost-effectiveness	B.3.5.2

Subject	Base-case assumption	Justification	Reference to section
		modelling and aims to capture the granularity of different HCRU across health states.	
AEs	THOR informed erdafitinib, and PLUTO informed paclitaxel ± carboplatin	These were identified to be the best available sources, whilst PLUTO data only considers paclitaxel monotherapy patients it was assumed generalising to include patients receiving paclitaxel in combination with carboplatin was an acceptable and conservative assumption.[92]	B.3.4.4 and B.3.5.3
General population utilities	General population utilities applied as a floor	It was assumed that utilities among all treatments would not exceed that of the general population	B.3.2.2
Key: AE, adverse event; DSU, Decision Support Unit; HCRU, healthcare resource utilisation; ITC, indirect treatment comparison; KM, Kaplan–Meier; mUC, metastatic urothelial carcinoma; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; OS, overall survival; PFS, progression-free survival; PSS, Personal Social Services; SMR, standard mortality ratio; TSD, Technical Support Document; TTD, time to discontinuation; TTNT, time to next treatment.			

B.3.9. Base case results

B.3.9.1. Base case incremental cost-effectiveness analysis results – List price for erdafitinib

All results presented in this section are inclusive of a confidential [redacted] PAS.

Our analysis demonstrates that erdafitinib is associated with an additional 0.61 QALYs (pre-severity modifier adjustments) compared to paclitaxel ± carboplatin ([redacted] QALYs versus 0.47 QALYs). As we have demonstrated in **Error! Reference s ource not found.** that erdafitinib meets the x1.7 severity disease modifier, the

severity modifier of x1.7 has been applied on all the reported results. The cost-effectiveness results for erdafitinib versus paclitaxel ± carboplatin are presented in Table 63Table , and disaggregated results are available in Appendix J. The results show that erdafitinib is estimated to offer a substantial incremental health benefit compared with paclitaxel ± carboplatin, offering an additional 0.93 LYs and [redacted] QALYs per patient lifetime (a total of 1.66 LYs and [redacted] QALYs for erdafitinib compared with 0.73 LYs and 0.80 QALYs for paclitaxel ± carboplatin).

This level of benefit demonstrates the importance of erdafitinib as a treatment option for patients with 2L+ metastatic urothelial cancer. Treatment with erdafitinib is associated with an additional cost of [redacted], resulting in an ICER of £26,210 per QALY gained for erdafitinib vs paclitaxel ± carboplatin. The ICER should be considered in the context of erdafitinib being an innovative, end-of-life technology that presents an improvement for patients with mUC, for whom current treatment options are extremely limited.

Table 63: Discounted base case results

Treatment	Total LYs	Total QALYs	Total costs	Incremental LYs	Incremental QALYs	Incremental costs	ICER (£/QALY)
Erdafitinib	1.66	[redacted]	£[redacted]	-	-	-	
Paclitaxel ± carboplatin	0.73	0.80	£[redacted]	0.93	[redacted]	£[redacted]	£26,210

Key: ICER, incremental cost-effectiveness ratio; LY, life year; NMB, net monetary benefit; QALY, quality-adjusted life year.

In both the progression-free and progressed disease states, erdafitinib treatment leads to a greater gain in QALYs, although a higher number of QALYs are gained after disease progression in patients receiving erdafitinib (Appendix J). The cost analysis demonstrates that treatment with erdafitinib results in an incremental cost of [redacted] in comparison to paclitaxel ± carboplatin. This cost difference is primarily attributed to the extended duration of treatment with erdafitinib, as well as the

discrepancy in costs between the two treatments since paclitaxel ± carboplatin is readily available in a generic formulation. In the chemotherapy arm, health care resource use are the main drivers of the cost. Subsequent treatment costs and the cost of managing adverse events are not major drivers of costs.

A positive net health benefit (NHB) of [redacted] QALYs demonstrates that overall population health would be increased because of introducing erdafitinib (Table 64).

Table 64: Net health benefit

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	NHB at WTP threshold (£51,000)
Erdafitinib	£[redacted]	[redacted]	-	-	-
Paclitaxel ± carboplatin	£[redacted]	0.80	£[redacted]	[redacted]	[redacted]

Key: ICER, incremental cost-effectiveness ratio; LYG, life years gained; NHB, net health benefit; QALYs, quality-adjusted life years; WTP, willingness to pay.

B.3.10. Exploring uncertainty

A full list of parameters which were included in the model and whether they were included in probabilistic and deterministic sensitivity analyses is included in Appendix R.

B.3.10.1. Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was performed to account for joint uncertainties in the key model inputs, in which multiple input parameters were varied simultaneously over a number of iterations by sampling their values from uncertainty distributions. Whenever available, the standard error (SE) of the selected distribution was obtained directly from the same data source that informed the mean value. In the absence of data on the variability around health state cost values, variability was assumed as 10% of the mean value.

The results of the PSA based on 1,500 simulations are presented in Table 65, along with the scatterplot in Figure 25. The mean ICER from the PSA is consistent with the base case ICER presented in Section B.3.10 (£26,197 per QALY gained compared

with £26,210 per QALY gained, respectively), with approximately 73.9% of the iterations being cost-effective at the £30,000/QALY willingness-to-pay threshold (Figure 26). Therefore, the outcomes from the cost-effectiveness model are considered robust to uncertainty from parameter distributions. Figure 26 shows the cost-effectiveness acceptability curve associated with erdafitinib versus paclitaxel.

Table 65: Mean results of PSA (1,500 runs) and comparison with deterministic results (erdafitinib versus paclitaxel ± carboplatin)

	Incremental LYs	Incremental QALYs	Incremental costs	ICER (£/QALY)
Deterministic analysis	0.927	[redacted]	£[redacted]	£26,210
Probabilistic analysis	0.936	[redacted]	£[redacted]	£26,197

Key: ICER, incremental cost-effectiveness ratio; LY, life year; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life year.

Figure 25: Cost-effectiveness plane versus paclitaxel ± carboplatin

Figure 26: Cost-effectiveness acceptability curve

B.3.10.2. Deterministic sensitivity analysis

In the one-way sensitivity analysis (OWSA), values for all parameters with univariate uncertainty distributions were set to their upper and lower limits of the confidence intervals reported in Appendix R. Multivariate parameters are treated as having univariate uncertainty distributions as is standard for this analysis.

DSA results indicate the parameters that influence the results and conclusions of the decision problem to the greatest degree (Table 66). Figure 27 shows a tornado diagram displaying 10 parameters with the greatest impact on the ICER. These results indicate that the parameters that influence the results and conclusions of the decision problem to the greatest degree are OS and TTD extrapolations for

erdafitinib, which is expected as these influence the efficacy and the cost of the intervention, respectively. It is important to note that the OS extrapolations for erdafitinib that resulted in high ICERs, predicted lower long-term estimates than the likely values suggested by clinical experts, for example, 3-year survival probability is around 10% (Table 66) versus the likely estimate of 15%, therefore these do not accurately reflect the expected long-term outcomes for erdafitinib.

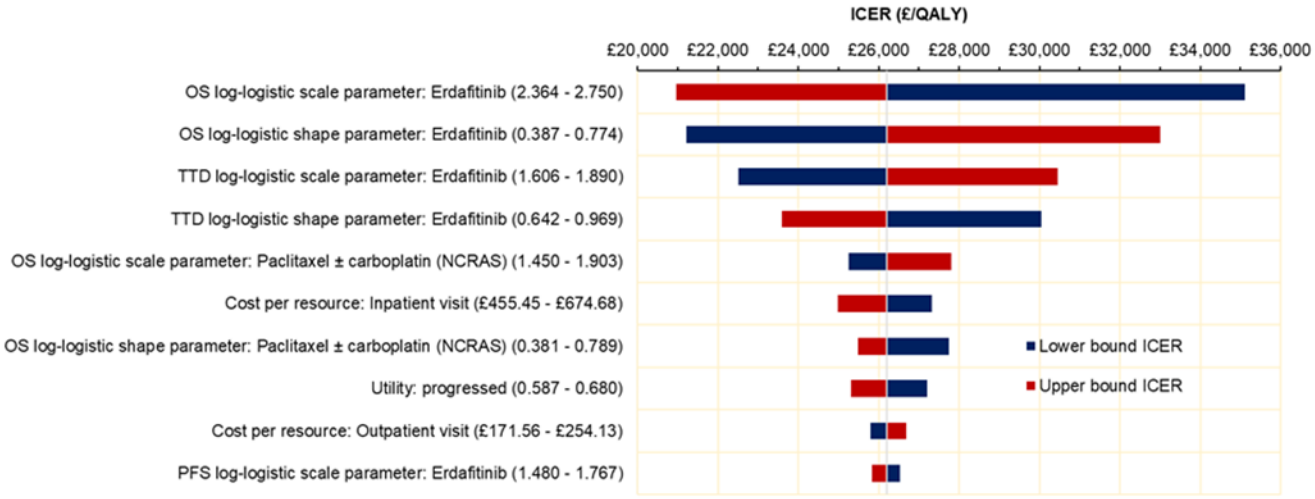
Table 66: Deterministic sensitivity analyses results

Parameter	Parameter variation	Incremental			ICER	Long-term estimates: erdafitinib			Long-term estimates: paclitaxel ± carboplatin		
		Costs	LY	QALY		3y	5y	10y	3y	5y	10y
Erdafitinib OS: log-logistic shape parameter	Lower: 0.387 (scale: 2.602)	[redacted]	1.29	[redacted]	£21,221	19.1%	10.0%	3.9%	3.2%	1.3%	0.4%
	Upper: 0.774 (scale: 2.513)		0.66		£32,995	8.9%	3.2%	0.7%	3.2%	1.3%	0.4%
Erdafitinib OS: log-logistic scale parameter	Lower: 2.364 (shape: 0.580)		0.61		£35,105	10.2%	4.4%	1.3%	3.2%	1.3%	0.4%
	Upper: 2.750 (shape: 0.580)		1.30		£20,972	18.4%	8.3%	2.6%	3.2%	1.3%	0.4%
Erdafitinib TTD: log-logistic shape parameter	Lower: 0.642 (scale: 1.758)		0.93		£30,042	13.8%	6.0%	1.8%	3.2%	1.3%	0.4%
	Upper: 0.969 (scale: 1.737)		0.93		£23,586	13.8%	6.0%	1.8%	3.2%	1.3%	0.4%
Erdafitinib TTD: log-logistic scale parameter	Lower: 1.606 (shape: 0.818)		0.93		£22,518	13.8%	6.0%	1.8%	3.2%	1.3%	0.4%
	Upper: 1.890 (shape: 0.793)		0.93		£30,461	13.8%	6.0%	1.8%	3.2%	1.3%	0.4%
Paclitaxel ± carboplatin OS: log-logistic shape parameter	Lower: 0.381 (scale: 1.672)		0.75		£27,757	13.8%	6.0%	1.8%	5.7%	2.8%	1.0%
	Upper: 0.789 (scale: 1.681)		1.04		£25,481	13.8%	6.0%	1.8%	1.5%	0.5%	0.1%
Paclitaxel ± carboplatin OS: log-logistic scale parameter	Lower: 1.450 (shape: 0.585)		1.07		£25,262	13.8%	6.0%	1.8%	2.1%	0.9%	0.2%
	Upper: 1.903 (shape: 0.585)		0.76		£27,808	13.8%	6.0%	1.8%	4.7%	1.9%	0.6%
Inpatient visit cost	Lower: £455.45		0.93		£27,323	13.8%	6.0%	1.8%	3.2%	1.3%	0.4%
	Upper: £674.68		0.93		£24,983	13.8%	6.0%	1.8%	3.2%	1.3%	0.4%
Progressed utility	Lower: 0.587		0.93		£27,205	13.8%	6.0%	1.8%	3.2%	1.3%	0.4%
	Upper: 0.680		0.93		£25,308	13.8%	6.0%	1.8%	3.2%	1.3%	0.4%
Outpatients visit cost	Lower: £171.56		0.93		£25,787	13.8%	6.0%	1.8%	3.2%	1.3%	0.4%
	Upper: £254.13		0.93		£26,675	13.8%	6.0%	1.8%	3.2%	1.3%	0.4%
Erdafitinib PFS: log-logistic scale parameter	Lower: 1.480 (shape: 0.805)		0.93		£26,529	13.8%	6.0%	1.8%	3.2%	1.3%	0.4%

	Upper: 1.767 (shape: 0.805)	[redacted]	0.93	[redacted]	£25,831	13.8%	6.0%	1.8%	3.2%	1.3%	0.4%
Advisory board consensus estimates: likely value (lower, upper) values						15.0% (5 –25)	5.0% (1–10)	1.0% (0–5)	3.0% (0–7)	1.0% (0–3)	0.0% (0–1)

Key: ICER, incremental cost-effectiveness ratio; LY, life years, QALY, quality adjusted life years; OS, overall survival; TTD, time to treatment discontinuation; PFS, progression-free survival. Note that each OS/PFS/TTD parameter was changed individually to its lower and upper 95% CI bound, while the other parameter was set to its conditional mean value.

Figure 27: Tornado diagram of the 10 most influential parameters on the ICER versus paclitaxel



Key: *FGFR*, fibroblast growth factor receptor; ICER, incremental cost-effectiveness ratio; IV, intravenous; RDI, relative dose intensity.

B.3.10.3. Scenario analysis

To provide a complete understanding of the impact of changing one or more model inputs (i.e., related to methodological, parameter-specific or structural assumptions), an extensive list of scenarios were tested. Table 67 describes the various scenarios tested, including a brief rationale for including each scenario, and the results.

The ICER was found to be most sensitive to the long-term OS extrapolation estimates for erdafitinib, with a maximum variation of +13.6% from the base case analysis observed, and the health state utility values (HSUVs) used to inform the PFS and PD health states (Table 67). Time to death utilities led to a 12.8% reduction in the ICER. None of the scenario analyses conducted with the same comparator dataset changed the cost-effectiveness conclusions of the base case analysis; erdafitinib remained cost-effective versus paclitaxel ± carboplatin in all analyses and the changes in the ICER were small, demonstrating that the base case results are associated with minimal uncertainty.

In a scenario utilising the efficacy profile from THOR comparators (docetaxel or vinflunine) and assuming the costs and AE profiles of paclitaxel ± carboplatin, our analysis demonstrates a 46% increase in the ICER. This is expected, considering that the trial population is typically selected based on their overall fitness, and therefore tend to experience better outcomes.

The use of the comparator arm from the PLUTO trial resulted in the same ICER. It is important to note that patients receiving paclitaxel monotherapy in the PLUTO trial were expected to have better outcomes than patients who would be treated with erdafitinib in a clinical setting, as they were fitter and less treated compared to the erdafitinib population.

Table 67: Scenario analyses

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER (% change)
Base case	**Not applicable**	**Not applicable**	**£26,210**
Excluding *FGFR3* testing costs	Cost of *FGFR3* test: £0	Impact of the upfront cost of identifying eligible patient population	£25,994 (-0.8%)
Subsequent treatments excluded	All subsequent treatments after erdafitinib and paclitaxel ± carboplatin are excluded.	Clinical experts confirmed that very few patients will end up on systemic treatments after progressing therefore we assess the impact of excluding subsequent treatment	£26,320 (+0.4%)
Paclitaxel ± carboplatin PFS curve informed by the comparator arm in the PLUTO trial	PFS informed by the PLUTO trial comparator arm (Paclitaxel)	PLUTO is study on UK patients in 2L mUC following prior chemotherapy treatment	£24,712 (-5.7%)
Alternative OS for erdafitinib	Gamma	Impact of alternative functional forms for OS extrapolation. Erdafitinib OS predictions to match the lower plausible long-term estimates.	£29,781 (+13.6%)
	Gompertz	Impact of alternative functional forms for OS extrapolation. Erdafitinib OS predictions match the upper plausible long-term estimates.	£22,846 (-12.8%)

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER (% change)
Alternative OS for paclitaxel ± carboplatin	Weibull	Impact of alternative functional forms for PFS extrapolation. Paclitaxel ± carboplatin OS predictions to match-lower plausible long-term estimates.	£25,370 (-3.2%)
Alternative OS for paclitaxel ± carboplatin	Weibull	Impact of alternative functional forms for PFS extrapolation. Paclitaxel ± carboplatin OS predictions to match-lower plausible long-term estimates.	£26,399 (+0.7%)
Alternative utility values from multivariable regression model	Progression-free: [redacted] Progressed disease: [redacted]	Assuming different utility values as they are close to prior Atezolizumab appraisal	£27,587 (+5.3%)
Alternative utility values based on time to death	Time to death ≥ 360 days: 0.778 180 – 359 days: 0.693 90 – 179 days: 0.590 30 – 89 days: 0.451 0 – 29 days: 0.325	The impact of time to death utilities over progression-based utilities	£23,513 (-10.3%)
Time horizon	20 years	Impact if no patient is expected to be alive 20 years after starting treatment.	£26,368 (+0.6%)
Paclitaxel arm in PLUTO trial as comparator	The comparator to erdafitinib is based on a clinical trial arm that assessed the efficacy of paclitaxel monotherapy.	Phase 2 RCT. PLUTO comparator arm was paclitaxel in UK patients. Although different from THOR populations, MAIC comparisons were used to derive erdafitinib comparative efficacy.	£26,043 (-0.6%)
THOR ITT arm as comparator	THOR's ITT comparison of erdafitinib versus chemotherapy (vinflunine and docetaxel)	The best phase 3, RCT data available for the target population, maintaining the power of randomisation with no evidence to suggest that the efficacy of the individual chemotherapies are significantly different from that each other. The costs and AE profile for vinflunine and docetaxel are assumed for this analysis.	£33,039 (+26.1%)

Scenario and cross reference	Scenario detail	Brief rationale	Impact on base-case ICER (% change)
		Efficacy same as above but the costs and AE profile for paclitaxel ± carboplatin are assumed for this analysis.	£38,286 (+46.1%)

B.3.11. Subgroup analysis

No subgroup analysis was performed as the trial results are representative of the whole eligible population as defined by the marketing authorisation.

B.3.12. Benefits not captured in the QALY calculation

A number of benefits of erdafitinib which are not explicitly captured in the QALY calculation framework include:

Introduction of an innovative class of mUC treatment: Due to the lack of novel, effective treatment options, patients with mUC experience a significant symptomatic burden coupled with high levels of emotional distress. Erdafitinib has a targeted mechanism of action compared with other existing treatment options in the UK mUC treatment pathway. Patients experience anxiety when treatments (particularly immunotherapy) fail with subsequent options being limited. By blocking the activity of FGFR, erdafitinib aims to inhibit the growth and spread of cancer cells. Since erdafitinib has a targeted, predictable mode of action compared to other treatments, it provides the opportunity to proactively manage treatment-related class events. For instance, chemotherapy exhibits a broad-spectrum and non-selective activity, resulting in a significant challenge for patients due to the manifestation of debilitating adverse events such as nausea, vomiting, asthenia and haematological side effects.[76]

Value of hope: Patients with mUC experience significant physical symptomatic burden directly impacting emotional distress including anxiety. The availability of

erdafitinib would fulfil an unmet need currently only filled by clinical trials. Erdafitinib provides patients much needed reassurance and hope for improved survival providing more time to spend with their loved ones.

Ease of use: Having a targeted treatment available instead of chemotherapy could potentially lead to more patients being treated with an active treatment, due to patient preference, ease of use, limited hospital visits and different mode of action compared to chemotherapy. The key experiences of patients and their caregivers highlight erdafitinib reduces the logistical burden of attending hospital for infusion administration, avoids the need to take time off work retaining autonomy and financial freedom. The value of this time at the end of life cannot be captured by the QALY. The impact on caregivers of improved prognosis for these patients is also not captured in the QALY calculation.

Opportunity to drive future innovations: The current lack of predictive biomarkers remains a concern in the management of patients with mUC. Apart from PD-1 or PD-(L)1 testing in first line, no other molecular biomarkers are used in routine clinical practice to predict sensitivity to specific agents to guide treatment options. The reimbursement of erdafitinib is expected to encourage continued innovation in this setting which has a critical unmet need for novel and effective and personalised treatment options.

B.3.13. Validation

B.3.13.1. Internal validity

The cost-effectiveness model was developed in line with the NICE reference case and guidance from the NICE DSU TSDs where appropriate. The cost-effectiveness model itself is quality-assured by the internal processes of the external economists who constructed the economic model. In these processes, an economist not involved in developing the cost-effectiveness model reviewed the technical implementation of calculations and coding for correctness, reviewing and testing inputs and checking for implementation and/or logical inconsistencies. The validation process was documented via a checklist of modelling errors and corrections applied.

The model's Visual Basic user defined functions were verified through double programming, in which equivalent worksheet derivations were performed demonstrating consistency in the generated output. Further, in the interest of transparency, comments detailing the functions' internal processes has been provided throughout the code.

B.3.13.2. External validity

Studies to which the economic model's outcomes could be compared were identified from a review of previous cost-effectiveness studies. The most appropriate appraisal is that atezolizumab (TA525).[58] The model outcomes were compared to the estimates of QALYs reported in Technology Appraisal 525 (TA525). The base case results of the ERG estimated 0.57 remaining QALYs in a population treated with taxanes (docetaxel and paclitaxel). However, in our model, we estimated a lower value of 0.47 remaining QALYs before weighting. Although not directly comparable, our estimates in this submission were lower than those estimated with taxanes. This difference in estimated QALYs can be attributed to several factors. Firstly, clinicians predicted slightly lower long-term estimates in our model population since these patients had already received immunotherapy and were later in the treatment pathway, whereas the population in TA525 had only received chemotherapy without immunotherapy. Additionally, it is worth noting that the trial population in TA525 tends to be generally fitter and younger compared to patients in standard clinical practice. Therefore, the observed lower QALY estimates in our model compared to TA525 are expected, considering the differences in treatment history and characteristics of the patient populations being analysed.

B.3.13.3. Validation based on UK clinician input

Expert clinical opinion was sought during the development of the cost-effectiveness model. This helped to ensure that the inputs and assumptions used in the base case analysis were relevant to UK clinical practice in order to validate the clinical plausibility of the outcomes predicted by the model. An advisory board was held, where model inputs and assumptions were discussed and validated with six clinical experts were.[26] The objective of the advisory board were:

- To perform a critical analysis of the Johnson & Johnson UK RW mUC study to identify relevant compactors to be used in the cost-effectiveness model
- Review healthcare resource utilisation cost components of the model
- Record consensus estimates of long-term overall survival projections for patients with mUC on erdafitinib, best supportive care, and chemotherapy in mUC

The clinician feedback from these interviews was directly incorporated into the model inputs and assumptions.

B.3.14. Interpretation and conclusions of economic evidence

The efficacy and tolerability of erdafitinib are supported by an extensive evidence base from the phase 2 BLC2001 trial and confirmatory registrational phase 3 THOR trial conducted in a diverse range of patients, incorporating factors such as prior mUC treatments and nationality, which broadens the applicability of the data across mUC PD-(L)1-experienced individuals.[76, 77] Adverse events due to erdafitinib are manageable through dose modifications. The manageable adverse events allow people to continue with their regular daily activities as clinicians can proactively manage side effects.

The ITC found that erdafitinib was associated with an OS HR of 0.35 and PFS HR of 0.33, which translate to a 65% reduction in risk of death and a 67% reduction in the risk of progression against the UK SoC (Appendix P). The results are valid for patients in routine clinical practice in England and Wales, with no major concerns identified regarding generalisability. Clinical expectations of survival in both treatment arms at 3, 5 and 10 years were obtained through using a structured elicitation framework to inform curve selection. The evidence was further strengthened by post hoc and exploratory analyses to estimate the comparative effectiveness of erdafitinib against clinical trial data for paclitaxel. These analyses indicate that erdafitinib improves survival.

The efficacy results for erdafitinib were reflected in the economic analysis, where erdafitinib was associated a substantial increase in LYG (0.94) and QALYs ([redacted]) versus paclitaxel ± carboplatin, providing almost four additional months of life for patients who otherwise face a poor prognosis. The findings from the QALY shortfall analysis highlight the severity of mUC disease with significant unmet healthcare needs under the SoC within the NHS. The results of the DSA and PSA found the base case economic results to be robust to uncertainty to key model inputs and assumptions, with all scenario analyses that matched long-term most likely OS estimates demonstrating that erdafitinib remained cost-effective versus paclitaxel ± carboplatin. Scenario analyses reveal that the base case cost-effectiveness estimates are sensitive to extrapolation of OS and TTD, and robust with respect to extrapolation of PFS, utilities, and costing assumptions. The structural and parametric uncertainties explored have minimal impact on the decision.

In addition to the clinical and economic value, the additional benefits of erdafitinib that are not captured in the QALY framework include the value of hope in an otherwise hopeless end-of-life situation, carer burden and the value of innovation to bridge current and future patients to being eligible for future innovation.

Strengths

Robust validation exercises were conducted by Johnson & Johnson with clinical and health economic experts in the UK to validate the treatment pathway, key model inputs and assumptions, including frequency of resource utilisation by treatment, subsequent treatment options and use of a structured framework for elicitation of long-term survival estimates for erdafitinib and chemotherapy.[25] An advisory board was conducted to critically review the UK RW mUC cohort study and review the baseline characteristics of patients enrolled in THOR, both of which were deemed to be representative of UK clinical practice.[25]

The economic model closely aligns to the NICE reference case, with robust results, therefore the results of the economic analyses are highly relevant and appropriate for decision making on the introduction of erdafitinib into NHS clinical practice.

Limitations

The comparators employed in the THOR study are considered irrelevant in the context of the UK. Furthermore, no studies meeting the criteria for the target FGFR3 population and relevant UK comparators were identified in SLR, rendering the conduct of a network meta-analysis (NMA) for this specific population and comparisons unfeasible. Vinflunine and docetaxel have similar clinical activity to paclitaxel, with docetaxel harbouring a less favourable toxicity profile.[5, 125-127] Additionally, there is paucity of evidence indicating significant variations in the effectiveness of different chemotherapy types. In our comparative MAIC analysis of the chemotherapy arm in the THOR study and the chemotherapy arm in the EV-301 study, no evidence was found to suggest discrepancies in OS, PFS, and ORR between the two chemotherapy groups.

To address the limitation, an ITC was conducted to obtain comparative efficacy estimates of erdafitinib versus paclitaxel ± carboplatin. To provide greater certainty on the decision-making, real world data from England was used. The analysis was conducted in line with best practices outlined in the NICE Real-World Evidence framework and NICE TSD 17 for treatments included in the ITC.[83, 84] Data uncertainty was also explored by using previously published RCT trial comparator arm (PLUTO) as recommended by clinical experts.[92] In spite of differences in prior treatments, the analyses demonstrated that erdafitinib's relative efficacy was better even in these less treated patients.

Although real-world data were available for patients with similar prior treatments, details on *FGFR* alterations were not available as the registry cohort includes an untested population. As described in our MAIC in Appendix Q1, there is no evidence to suggest that the efficacy described in the UK RW mUC study would be comparable, if not conservative, compared to an FGFR3+ population.

Conclusions

There are limited treatment options available for mUC patients, with a proportion of patients being treated without an active treatment because of ineligibility to receive

paclitaxel ± carboplatin or opting not to receive chemotherapy due to severe adverse events or lack of efficacy. For patients that are eligible for paclitaxel ± carboplatin, prognosis is short, and the efficacy is limited. The severe symptoms of the disease and extremely poor prognosis highlight a critical unmet need for innovative, oral, targeted and effective treatments for this population. Erdafitinib will be the first targeted treatment in mUC representing the most valuable advance in the management of mUC since the use of immunotherapies. Erdafitinib is an effective, well tolerated oral treatment that provides a paradigm shift in the management of eligible mUC patients harbouring FGFR3 alterations and is cost-effective over a lifetime horizon. The recommendation of erdafitinib for use in the NHS would address the critical need of providing a targeted oral treatment that prolongs survival, maintain the quality of life and is cost-effective use of NHS resources delivered on a limited and predictable budget impact.

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B.5. Appendices

Appendix C: Summary of product characteristics (SmPC) and European Public Assessment Report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

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Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Price details of treatments included in the submission

Appendix L: Checklist of confidential information

Appendix M: Additional information on THOR

Appendix N: Additional information on BLC2001

Appendix O: Description of registry study for mUC in England (UK RW mUC study)

Appendix P: ITCs between THOR and UK RW mUC study

Appendix Q: Exploratory MAIC studies

Appendix R: Additional cost-effectiveness information

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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

Summary of Information for Patients (SIP)

Template version	Date amended	Changes since previous version
2.0	Dec 2023	Clarifications made to guidance notes in section 3i regarding inclusion of statements on cost effectiveness.

File name	Version	Contains confidential information	Date
Summary of Information for Patients (SIP)	**V2**	**No**	**04 July 2024**

Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Erdafitinib (Balversa®)

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Erdafitinib is intended for patients with advanced bladder cancer that cannot be removed by surgery or has spread to other parts of the body. These patients must have an abnormal form of FGFR protein and must have received at least one other medicine, including immunotherapy that did not work or is no longer working.

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Erdafitinib does not yet have marketing authorisation in the United Kingdom (UK). The application for marketing authorisation with the UK Medicines and Healthcare products Regulatory Agency (MHRA) and the marketing authorisation are planned in 2024.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:

Patient Group	Engagement/Activity (correct as of 11/06/2024)	Financial Support Provided

Action Bladder Cancer	Patient support and information, and healthcare professional education program	£6,000 (2022)
Action Bladder Cancer UK	Core funding support towards their information and advocacy services for people living with bladder cancer	£4,500 (2021)
Action Bladder Cancer	Core funding to continue to deliver support for patients living with bladder cancer during the pandemic	£11,000 (2020)
Fight Bladder Cancer	'Enhancing Bladder Cancer Awareness and Referrals in the UK' conference initiative	£9,000 (2024)
Fight Bladder Cancer	Developing a policy white paper titled 'Updating the Exemplar Pathway. Advancing bladder Cancer Care in the UK	£30,000 (2024)
Fight Bladder Cancer	Publishing, printing and distributing their magazine FIGHT to patients and healthcare professionals	£8,268 (2023)
Fight Bladder Cancer	Printing and posting their clinician and patient support materials	£9,094.80 (2024)
Fight Bladder Cancer	Insights training and team building day (Non-financial support: staff expertise and materials)	£293 (2022)
Fight Bladder Cancer	Insights training and team building day (Financial support: £200, Non-financial support: £400)	£600 (2021)
Fight Bladder Cancer	Core funding support towards their awareness and information services for people living with bladder cancer	£10,000 (2020)

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Urothelial carcinoma is a type of bladder cancer that starts in the cells lining the inside of the bladder. It makes up about 90% of all bladder cancer cases.[1] In the UK, bladder cancer accounts for 3% of all new cancer cases, making it the 11th most common cancer.[2, 3] In 2020 16,547 new cases of bladder cancer were diagnosed in England.[4] When the cancer spreads from the inner lining of the bladder to other parts of the body, it is called advanced or metastatic urothelial carcinoma.[5-7] Approximately 10% of patients with urothelial carcinoma have advanced or metastatic disease.[8] Among these patients, approximately 20% have alterations of the *FGFR* gene.[9-13] The average life expectancy for patients with metastatic urothelial carcinoma is less than 6 months from diagnosis.[13]

Patients with metastatic urothelial carcinoma often experience common symptoms such as blood or blood clots in urine, pelvic pain, bone pain, unintentional weight loss, swelling of the legs, and frequent urinary tract infections.[14, 15] Smoking is a major factor in the cause of bladder cancer.[15]

Living with unresectable or metastatic urothelial carcinoma can bring several changes to the daily lives of patients and their carers. In addition to the physical impact of the disease and its treatments, frequent hospital visits are required for treatments, which can have significant effect on a patient's quality of life. Everyday tasks, such as getting washed and dressed, walking, household chores, enjoying hobbies and spending time with friends and family, can become challenging, especially with the potential increase in hospital visits.[16, 17]

A carer, often a family member or friend, is someone who provides support to individuals requiring help.[18] They help with proving medications, coordinating with healthcare professionals and supporting the management of symptoms and side effects. Carrying out these duties may require them to take time off work and sacrifice their leisure time.

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

In the UK, there is currently no national screening programme for detecting bladder cancer.[19] Instead, most cases are identified within A&E (Accident and Emergency) following blood appearing in the urine, which is the most common symptom of bladder cancer in both men and women.[14] When a patient presents with this symptom, they are typically referred for several tests, including a urine test, a test to look inside the bladder (cystoscopy), tests to look at the kidney and ureters (computed tomography [CT] urogram), and scans to look at the bladder and the rest of the body (such as ultrasound, magnetic resonance imaging (MRI) scan, CT scan, positron emission tomography [PET] scan).[16, 19] If abnormalities are identified, an operation to take a biopsy (remove a sample tissue) or remove cancer from inside the bladder is recommended; this procedure is known as white-light-guided transurethral resection of bladder tumour (TURBT).[16, 20] With the new treatment, patients would need an additional genetic test to confirm the presence of the *FGFR* alteration. This pathway is not currently undertaken due to no other *FGFR*-targeted treatments in bladder cancer. To do this, a tissue sample of the tumour will be sent to a laboratory for analysis. This can be done with tissue from a new biopsy or with tissue that was already removed, so an additional procedure may not be required.[21]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

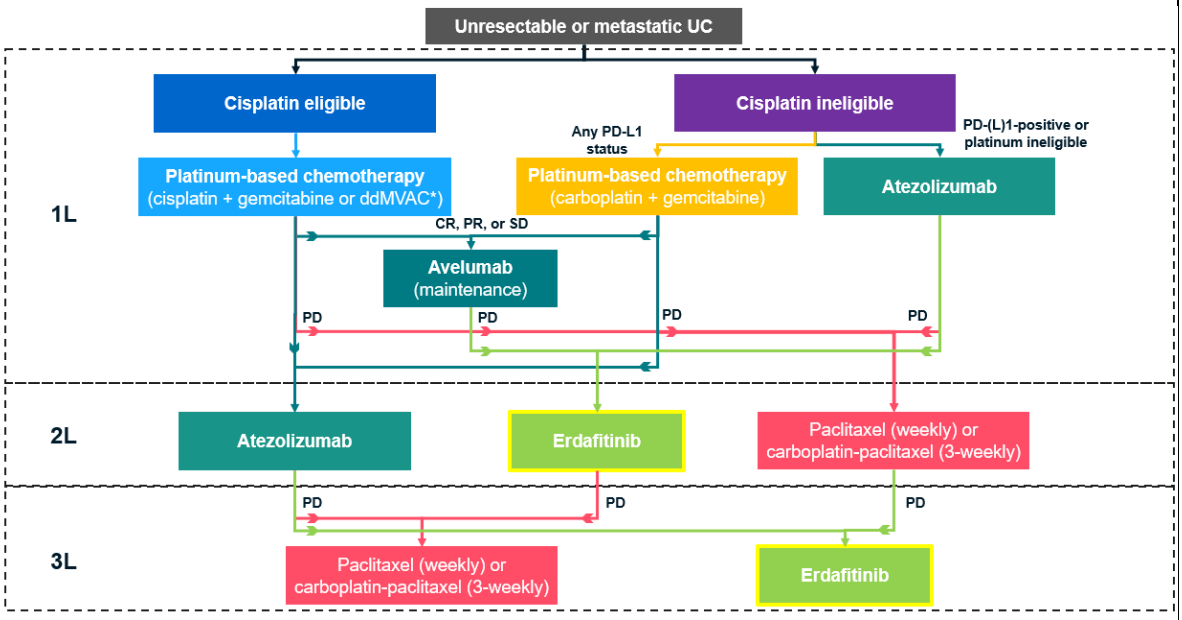
- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

The aim of treatment for patients with urothelial carcinoma that cannot be surgically removed (unresectable) or has spread to other parts of the body (metastatic) is to reduce symptoms, maintain a good quality of life, stop the cancer from getting worse, delay the need for a next treatment, and extend life. In the UK, there are not many treatment options available, and there has not been much progress in introducing new effective treatments. The most recent guidelines

from NICE, published in 2015 and reviewed in 2019, provide recommendations on how to diagnose and manage bladder cancer.[16]

The guidelines do not incorporate some of the recently approved treatments and therefore require additional updates. Figure 1**Error! Reference source not found.** shows the steps patients take in their treatment journey for metastatic urothelial carcinoma, and where erdafitinib would be used, which would be as a second line or later option.

Figure 1: Clinical pathway of care for patients with metastatic urothelial carcinoma, and the proposed positioning of erdafitinib



Key: 1L, first line; 2L, second line; 3L, third line; CR, complete response; ddMVAC, dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin; ECOG PS, Eastern Cooperative Oncology Group performance status; GFR, glomerular filtration rate; PD, progressive disease; PR, partial response; PD-(L)1, programmed cell death-ligand 1; SD, stable disease; UC, urothelial carcinoma. **Notes:** *Patients can be treated with ddMVAC if: their renal function is adequate (typically defined as a GFR of ≥ 60 ml/min/1.73 m^2) and they are otherwise physically fit (have an ECOG PS of 0–1).[16]

First-line treatment

For the first course of treatment, the use of platinum-based chemotherapy is recommended. If patients are generally in good physical condition, they are advised to take a combination of cisplatin and gemcitabine. However, if they cannot use cisplatin, they are recommended to take carboplatin and gemcitabine instead.

After undergoing these treatments and showing a positive response or stable condition, doctors may recommend using a medicine called avelumab for maintenance. This medicine falls under the category of immunotherapy, and is also known as a PD-(L)1 blocker.[6, 22]

In some cases, if patients cannot use platinum-based chemotherapy and have tumours that test positive for a protein called PD-(L)1, they may be offered a different type of immunotherapy called atezolizumab. This treatment also blocks the PD-(L)1 protein.[6]

Second-line treatment

After the initial treatment, there isn't a well-defined standard approach for treating metastatic bladder cancer. The treatment options available depend on the type of treatment the patient had before. Johnson & Johnson, a healthcare company, started a study in real-world situations to gather information from patients in England who have metastatic bladder cancer.[13] Real-world

data is data relating to patient health, experience or care delivery collected outside the context of a highly controlled clinical trial.[23] The study results, and consultation with UK doctors, confirm that the most frequently selected treatment in the second-line setting is taxane-based chemotherapy (e.g. carboplatin-paclitaxel or paclitaxel monotherapy, denoted as paclitaxel ± carboplatin).[24, 25]

Besides carboplatin-paclitaxel or paclitaxel monotherapy, there are not many options available. When patients have progressed after receiving immunotherapy as a first line, maintenance or second-line treatment, patients tend to receive palliative/best supportive care (BSC). Some patients may be able to try the initial treatments again, but this is only for a small group of patients who are considered healthy enough for the treatment again.

There is a great and urgent need for new and better treatments. Erdafitinib is a new kind of treatment that specifically targets a protein called *FGFR*, which is important for the growth of cancer cells. It is expected to play a critical role in the treatment pathway for patients progressing from immunotherapy, providing them with a new and promising treatment option.

Drug–drug interactions

If you take other medicines, some of these medicines may affect the way your body processes erdafitinib.This could potentially lead to either increased erdafitinib exposure resulting in possibly more side effects from erdafitinib or decreased erdafitinib exposure. In such cases, your doctor may need to adjust your dose of erdafitinib[26].[26]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Patients, and the carers of patients, suffering from bladder cancer find that their financial situation and quality of life can be negatively impacted by both the disease and the medicines used to treat it. A recent survey to collect real-world experiences of people with bladder cancer found that financial burden is a major concern, particularly in patients with advanced/metastatic disease.[27] To note, of the survey respondents, only 2% had a primary diagnosis of advanced/metastatic urothelial carcinoma; therefore, the sample size for this population was limited (n= 28).

The majority of carers in the study (91%) reported to have been emotionally affected by the disease.[27] Almost all (93%) the responses from patients and carers were from high-income countries, with a large proportion from the UK (20%), the US (13%), and Australia (10%). Most respondents lived in the European region (58%) or the region of the Americas (27%), where there is access to universal healthcare and patients were more likely to have better treatment and care experiences overall.[27]

Another study, which investigated patient-reported symptoms and the impact of metastatic urothelial carcinoma after chemotherapy followed by an immunotherapy, reported that some patients described challenges with basic activities of daily living, such as shopping and cooking.[28] It

also found that most patients reported an increased reliance on friends and relatives for assistance.

A market research study, in the form of in-depth interviews with patients with metastatic bladder cancer and their caregivers, showed that bladder cancer and its treatments have a clear physical impact on patients, which is directly related to emotional wellbeing and quality of life.[29] The study also described the direct impact on caregivers, including the experience of sharing the emotional burden with the patient; the challenges faced with their own emotional wellbeing; and the need to take on additional tasks, which leads to reduced social interactions and activities.[29]

In summary, metastatic urothelial carcinoma has an impact on patients' financial situation and imposes a burden on patients and carers, with a direct impact on wellbeing and daily activities.

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

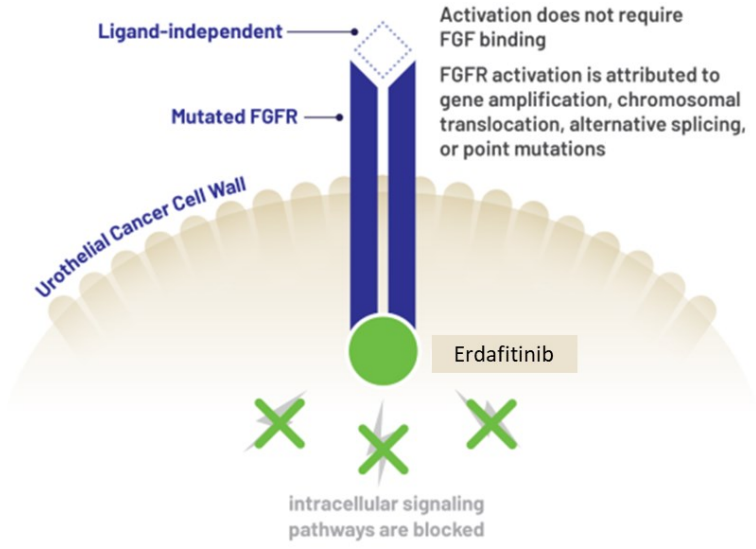
Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Erdafitinib is a medicine that stops a protein called kinase from working[21]. This protein is important for helping cancer cells grow and multiply. In some kinds of cancer, like urothelial carcinoma, there can be changes in a gene called *FGFR*. These changes, called *FGFR* alterations, make cancer cells develop and make the cancer get worse. Erdafitinib focuses on the *FGFR* pathway, which is like a communication system that helps cancer cells grow. By targeting this pathway, erdafitinib aims to slow down or stop the cancer from growing by stopping *FGFR* from working[30, 31]. You can see how erdafitinib works in Figure 2.

FGFR is present in cancer cells as well as healthy cells throughout the body. Since erdafitinib targets the *FGFR* protein, it can affect all cells with this receptor, which may cause side effects, although it is generally well tolerated and manageable with dose modifications.[21]

Figure 2: Erdafitinib mode of action



Key: FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor. **Source:** Balversahcp.com (mode of action diagram).[32]

A link to the Patient Information Leaflet for erdafitinib is provided here: https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/BALVERSA-pi.pdf#page=9

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

No

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Erdafitinib is an oral treatment option for adult patients that should be initiated and supervised by a doctor experienced in the use of anti-cancer therapies.[26] Patients are started on an 8 mg once-daily dose. The tablets should be swallowed whole, with or without food, at about the same time each day. Patients must visit the doctor after 14 days of taking erdafitinib; this is so the doctor can check if their phosphate levels are within range and check for any side effects. If phosphate levels are normal, the dose is increased to 9 mg daily, maintaining the oral administration. Treatment should continue until disease progression or unacceptable toxicity occurs.[26]

Current treatments involve up to six cycles of intravenous, delivered into the vein, (IV) chemotherapy, administered every 21 days.[33, 34] These treatments require blood tests and additional IV medications prior to treatment.[33, 34] In addition, treatment with chemotherapy often leads to adverse events, such as anaemia, diarrhoea, pneumonia, fatigue, pain, nausea/vomiting, and hair loss.[28] Both the administration and the adverse events of chemotherapy require frequent hospital visits, imposing a burden on patients and carers. This can seriously impact the patient's quality of life and reduces their time available to spend with friends and family, which can further impact their quality of life.[17, 35-38] As erdafitinib is a tablet format administered orally, it is expected to have a less disruptive administration schedule and burden compared with current treatments as it can be taken at home.

3d) Current clinical trials

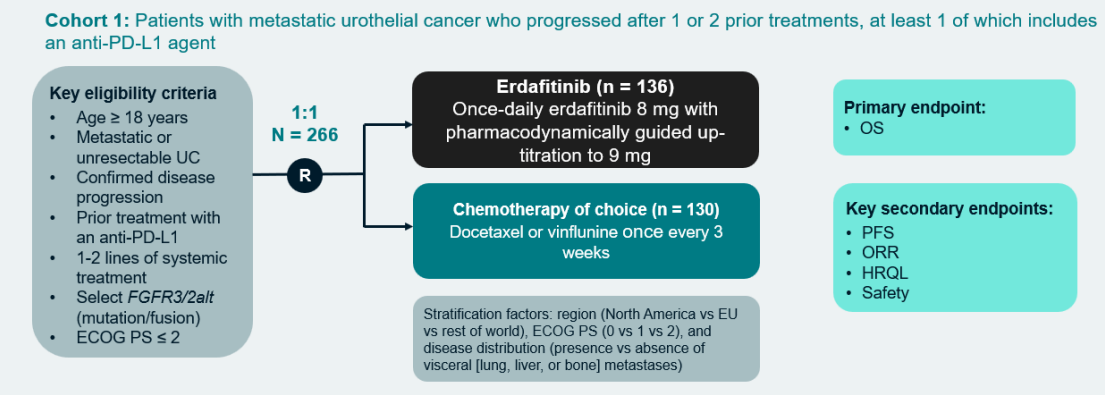
Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

To support the use of erdafitinib, researchers conducted a large study called the THOR trial. In this trial, patients with cancer were split into two groups - one group received erdafitinib, while the

other group received chemotherapy medications like vinflunine or docetaxel. This trial is still ongoing all over the world. The results of this trial provide important evidence for the effectiveness of erdafitinib as a treatment option.[39]

In Figure 3, we can see the plan for the THOR trial. The trial is split into two groups, but we will only talk about Cohort 1 in this document. To be part of Cohort 1, patients must have had urothelial carcinoma that has spread or cannot be operated on. They also needed a new treatment because their condition is getting worse. Additionally, they must have tried specific treatments before, have certain gene changes called *FGFR* alterations, and meet certain health criteria.

Figure 3: THOR trial design, Cohort 1



Key: alt, alterations; ECOG PS, Eastern Cooperative Oncology Group performance status; HRQL, health-related quality of life; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed death-ligand 1; PFS, progression-free survival; R, randomised; UC, urothelial carcinoma. **Source:** Loriot et al., 2023.[40]

Further information/publications for THOR can be found below:

- Clinicaltrials.gov (NCT03390504) – https://classic.clinicaltrials.gov/ct2/show/NCT03390504
- Publication (Loriot 2023) – https://pubmed.ncbi.nlm.nih.gov/37870920/

The BLC2001 study was a research study that looked at whether erdafitinib works as intended in people with advanced urothelial carcinoma. This study was done to see if erdafitinib is effective and safe for patients who have specific genetic changes in their FGFR genes. The study was designed to test the medicine in a smaller group of patients to see if it works as expected and to gather evidence to support its use.[10, 41]

Further information/publications for BLC2001 can be found below:

- Clinicaltrials.gov (NCT02365597) – https://clinicaltrials.gov/study/NCT02365597
- Publication (Siefker-Radtke et al., 2022)[10] – https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00660-4/abstract

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

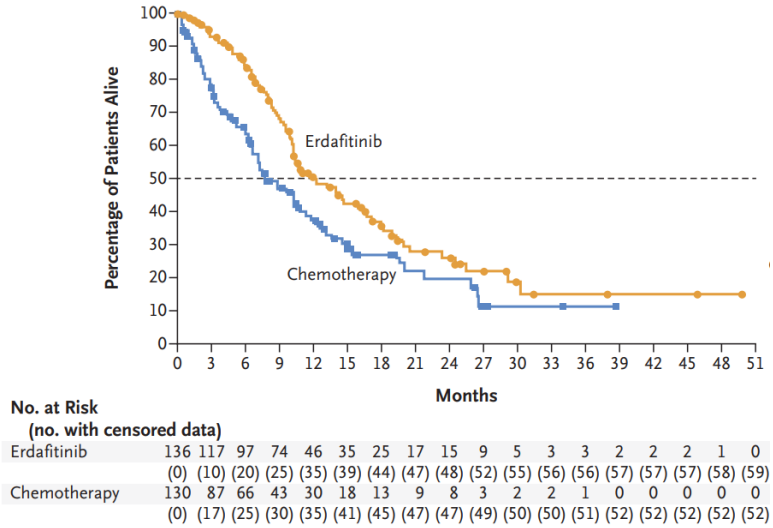
In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Evidence from the THOR trial

The THOR trial demonstrated that erdafitinib has superior efficacy when compared with chemotherapy.[39, 40] This is similar to the findings of the BLC2001 trial.[39-41]

Overall survival is the length of time patients remain alive after starting treatment. Erdafitinib significantly prolonged overall survival compared with chemotherapy.[40] The median overall survival was 12.1 months with erdafitinib and 7.8 months with chemotherapy, meaning patients receiving erdafitinib lived 4.3 months longer than patients receiving chemotherapy.[40] Figure 4 shows the overall survival rates from the THOR trial.

Figure 4: THOR overall survival

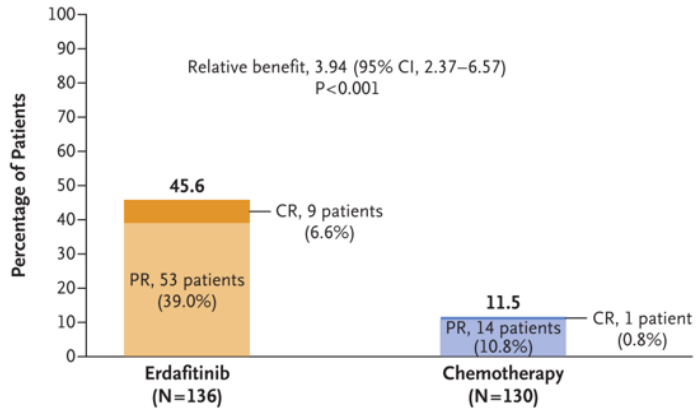


Source: Loriot et al., 2023.[40]

Progression-free survival is the length of time during which patients stay alive and their disease does not progress. A significant improvement in progression-free survival was observed with erdafitinib compared with chemotherapy.[40] The median progression-free survival was 5.6 months with erdafitinib and 2.7 months with chemotherapy, representing a 42% relative reduction in the risk of disease progression or death.[40]

Objective response rate is the total number of patients whose cancer has either gone away or shrunk after treatment. Erdafitinib also provides a rapid objective response rate. This combined means that compared with chemotherapy, more patients taking erdafitinib experienced their tumours completely or partially shrinking in a shorter period of time.[40] The percentage of patients with an objective response was 45.6% with erdafitinib compared to 11.5% with chemotherapy. Figure 5 presents the objective response rate in patients in the THOR trial.

Figure 5: THOR objective response rate



Key: CI, confidence interval; CR, complete response; PR, partial response. **Notes:** CR is defined as when the tumour disappears completely. PR is defined as when the tumour partially shrinks. **Source:** Loriot et al., 2023.[40]

Data limitations

As the THOR trial was conducted on a broad and global scale, it is not fully consistent with the patient population and treatments available and used in UK clinical practice. This is clearly seen in the comparator arm of THOR, which consists of two chemotherapy drugs: vinflunine, which is not reimbursed in the UK; and docetaxel, which is available, but not commonly used.[39, 40]

Comparative evidence

As the comparators in THOR are not used in UK clinical practice, overall survival and progression-free survival of patients receiving erdafitinib in THOR were compared with real-world data collected from a national UK registry containing data on similar types of patients receiving taxanes.[42] Statistical analyses of these data suggest statistically significant and clinically meaningful differences in overall survival and time to next treatment between erdafitinib and paclitaxel ± carboplatin, in favour of erdafitinib.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

The THOR trial evaluated the quality of life of patients who received treatment. Quality of life, symptoms, and functioning were captured using three patient-reported outcome measures: the Functional Assessment of Cancer Therapy – Bladder Cancer (FACT-BI), the EuroQol 5-Dimension 5-level (EQ-5D-5L) questionnaire, the Patient Global Impression of Severity (PGI-S), and time until urinary bladder cancer symptom deterioration (subset of FACT-BI items).[39]

Results from the FACT-BI and EQ-5D-5L assessments showed that patient quality of life was maintained on treatment, with few differences between the treatment groups. Analysis of time until urinary bladder cancer symptom deterioration showed no significant difference compared with chemotherapy. Quality of life was maintained across all aspects: physical, emotional, functional, and social, while providing meaningful extension of life.[39]

For more information regarding the burden of unresectable or metastatic urothelial carcinoma on patients' quality of life, please refer to Question 2d.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

The safety profile of erdafitinib demonstrated by the THOR trial was consistent with the prior BLC2001 trial, and the known safety profile of erdafitinib.[41] Erdafitinib has a different side effect profile compared with chemotherapy, but it is generally well tolerated and manageable with dose modifications.[40]

In the THOR trial, one treatment-related death occurred with erdafitinib, compared with six treatment-related deaths with chemotherapy. Eighteen patients (13%) had serious treatment-related adverse events, compared with 27 patients (24.1%) with chemotherapy. Eleven patients (8.1%) stopped treatment because of adverse events with erdafitinib, compared with 15 patients (13.4%) with chemotherapy.[9]

Table 1 presents the most commonly reported adverse events in the THOR trial.[39] There was some variation in the type of adverse events experienced between treatment arms. The adverse events were graded according to severity, with Grade ≥ 3 adverse events being more serious. As shown in Table 1, there are very few adverse events that are Grade 3 and above that occurred in ≥ 5% of patients.

Table 1: Frequently reported treatment-related adverse events

	Erdafitinib (n = 135)[a]		**Chemotherapy (n = 112)[b]**	
	Any grade	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
No. of patients, n (%)				
Diarrhoea (*Frequent and watery bowel movements)*	74 (54.8)	4 (3.0)	12 (10.7)	3 (2.7)
Stomatitis (*Inflamed or irritated mouth)*	62 (45.9)	11 (8.1)	13 (11.6)	2 (1.8)
Dry mouth *(Dryness in the mouth)*	52 (38.5)	-	3 (2.7)	-
Palmar-plantar erythrodysesthesia syndrome (*Pain, swelling, numbness, or redness of the hands or feet)*	41 (30.4)	13 (9.6)	1 (0.9)	0 (0.0)
Onycholysis (*Nail separating from the nail bed)*	31 (23.0)	8 (5.9)	1 (0.9)	0 (0.0)
Anaemia (*Lack of red blood cells)*	16 (11.9)	4 (3.0)	31 (27.7)	7 (6.3)
Alopecia (*Hair loss)*	32 (23.7)	-	24 (21.4)	-
Nausea (*Feeling of sickness)*	14 (10.4)	-	22 (19.6)	-

Neutropenia (*Lack of neutrophils (a type of white blood cells*))	0	0	21 (18.8)	15 (13.4)
Leukopenia (*Lack of white blood cells)*	0	0	13 (11.6)	9 (8.0)
Febrile neutropenia (*Fever and a lack of neutrophils (a type of white blood cell))*	0	0	9 (8.0)	10 (8.9)

Key: AE, adverse event; TRAE, treatment-related adverse events. **Notes:** [a]AEs listed if events of any grade occurred in ≥ 30% of patients in the erdafitinib group or if events of Grade 3–4 occurred in ≥ 5% of patients. [b]AEs by preferred term are listed if events of any grade occurred in ≥ 20% of patients in the chemotherapy group or if events of Grade 3–4 occurred in ≥ 5% of patients. **Source:** THOR clinical study report.[39]

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration

Erdafitinib has demonstrated several benefits over treatment with chemotherapy in terms of safety and efficacy, enabling patients to spend more time out of hospital with friends and/or family.

Results of the THOR trial demonstrate that erdafitinib[40]:

- Prolongs life by about 4 months compared to chemotherapy
- Delays cancer progression by about 2 months compared to chemotherapy
- Provides a rapid objective response rate, which is nearly four-fold higher than compared with chemotherapy
- Quality of life is maintained, while providing meaningful extension of life, compared to chemotherapy
- Causes fewer treatment-related serious adverse events compared to chemotherapy
- Can be taken at home, reducing hospital visits compared to chemotherapy

Doctors can proactively manage side effects as they can stop giving patients medicines or reduce dosage size. The administration of erdafitinib is also less disruptive compared with current treatments; as a once-daily oral tablet, it does not require frequent hospital visits, unlike the IV-administered chemotherapies currently used. The ability to receive treatment at home imposes less of a burden on patients and carers and may improve quality of life.[17, 35-38]

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

To be prescribed erdafitinib, diagnostic testing is required to confirm *FGFR* mutations. In the NHS, *FGFR* testing is currently not being performed extensively since erdafitinib is not licensed, and apart from PD-(L)1 testing in the first line, no other molecular biomarkers are used in routine clinical practice to predict sensitivity to specific medicines to guide therapy. Consequently, there is a need for an uptake in *FGFR* alteration testing in the NHS for patients with metastatic urothelial

carcinoma after immunotherapy. Additionally, there is a potential risk that patients might experience delays in receiving *FGFR* tests. This could delay their start to treatment.

While erdafitinib has a manageable safety profile, the adverse events observed are different to those typically seen with chemotherapy treatment. Adverse events seen with erdafitinib include nail, skin, and gastrointestinal disorders, and central serous retinopathy, an eye condition that affects vision. The risk of central serous retinopathy could impact patients further, as ophthalmology tests may be required during the first months of starting treatment. [39, 43] This could mean that some doctors would be unaware of how to manage these events. However, Johnson & Johnson has a responsibility to inform doctors with the correct and legal information, as per the Summary of Product Characteristics (SmPC) and trial data.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Cost-effectiveness model approach

Johnson & Johnson has developed an economic model to understand the cost-effectiveness of erdafitinib versus paclitaxel ± carboplatin, which is regarded to be a representative comparator of which treatment patients currently receive after first-line therapy. The model accounts for resources and costs for managing the disease, treating side effects, as well as the impact on quality of life and survival of patients on the potential treatment options (erdafitinib, paclitaxel ± carboplatin).

This model simulates a patient's progression through a set of distinct relevant health states. Each health state is associated with a specific cost and a specific quality-of-life benefit.

The following health states were used in this cost-effectiveness model:

- **Progression-free**: a patient's disease is stable or responding to treatment and not actively progressing. Costs in this health state are associated with treatment received, treatment administration costs, management of disease and adverse events, with costs varying over time. Quality of life is higher compared with patients with progressed disease and is also affected by adverse events
- **Progressed disease**: a patient's disease is assumed to have progressed. Costs in this health state are associated with treatment received, treatment administration costs and management of disease. Quality of life is lower compared with patients with progression-free disease and is also affected by adverse events
- **Death**: this state includes costs associated with palliative care and end-of-life costs.

The model utilises clinical data and real-world evidence to estimate the progression of patients through different health states in response to erdafitinib and comparators including paclitaxel ± carboplatin. It considers progression-free survival and overall survival data from clinical trials to estimate time spent in each health state. This is then adjusted for quality of life to calculate the total number of quality-adjusted life years (QALYs) gained from erdafitinib treatment for metastatic urothelial carcinoma.

The model also takes into account various costs associated with treatment acquisition, including treatment administration costs, subsequent treatment costs, adverse event costs, healthcare resource use costs to manage the disease, end-of-life costs, and testing costs. By comparing these costs with the additional QALYs gained, the model assesses the justification of erdafitinib's expenses.

Based on the model's predictions, erdafitinib treatment is expected to result in more clinical benefit, with higher gains in life years (LYs) and QALYs compared to paclitaxel ± carboplatin. This benefit is mainly driven by erdafitinib's superior progression-free survival and overall survival outcomes, leading to longer time in the progression-free health state and improved overall quality of life.

NICE looks at how severe a disease is when evaluating medicines. There are two modifiers to determine the severity: a “medium” severity modifier of 1.2 and a “high” severity modifier of 1.7. These modifiers give more value to the health benefits (multiples the QALYs by 1.2 or 1.7) over the costs and indirectly increase the amount the NHS can pay for very severe conditions. In the case of erdafitinib, it qualifies for the 1.7 severity modifier, which, given the stringent criteria in NICE methods to classify as high severity, shows that patients with this condition have a critical level of unmet need. This included in the economic model.

The findings from the model indicate that patients taking erdafitinib have higher costs, primarily due to the expenses associated with using a newer and innovative medicine.

It is important to note that the model does not consider the costs faced by patients, caregivers, families, and society resulting from the disease. Additionally, the model does not take into account the other positive aspects of the medicine, such as the hope it brings to families and the opportunity to spend more quality time with their loved ones.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a ‘step change’ in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

The medicine’s mode of action is the first step change in bladder cancer. The rapid absorption and long terminal half-life (50–60 hours) of erdafitinib results in sustained intracellular release. This may contribute to its long-lasting activity, as shown in the demonstrated extension of progression-free living and overall survival.[40, 44] Secondly, it is the first targeted treatment option instead of chemotherapy that could potentially lead to more patients being treated with an active treatment, due to patient preference, ease of use, limited hospital visits and different mode of action compared to chemotherapy.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
No equality considerations relating to the use of erdafitinib have been identified or are anticipated.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Patient groups and charities: • Fight bladder cancer UK: https://fightbladdercancer.co.uk/ • Action bladder cancer UK: https://actionbladdercanceruk.org/about-us/ • World bladder cancer patient coalition: https://worldbladdercancer.org/ • WBCPC survey: https://worldbladdercancer.org/news_events/global-bladder-cancer-patient-survey-results-point-to-areas-of-unmet-need/ **Publications:** • Systemic anticancer therapy for urothelial carcinoma: UK oncologists' perspective: https://www.nature.com/articles/s41416-023-02543-0 • Erdafitinib or Chemotherapy in Advanced or Metastatic Urothelial Carcinoma: https://pubmed.ncbi.nlm.nih.gov/37870920/ • Erdafitinib in Unresectable or Metastatic Urothelial Carcinoma: https://pubmed.ncbi.nlm.nih.gov/31340094/ **Further information on NICE and the role of patients:** • Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • EUPATI guidance on patient involvement in NICE: https://toolbox.eupati.eu/resources/patient-toolbox/guidance-for-patient-involvement-in-regulatory-processes/ • EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf • National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/ • INAHTA: http://www.inahta.org/ • European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe:

https://eurohealthobservatory.who.int/publications/i/health-technology-assessment-an-introduction-to-objectives-role-of-evidence-and-structure-in-europe-study

4b) Glossary of terms

Advanced cancer: Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumour, slow the growth of cancer cells, or relieve symptoms.[18]

Adverse event/side effect: An unexpected medical event that arises during treatment with a drug or other therapy. Adverse events can be classified as mild, moderate or severe.[18]

Biopsy: The removal of cells or tissues for examination by a pathologist.[18]

Diagnosis: The process of identifying a disease, condition, or injury from its signs and symptoms. A health history, physical exam, and tests, such as blood tests, imaging tests, and biopsies, may be used to help make a diagnosis.[18]

Disease progression: Cancer that continues to grow or spread.[18]

Clinical staging: A method used to find out the stage of cancer (amount or spread of cancer in the body) using tests that are done before surgery. These include physical exams, imaging tests, laboratory tests (such as blood tests), and biopsies.[18]

Clinical guidelines: Guidelines developed to help health care professionals and patients make decisions about screening, prevention, or treatment of a specific health condition.[18]

Clinical trial: A type of research that studies new tests and treatments and evaluates their effects on human health outcomes.[18]

Eligibility criteria: In clinical trials, requirements that must be met for a person to be included in a trial. These requirements help make sure that participants in a trial are like each other in terms of specific factors such as age, type and stage of cancer, general health, and previous treatment. When all participants meet the same eligibility criteria, it is more likely that results of the study are caused by the intervention being tested and not by other factors or by chance.[18]

Endpoint: In clinical trials, an event or outcome that can be measured objectively to determine whether the intervention being studied is beneficial. The endpoints of a clinical trial are usually included in the study objectives. Some examples of endpoints are survival, improvements in quality of life, relief of symptoms, and disappearance of the tumour.[18]

Financial burden: In medicine, a term used to describe problems a patient has related to the cost of medical care. Not having health insurance or having a lot of costs for medical care not covered by health insurance can cause financial problems and may lead to debt and bankruptcy.[18]

First-line therapy: The first treatment given for a disease. It is often part of a standard set of treatments, such as surgery followed by chemotherapy and radiation. When used by itself, first-line therapy is the one accepted as the best treatment.[18]

Immunotherapy: A type of therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Some types of immunotherapy only target certain cells of the immune system. Others affect the immune system in a general way.[18]

Intravenous (IV): Into or within a vein. Intravenous usually refers to a way of giving a drug or other substance through a needle or tube inserted into a vein.[18]

Maintenance therapy: Treatment that is given to help keep cancer from coming back after it has disappeared following the initial therapy. It may include treatment with drugs, vaccines, or antibodies that kill cancer cells, and it may be given for a long time.[18]

Metastatic: Having to do with metastasis, which is the spread of cancer from the primary site (place where it started) to other places in the body.[18]

Patient access scheme: Confidential pricing agreements proposed by pharmaceutical companies to enable patients to gain access to drugs or other treatments that may not be considered to be cost-effective under normal circumstances.[45]

Performance status: A measure of how well a patient is able to perform ordinary tasks and carry out daily activities.[18]

QALY: A measure of health outcomes pertaining to disease burden and is used to assess the value of medical interventions. As health can be defined as the length of life and the quality of life, the QALY combines the two factors into a single figure.[46]

Quality of life: An individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns.[47]

Real-world data: real-world data as data relating to patient health or experience or care delivery collected outside the context of a highly controlled clinical trial.[23]

Real-world evidence: Evidence generated from the analysis of real-world data. It can cover a large array of evidence types including disease epidemiology, health service research or causal estimation.[23]

Registry: A registry is a collection of all the official records relating to something, or the place where they are kept.[48]

Reimbursement: In the pharmaceutical industry, reimbursement refers to the process by which drug costs are covered by health insurance providers or national healthcare systems. A successful reimbursement strategy ensures that a drug is included on the list of drugs that are covered by insurance companies or national health systems, making it accessible to patients.[49]

Second-line therapy: Treatment that is given when initial treatment (first-line therapy) does not work, or stops working.[18]

Symptom: Something that a person feels or experiences that may indicate that they have a disease or condition.[18]

Unresectable: Unable to be removed by surgery.[18]

Urothelial carcinoma: Cancer that begins in cells called urothelial cells that line the urethra, bladder, ureters, renal pelvis, and some other organs. Urothelial cells are also called transitional cells. These cells can change shape and stretch without breaking apart. Also called transitional cell cancer.[18]

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

[August 2024]

File name	Version	Contains confidential information	Date
ID1333 erdafitinib clarification questions to PM for company [CON]_Priority_FULLY_REDACTED.docx	V1	Yes	2 August 2024

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

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Note: Correction to company base case

In addition to the Clarification Questions' responses, J&J IM have identified an error in the cost-effectiveness model. The inpatient hospitalisations for comparators were overestimated in the model version submitted in the Company submission (CS).

Results of scenarios provided as part of the Clarification Questions' responses include the corrected value for the frequency of inpatient hospitalisations for comparators and other changes that led to a revised base case. The revised economic model submitted with the company response includes the corrected value. Further details regarding the correction (and other updates based on clarification questions) and updated base case results are given in Appendix A.

Section A: Clarification on effectiveness data

Literature searches and reporting

A1. Priority question. The overall reporting of the searches for the clinical systematic literature review (SLR) is unclear i.e., there are multiple sections and embedded document which contain conflicting and inconsistent information. In order to facilitate the Evidence Assessment Group (EAG) critique, please provide a single document in chronological order containing full search methods for both the original and update searches (including strategies, date span, date searched and hits per resource) for all searches including grey literature, including but limited to the following areas of uncertainty:

a. **Appendix D section D.1.1.1. (which erroneously refers to the economics SLR) reports a search of MEDLINE in Process via Pubmed. A Pubmed search is also mentioned in the embedded document in Sections 3.1 and 3.2, however the strategies included for the original (2023) SLR only report a search of Ovid MEDLINE, and the update states that MEDLINE was searched via Embase.com. Please confirm if this was reported in error or provide full details of the Pubmed search.**

b. **The update search (March 2024) reports a single search strategy for both MEDLINE and Embase searches via Embase.com. Please confirm if this is a simultaneous search of both resources using a single strategy or a single search of the Embase database conducted on the understanding that it now contains all records from MEDLINE.**

c. **Appendix D Section D.1.1.2. and Section 3.1 of the embedded document (Genesis Research. Balversa for treatment of metastatic urothelial cancer: clinical systematic literature review report (V1.0) [PDF provided by the company], 2024 [accessed 27.6.24) Table 1: Treatment efficacy and safety systematic review PICO elements), lists four conference proceedings (ASCO, ESMO, ECCO & ISPOR) that were searched as part of the SLR. These were not included in the search strategies reported in the embedded document (Genesis research, 2024). Please provide full details including search strategies used (original and update searches if**

applicable), date searched, and hits retrieved. If relevant papers were retrieved, please add these to the PRISMA flow chart as they do not appear to be included.

d. **The PRISMA flow chart reported in Appendix D, Figure 2 mentions a search of trial registries, and these resources are also mentioned in Section 3.1 of the embedded document (Genesis Research, 2024) Table 1: Treatment efficacy and safety systematic review PICO elements, which lists searches for ClinicalTrials.gov, WHO ICTRP, Health Canada Clinical Trials Database and EU Clinical Trials Register. Strategies for these resources are not provided in the appendices of the embedded SLR document. Please confirm if these were searched and provide full search details including strategy used (original and update searches if applicable), date searched and hits per resource.**

e. **There appears to be a typo in line #60 of the Cochrane search strategy (Table 33, Genesis Research 2024) an unformatted EndNote reference looks to have been included instead of a line combination, please can you provide a copy of the corrected strategy and confirm that this is a search of both CDSR and CENTRAL**

J&J apologise for the inconvenience caused by the reporting of the SLRs, this was in part a result of time constraints due to an earlier than expected submission date. The single document requested is provided as an Appendix with the specific points raised in the question detailed below.

a/b) The reported search of MEDLINE in Process via Pubmed was made in error. The original (2023) systematic literature review (SLR) included a search in MEDLINE and Embase using Ovid platform. Search strategies were prepared separately in Ovid for MEDLINE and Embase, as presented in Table 1 and Table 2, respectively, of the Appendix.

The updated (2024) SLR included a search in MEDLINE and Embase but instead of Ovid, the Embase platform was used. Since the Embase platform can integrate both MEDLINE and Embase databases using a common search syntax, a single

search strategy was used for both the databases, as depicted in Table 4 in the Appendix.

Nevertheless, search syntax used in Ovid for original (2023) SLR were accurately mapped and translated into search syntax used in Embase.com before running the searches for updated (2024) SLR.

Text has been modified in the Appendix Section D.1.1 to provide better clarity on the use of different search platforms for Embase and MEDLINE in the two SLR iterations.

c) The ASCO, ESMO, and ISPOR conferences were searched as part of the original as well as updated SLRs. In addition, European Cancer Organization (ECO) was also searched, which was inadvertently mentioned as European Crohn's and colitis organization (ECCO). This has been rectified in Appendix Section D.1.1.1.

All four conferences were searched on the same dates as the original (March 10, 2023) and updated SLRs (May 01, 2024) were conducted. Searches were conducted using specific keywords of interest related to disease (i.e., urothelial cancer) and interventions of interest (i.e., erdafitinib, carboplatin + gemcitabine, cisplatin + gemcitabine, paclitaxel, docetaxel, pembrolizumab, or atezolizumab). However, no relevant papers of interest were retrieved (see Appendix D.1.1.1.).

d) Searches were conducted in trial registries (i.e., ClinicalTrials.gov, WHO ICTRP, Health Canada Clinical Trials Database and EU Clinical Trials Register) during the original (2023) SLR as well as the updated (2024) SLR using specific keywords of interest related to disease (i.e., urothelial cancer) and interventions of interest (i.e., erdafitinib, carboplatin + gemcitabine, cisplatin + gemcitabine, paclitaxel, docetaxel, pembrolizumab, or atezolizumab).

The original SLR yielded 543 hits from registries, of which 117 were sought for retrieval and full-text screening. However, all 117 hits were found to be duplicates of searches already conducted via Embase, MEDLINE and Cochrane (see Appendix D.1.1.1.).

These trial registries were again searched during updated (2024) SLR using the same keywords related to disease and interventions of interest to check for any new trials identified since March 2023. However, no new trials were identified from trial registries (See Appendix D.1.1.1.).

e) There was an inadvertent conversion of numerical data by EndNote software into a reference citation, which should have depicted a combination of the Cochrane search strings from #34 to #59 in Table 32 (previously numbered as Table 33) of the embedded SLR report. This has been rectified in the Appendix..

The search strategy presented in Table 32 (Table 4 in the Appendix) applies to all content in the Cochrane Library, including Cochrane Database of Systematic Reviews (CDSR) and Cochrane Central Register of Controlled Trials (CENTRAL).

A2. Priority question. As with the clinical SLR, the reporting of the searches for the economics SLR (Costs, resource use) are also unclear with different sections containing conflicting and inconsistent information. In order to facilitate the EAG's critique, please provide a single document in chronological order containing full search methods for both the original and update searches (including strategies, date span, date searched and hits per resource) for all searches including grey literature. Please see below for particular areas of uncertainty:

a. **Appendix G, Section G1.1 reports a search of MEDLINE and Embase via Embase.com. Whilst the searches provided in the appendices of the embedded document (Genesis Research. Locally advanced and metastatic urothelial cancer: systematic literature review on economic evaluations, costs, and resource use associated with locally advanced, metastatic, and surgically unresectable urothelial cancer (V1.0) [PDF provided by the company], 2024 [accessed 27.6.24]) provide separate strategies for each resource conducted in Ovid, it appears that only the update searches were conducted using Embase.com. Please confirm if this is correct.**

b. **Section G1.1 also reports searches of the Health Technology Assessment Database and NHS EED, however these do not appear in the appendices of the embedded document (Genesis Research, 2024). Please confirm if these were reported in error or provide full details of any searches conducted.**

c. **As with the clinical SLR, searches are reported for a range of grey literature resources including four conference proceedings and six health technology assessment (HTA) agencies. No strategies, dates searched or hits per line are reported in the embedded documents (Genesis Research, 2024). Please provide full details for all searches (original and updates) as necessary.**

d. **The PRISMA flowchart in Appendix G does not match that in the embedded document (for example in Appendix G the results for Embase are reported as 8542, and in the embedded document (Genesis Research, 2024) this is reported as 7666). Please confirm which is correct.**

e. **Table 4, Section 3.1 of the embedded document (Genesis Research, 2024) lists additional searches of Econlit, The International HTA database (INAHTA), Tufts Medical Center Cost-Effectiveness Analysis registry database (CEA registry), Clinicaltrials.gov and clinicaltrialsregister.eu. Please confirm if these were searched and provide full details for all searches (original and updates) including strategy used, date searched and hits per resource.**

f. **Only one set of search strategies is reported in the appendices of the embedded document for the original searches (Genesis Research, 2024). These appear to match the search numbers reported for the 2022 SLR (the EAG note that the searches for this SLR were conducted in 2021 but presume they are what is referred to as the 2022 SLR, please correct if wrong). Please provide full search details including search strategies, date searched and hits per line for all searches (i.e. searches conducted in 2018 and 2023).**

g. The section pertaining to the 2024 update (Genesis Research, 2024) contains two sets of searches, one for costs and resource use as above (Econlit and Cochrane Library) and a second separate search for health-related quality of life (HRQoL) data (Embase.com, Econlit and Cochrane Library). No strategies are reported for an update of the costs/resource use search on Embase or MEDLINE. Please confirm if this was omitted in error and provide full search details.

a) As with the clinical SLR, the previous (2018, 2022 and 2023) economic evaluations/HCRU SLRs included a search in MEDLINE and Embase using Ovid platform. Search strategies were prepared separately in Ovid for Embase and MEDLINE, as presented in the embedded document.

The updated (2024) economic evaluations/HCRU SLR also included a search in MEDLINE and Embase but instead of Ovid, the Embase platform was used. Since the Embase platform can integrate both MEDLINE and Embase databases using a common search syntax, a single search strategy was used for both the databases, as depicted in Table 50 of the embedded document.

Nevertheless, search syntax used in Ovid for previous (2018, 2022 and 2023) SLRs were accurately mapped and translated into search syntax used in Embase.com before running the searches for 2024 SLR update.

b) While conducting the updated (2024) SLR, relevant reports within the Health Technology Assessment Database (HTAD) and National Health Service Economic Evaluation Database (NHS EED) databases were searched from 2023 to 2024 using CRD York.com. Search was conducted using keyword for disease (i.e., urothelial cancer). However, no relevant articles were retrieved in HTAD or NHS EED (see Appendix G.1.1).

c) As with the clinical SLR, searches were conducted in ASCO, ESMO, ECO and ISPOR conferences as part of the original as well as updated SLRs. Searches were conducted for the updated (2024) SLR within the time frame of May 2023 to April 2024 using specific keyword of interest related to disease (i.e., urothelial

cancer) and economic outcomes of interest (economic model, health economics, utility, HRQoL, cost and resource use). However, no relevant papers of interest were retrieved during the 2024 SLR update (see Appendix G.1.1).

d) PRISMA flow diagram in Appendix G was depicting the total number of hits after combining the previous SLRs and the 2024 SLR update, while the PRISMA flow diagram compared within the embedded document was presenting only the previous SLR evidence. To avoid further confusion, two separate PRISMA flow diagrams have been added to the Appendix, presenting previous SLR evidence and an SLR update as per the PRISMA 2020 format for SLR updates in Section E.3.

e) EconLit, INAHTA, Clinicaltrials.gov and clinicaltrialsregister.eu were searched across all SLR iterations. No new records were identified in trial registries during the 2024 SLR update (see Appendix G.1.1). The Tufts Medical Center Cost-Effectiveness Analysis registry database (CEA registry) was searched during 2018 SLR and yielded seven records. Due to a lack of subscription/access to the CEA registry during 2024 SLR update, the Tufts Medical Center Cost-Effectiveness Analysis registry database was not searched. Instead, HTAD and NHS EED databases were searched, which did not yield any records of interest between May 2023 and April 2024 (see Appendix G.1.1).

f) Search strategies and results for all databases have now been added to the Appendix for the years 2018, 2022, 2023 and 2024.

g) Search strategies and results for economic evaluations and costs/resource use SLRs have now been added to the Appendix of economic SLRs.

A3. Priority question. Appendix H states that "*The search strategy used, including databases searched, was the same as that used for the SLR of published cost-effectiveness studies (Appendix G.1)*".

a. However, the only searches including terms for utilities/HRQoL are reported in the Section relating to the 2024 update search (conducted on 10 April 2024 in (Genesis Research, 2024). These searches appear to only cover the last year. Please confirm if these were the only searches conducted to identify HRQoL data and explain why this approach was

taken. If earlier searches were undertaken, please provide full search details.

b. **The searches reported for HRQoL were conducted on Embase.com, Econlit and Cochrane Library. Please confirm if the other grey literature sources mentioned in Appendix G were also used to inform this section.**

c. **The numbers that appear in the PRISMA Flow Chart in Figure 8, Appendix H, currently do not appear to match the searches provided. MEDLINE and Embase also appear separately rather than as a joint search as reported in the update search). Please provide clarity.**

d. **At the end of Appendix H, it states that "*Further information on results from the HRQL studies can be found in the reports below*" however the embedded document is actually the clinical SLR. Please confirm if this was included in error and should have been the same document as provided in Appendix G.**

e. **In line #40 of the Cochrane HRQoL search line #11 (MeSH descriptor for Quality of life), appears to be missing from the final line combination for the HRQoL facet, please confirm if this is due to a typo or an error in the search.**

a) The statement "The search strategy used, including databases searched, was the same as that used for the SLR of published cost-effectiveness studies" refer to the common search strategy used to retrieve evidence for economic evaluations (including cost-effectiveness studies) and HCRU. This was done consistently across all SLR iterations due to the similarity in the scope defined for economic evaluations and HCRU in the PICO statement.

Although the search strategy remained same for economic evaluations and HCRU, the screening of relevant abstracts and full-text records was done separately for economic evaluations and HCRU.

HRQoL search strategy was prepared separately since the focus was on utility or HRQoL outcomes and not on cost outcomes. We have now added search strategies and results for each iteration of the HRQoL SLRs in Appendix E.

b) We confirm that the other grey literature sources mentioned in Appendix G were also used to inform this section. However, searches were conducted using keywords as per disease and outcomes defined in PICO table. No new records were retrieved from grey literature during the 2024 SLR update (see Appendix G).

c) As elaborated earlier, the 2024 SLR update was performed using embase.com platform, which can integrate both MEDLINE and Embase databases using a common search syntax. However, Embase and MEDLINE searches for the previous SLRs were conducted using Ovid platform, wherein search strategies were prepared separately for Embase and MEDLINE.

We ensured that the search syntax used in Ovid for previous (2018, 2022 and 2023) SLRs were accurately mapped and translated into search syntax used in Embase.com before running the searches for 2024 SLR update.

The numbers in the PRISMA flow chart were not matching the searches since the searches were for a specific iteration while the PRISMA flow chart was for overall SLR iterations. The PRISMA flow chart for HRQoL evidence has now been separated into two diagrams, with one depicting the evidence generated prior to 2024 and the other depicting hits retrieved during 2024 SLR update.

d) This was in error, our apologies, we have now provided all the details of the searches and results for clinical (Appendix D), cost-effectiveness (Appendix E), HRQoL (Appendix F) and cost and resource utilisation SLRs (Appendix G).

e) Thank you for highlighting the omission of #11 from the search string in line #40 of Cochrane HRQoL 2024 SLR update. This was a typo and we have checked and confirmed that addition of #11 within line #40 does not impact the number of hits retrieved (n=325).

A4. Priority question. In the strategies reported for the 2024 update of the clinical effectiveness searches Appendix 2, Tables 31 & 32 (Genesis Research.

Balversa for treatment of metastatic urothelial cancer: clinical systematic literature review report (V1.0) [PDF provided by the company], 2024 [accessed 27.6.24), the interventions facet appears more limited than in the original searches. Please explain the rationale for not including all interventions listed in the 2023 strategies. Erdafitinib also appears to be missing from the 2024 searches, please confirm if a separate search was undertaken for this and provide full details, if not please provide an update to ensure no new relevant papers have been missed.

While the original (2023) SLR was conducted in all treatment comparators without geographical limits, the updated (2024).SLR was focused on informing clinical evidence specific to the UK treatment landscape as part of the NICE submission. Therefore, instead of conducting an SLR update on all treatment comparators, we limited the 2024 SLR update to only the following comparators that are currently available in the UK:

- Carboplatin + gemcitabine
- Cisplatin + gemcitabine
- Paclitaxel
- Docetaxel
- Pembrolizumab
- Atezolizumab

Erdafitinib was missed inadvertently while preparing the search strategy tables and to ensure that no new relevant papers have been missed, we reran the searches after including erdafitinib. 18 additional records were retrieved from Embase while no new studies were found in other databases, including Cochrane. None of the 18 records were relevant as per the 2024 SLR PICOS criteria and. These 18 records have been excluded at abstract screening stage in an updated PRISMA flow diagram.

Population and generalisability

A5. Priority question. The population assessed in this appraisal is narrower than the final scope by NICE, in order to align it with the final marketing authorisation of erdafitinib. The population selected by the company entails "[redacted]." Please include transparent, detailed justification for this more restrictive focus and discuss how it may limit

the generalisability of results to the broader population in the National Institute for Health and Care Excellence (NICE) scope. Additionally, address the following points with supporting evidence from available literature:

a. Discuss whether receiving at least one line of therapy containing a PD-1 or PD-(L)1 inhibitor is a disease/treatment effect modifier.

b. Discuss whether FGFR3 genetic alteration is a disease/treatment effect modifier.

c. Discuss if there would be an expected difference in prognosis or treatment effect for patients with FGFR3 genetic alterations.

d. Discuss if there would be an expected difference in prognosis or treatment effect for patients who have received at least one line of therapy containing a PD-1 or PD-(L)1 inhibitor.

Before addressing questions a. – d., J&J would like to emphasise that the "more restrictive focus" suggested by the EAG aligns with the anticipated marketing authorisation. It is important to note that, although the final scope may be broader, the remit of NICE is to appraise in accordance with the marketing authorisation. As a result, we do not anticipate any limitations on the generalizability of the results to patient population relevant to the decision problem.

a. THOR is an ongoing global, Phase III, randomised, open-label, multicentre, confirmatory registrational trial evaluating erdafitinib in patients with advanced UC and susceptible *FGFR* alterations who had progressed on or after one or two prior treatments.[1, 2]

Aligning with the decision problem and marketing authorisation (aligned as per NICE's remit) presented in Doc B.1.1 this submission will focus on Cohort 1 of the THOR trial. This cohort only included patients that had progressed on or after one or two prior treatments, one of which being an anti-PD-(L)1 agent.[3]
As treatment with a PD-(L)1 inhibitor is a requirement of the marketing authorisation and thus the patient population relevant to this decision problem, considering whether a patient has received prior therapy with a PD-1 or PD-(L)1 inhibitor as a disease/treatment effect modifier becomes irrelevant, the

evidence from THOR and UK RW mUC study align to the anticipated marketing authorisation, as all patients analysed have received a prior PD-(L)1.

b. FGFR3 genetic alteration is a treatment effect modifier. Results from THOR Cohort 1 demonstrate that a targeted patient population harbouring positive FGFR3 alteration status have a statistically significant superior overall and progression-free survival to erdafitinib versus chemotherapy. Therefore, FGFR3 genetic alterations are predictive of response to erdafitinib.

c. The prognostic role of FGFR3 alterations is not fully characterised in metastatic urothelial carcinoma. Understanding of the effect FGFR3 alterations have on clinical outcomes has been limited to real-world retrospective studies.

   J&J provided evidence to inform the prognostic value of FGFR3-positive alterations in a MAIC that was provided in the submission (see Document B, B 3.7). The MAIC analysis (Appendix Q1) was conducted to explore any potential differences in chemotherapy efficacy in a FGFR3-positive (THOR) or untested population (EV301). The MAIC revealed that there was no statistically significant difference in OS, PFS and responses between the chemotherapy arms of the THOR trial (vinflunine or docetaxel) and the EV301 trial (vinflunine, docetaxel, or paclitaxel), with a slight positive trend towards chemotherapy efficacy in the untested EV-301 population. The results of the MAIC provide some confidence that it can be assumed that the efficacy described in the UK RW mUC study would be comparable, if not conservative, compared to an FGFR3-positive population.

   This is supported by a real-world study, where FGFR status did not influence PFS from time of mUC diagnosis or among 224 stratified patients receiving either chemotherapy or chemotherapy + ICI.[4]

   However, as explained in part b. the THOR Cohort 1 trial provides level 1 evidence of the expected difference in treatment effect for patients with FGFR3 genetic alterations.

d. Given the recent marketing authorisation approvals for PD-(L)1 inhibitors, real-world evidence is limited. However, in the retrospective study described above,

the cohort of 97 patients who received first-line anti-PD-(L)-1 only, PFS was significantly shorter for those with FGFR alterations. Nevertheless, as described in part a. of this question, as PD-(L)1 exposure is a requirement for the marketing authorisation of erdafitinib and thus the decision problem, a thorough analysis on whether or not PD-(L)1 treatment could impact prognosis for this disease is not relevant for this submission.

In conclusion, with chemotherapy treatment alone and no erdafitinib availability, there is no evidence to suggest that FGFR3 positive patients have a different outcome than an untested population. However, as erdafitinib has shown a benefit over chemotherapy in the THOR trial, FGFR3 positivity is a predictive factor, if erdafitinib would be available for these patients.

A7. Priority question. Please ensure that data on censoring rates across each time point are included with Kaplan-Meier curves as appropriate. Accompany each Kaplan-Meier curve with a table showing the following for each arm and time point: the number of patients at risk, the number of events occurring during the interval, the number of patients censored during the interval, the cumulative number of events, the cumulative number of censored observations, and the censoring rate.

The Kaplan-Meier curves for OS and PFS for erdafitinib are presented in

Figure 1 and Figure 2, with the corresponding summary of overall survival events and censoring by time point presented in Table 1 and Table 2, respectively.

Figure 1. THOR Kaplan–Meier Plot of OS

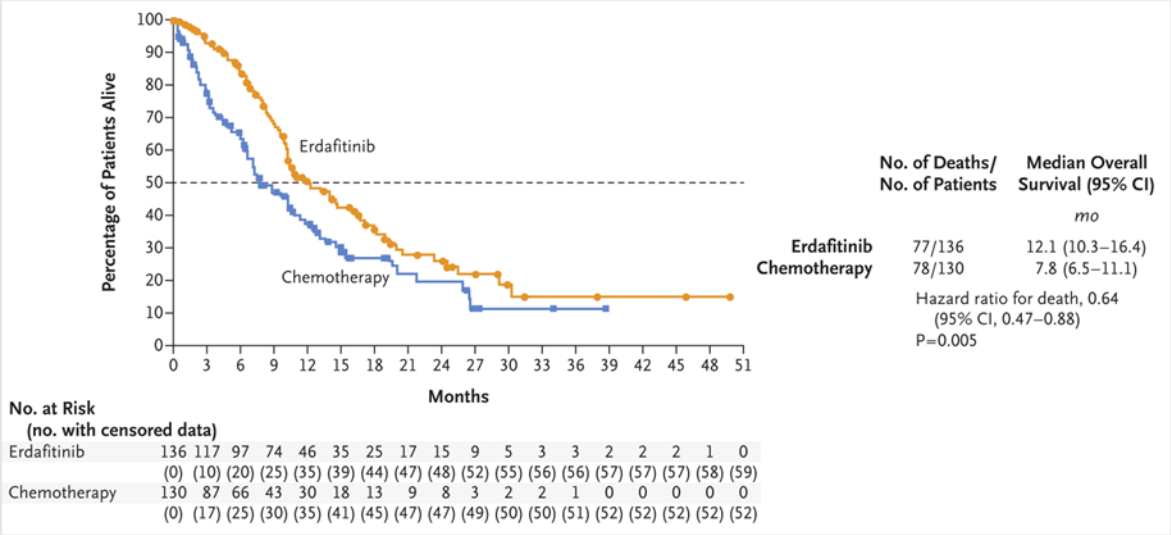


Figure 2. THOR Kaplan–Meier Plot of PFS

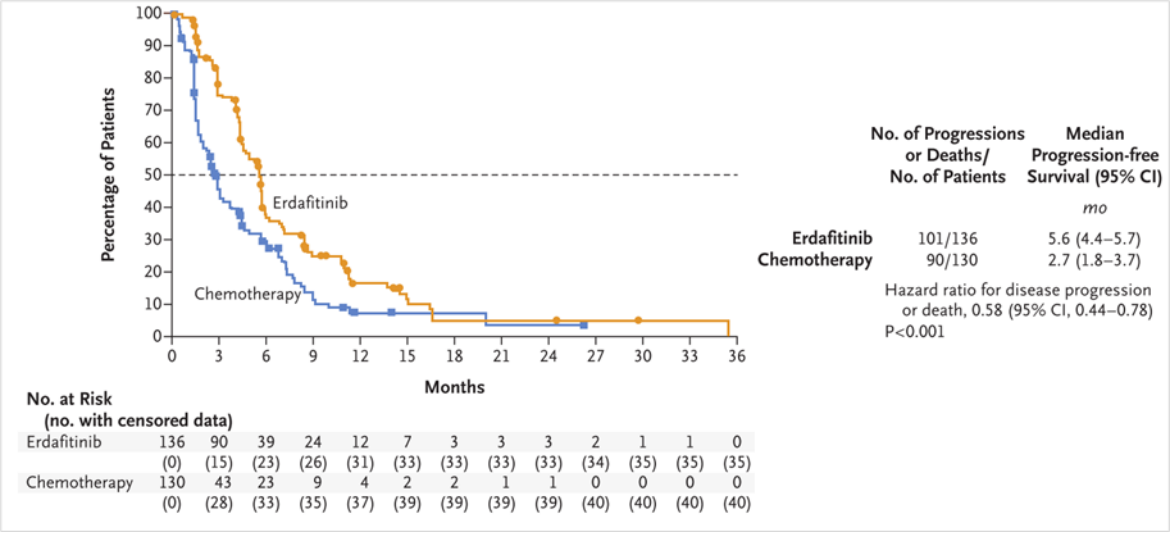
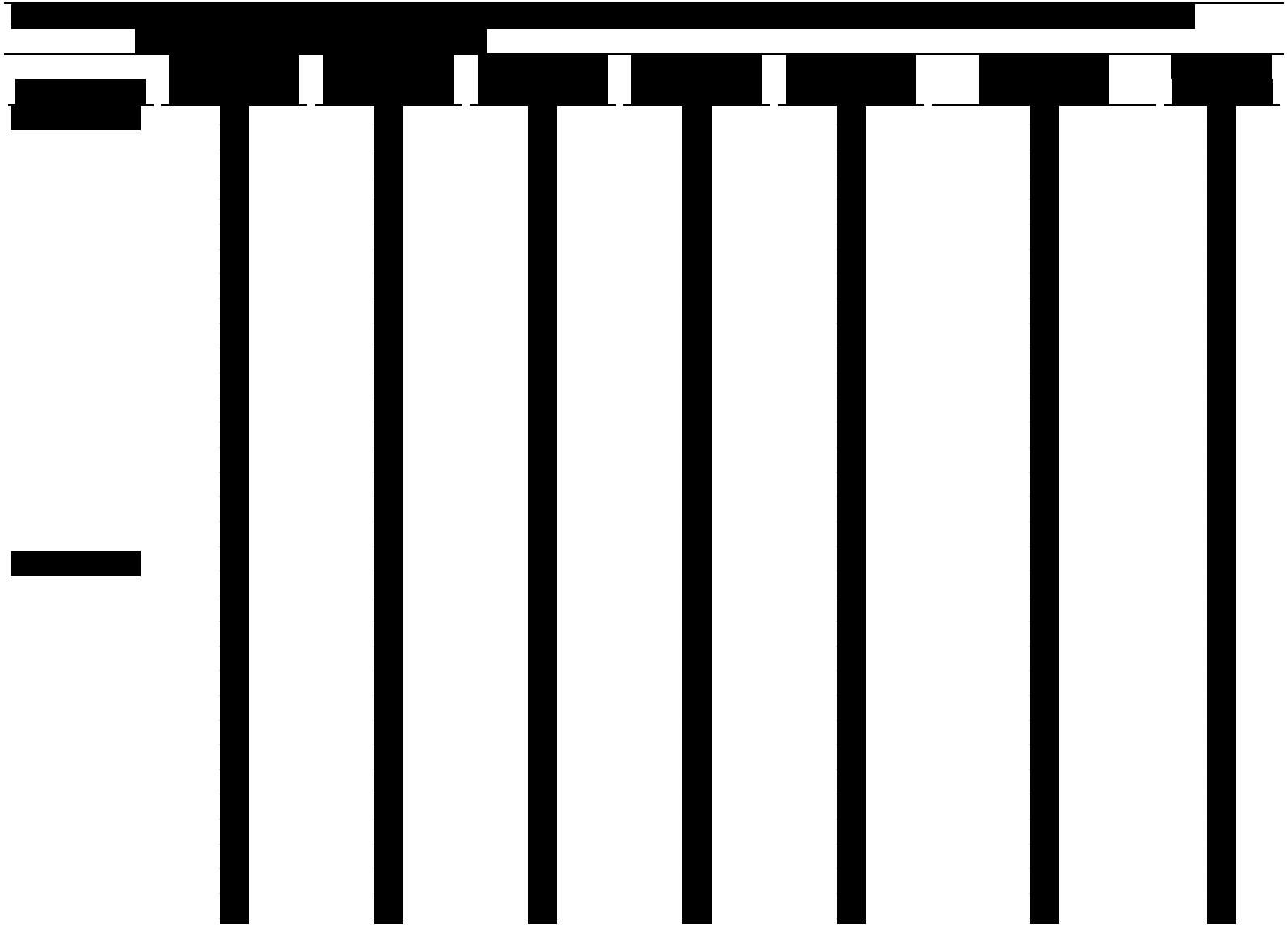


Table 1. Summary of Overall Survival Events and Censoring for Erdafitinib and Chemotherapy by Time Point



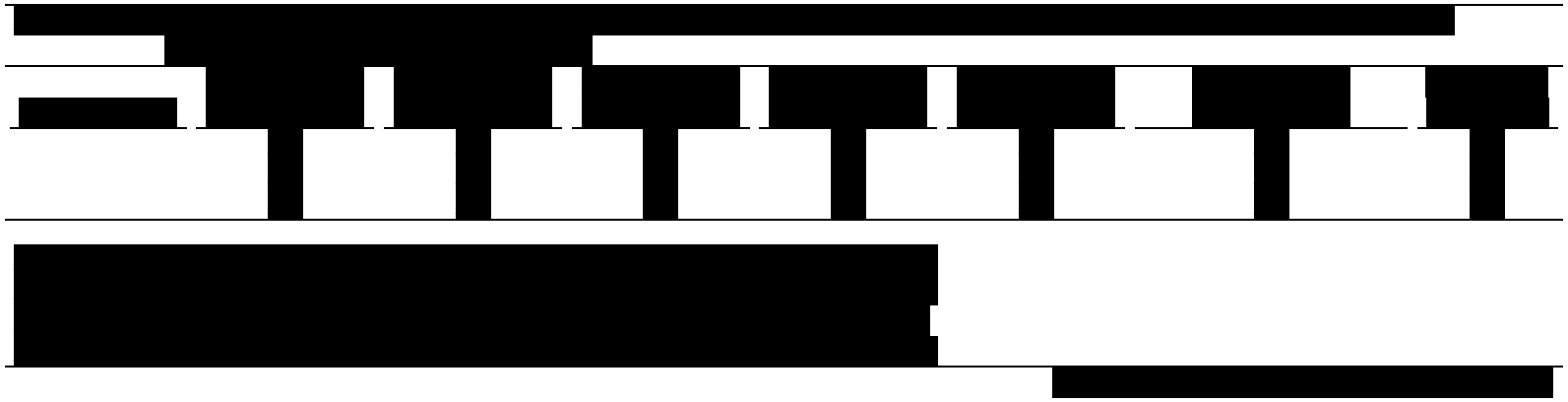
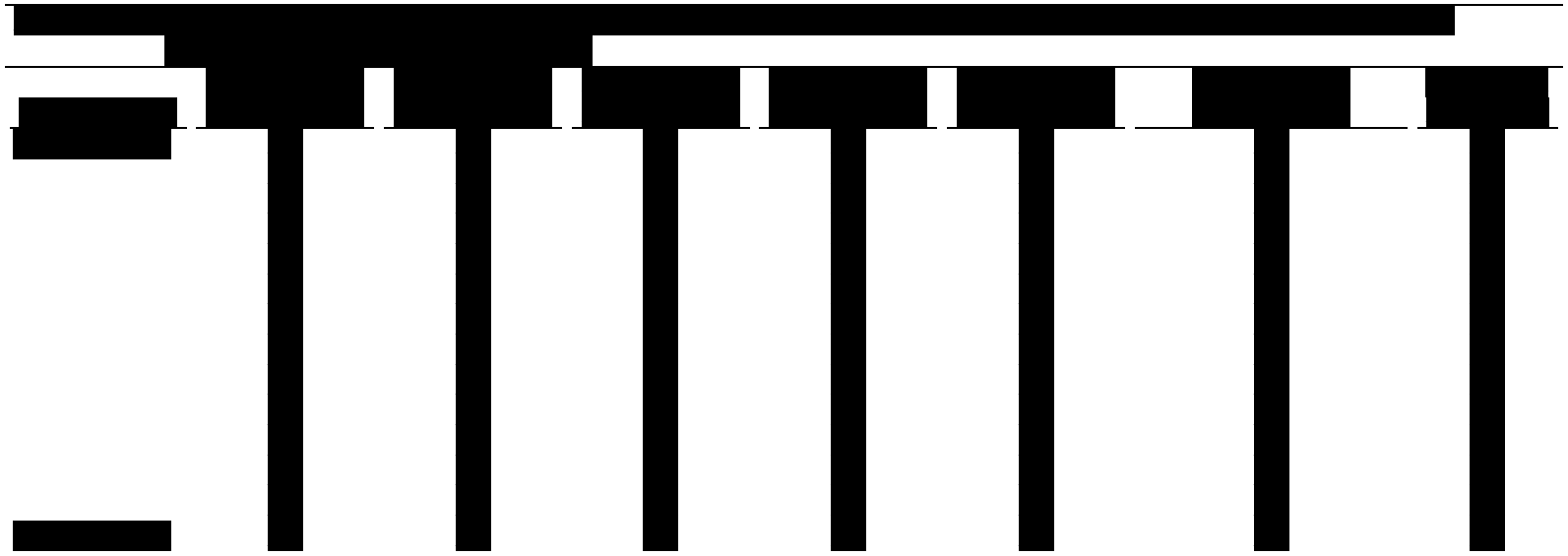


Table 2. Summary of Progression-Free Survival Events for Erdafitinib and Chemotherapy and Censoring by Time Point



We present the Kaplan-Meir curves for ATC-adjusted OS comparison for erdafitinib versus paclitaxel ± carboplatin in Figure 3 and the associated number of patients at risk, number of events occurring during the interval and number of patients censored in Table 3.

Figure 3. Kaplan-Meier curve for ATC-adjusted OS comparison for erdafitinib versus paclitaxel ± carboplatin

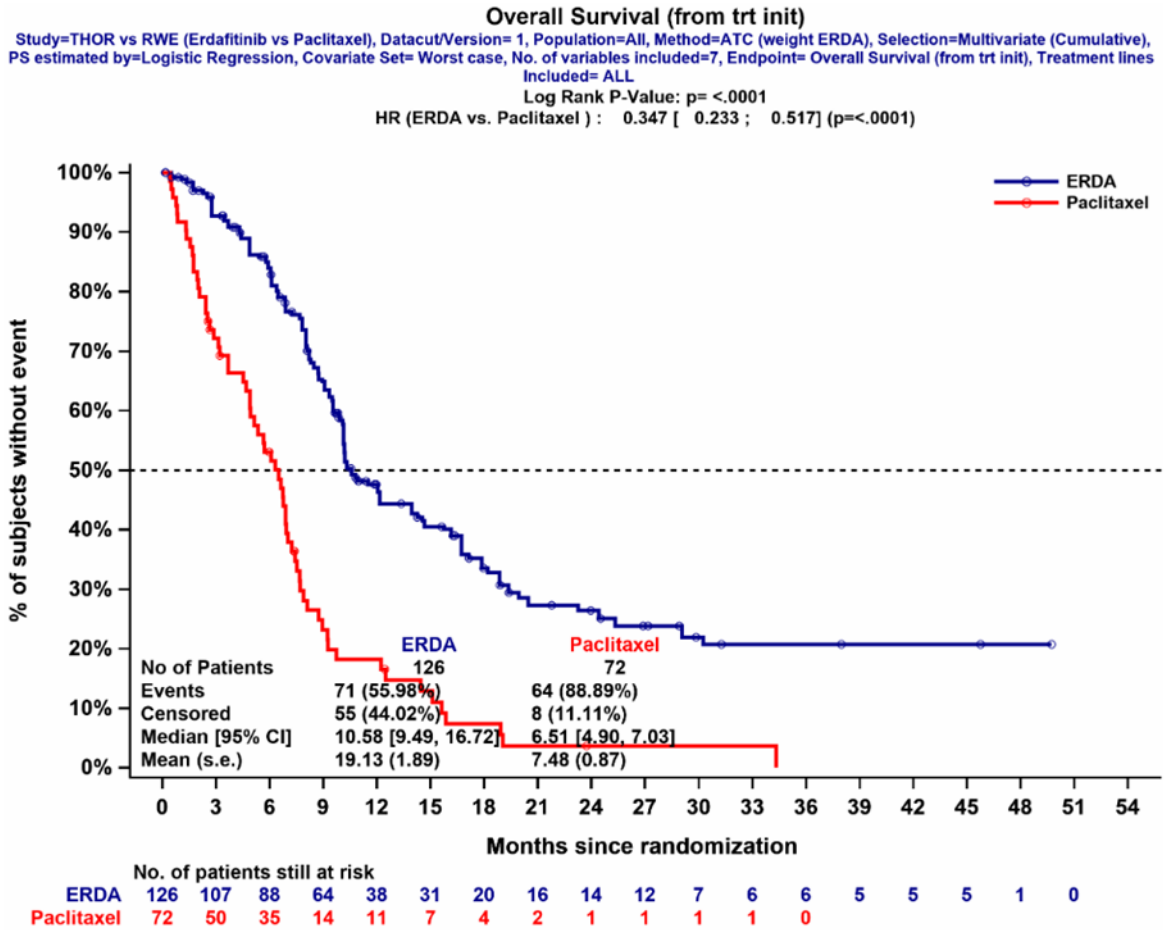


Table 3. Count of patients at risk, events, and number of patients censored during the interval for ATC-adjusted OS comparison for erdafitinib versus paclitaxel ± carboplatin.

Treatment	Time	Number at risk	Events*	Cum. N of events	Censored patients*	Cum. N of censoring
Erdafitinib	0	126	0	0	0	0
	3	107	9	9	10	10
	6	88	10	18	10	20
	9	64	19	37	4	24
	12	38	16	54	10	34
	15	31	6	59	2	36

	18	20	5	64	5	42
	21	16	4	68	1	43
	24	14	0	68	1	44
	27	12	1	70	1	45
	30	7	1	70	4	49
	33	6	0	71	1	50
	36	6	0	71	0	50
	39	5	0	71	0	50
	42	5	0	71	0	50
	45	5	0	71	0	50
	48	1	0	71	4	54
	51	0	0	71	1	55
Paclitaxel ± carboplatin	0	72	0	0	0	0
	3	50	20	20	2	2
	6	35	13	33	2	4
	9	14	19	52	2	6
	12	11	3	55	0	6
	15	7	3	58	1	7
	18	4	3	61	0	7
	21	2	2	63	0	7
	24	1	0	63	1	8
	27	1	0	63	0	8
	30	1	0	63	0	8
	33	1	0	63	0	8
	36	0	1	64	0	8

*Number of event and censored patients in the Erdafitinib arm are obtained from the re-weighted population and the numbers are rounded to make the table more readable

The Kaplan-Meir curves for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel ± carboplatin is presented in

Figure 4 and the associated number of patients at risk, number of events occurring during the interval and number of patients censored in Table 4.

Figure 4. Kaplan-Meier curve for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel ± carboplatin

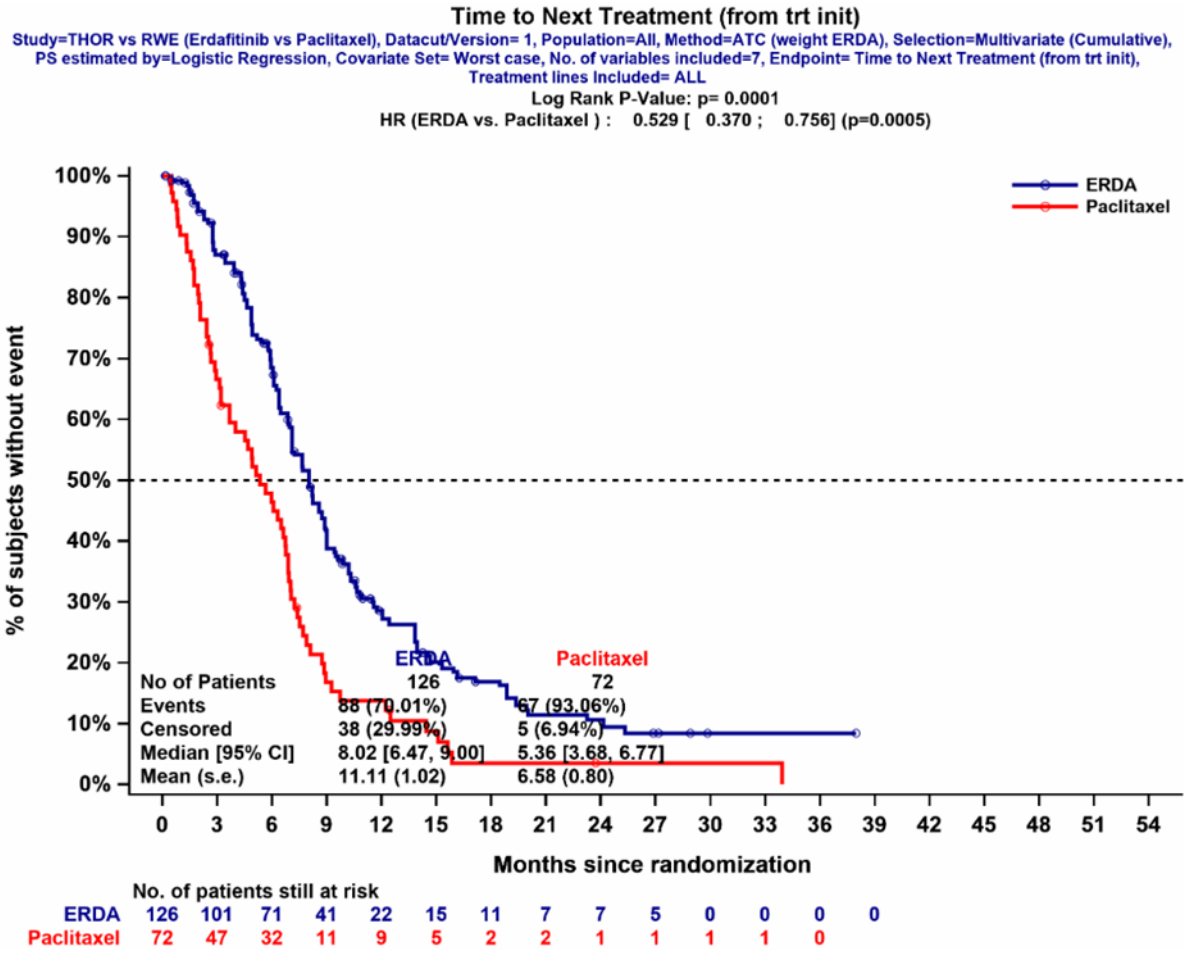


Table 4. Count of patients at risk, events, and number of patients censored during the interval for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel ± carboplatin.

Treatment	Time	Number at risk	Events*	Cum. N of events	Censored patients*	Cum. N of censoring
Erdafitinib	0	126	0	0	0	0

	3	101	15	15	10	10
	6	71	20	35	10	20
	9	41	27	62	3	23
	12	22	12	74	7	30
	15	15	6	81	1	31
	18	11	2	83	2	33
	21	7	3	86	0	33
	24	7	0	87	0	33
	27	5	1	88	0	33
	30	0	0	88	4	37
	33	0	0	88	0	37
	36	0	0	88	0	37
	39	0	0	88	0	38
Paclitaxel ± carboplatin	0	72	0	0	0	0
	3	47	24	24	1	1
	6	32	14	38	1	2
	9	11	20	58	1	3
	12	9	2	60	0	3
	15	5	3	63	1	4
	18	2	3	66	0	4
	21	2	0	66	0	4
	24	1	0	66	1	5
	27	1	0	66	0	5
	30	1	0	66	0	5
	33	1	0	66	0	5
	36	0	1	67	0	5

The following tables show the count of patients at risk, events, and number of patients censored during the interval for ATC-adjusted PFS (Table 5) and TTD (Table 6) comparison for erdafitinib versus chemotherapy.

Table 5. Count of patients at risk, events, and number of patients censored during the interval for ATC-adjusted PFS comparison for erdafitinib and chemotherapy

Treatment	Scenario	Time (months)	Number at risk	Number of events	Cumulative number of events	Number censored	Cumulative number censored
Erdafitinib	Base case	0	126	0	0	0	0
Erdafitinib	Base case	3	80	30	30	16	16
Erdafitinib	Base case	6	30	46	76	5	20
Erdafitinib	Base case	9	17	11	86	3	23

Erdafitinib	Base case	12	9	3	90	4	27
Erdafitinib	Base case	15	4	1	91	4	31
Erdafitinib	Base case	18	2	2	93	0	31
Erdafitinib	Base case	21	2	0	93	0	31
Erdafitinib	Base case	24	2	0	93	0	31
Erdafitinib	Base case	27	1	0	93	0	31
Erdafitinib	Base case	30	0	0	93	1	32
Erdafitinib	Base case	33	0	0	93	0	32
Erdafitinib	Base case	36	0	0	94	0	32
Erdafitinib	Base case	39	0	0	94	0	32
Erdafitinib	Exclude missing	0	92	0	0	0	0
Erdafitinib	Exclude missing	3	65	19	19	9	9
Erdafitinib	Exclude missing	6	29	31	50	5	13
Erdafitinib	Exclude missing	9	21	5	55	3	16
Erdafitinib	Exclude missing	12	9	5	60	7	23
Erdafitinib	Exclude missing	15	4	3	62	3	26
Erdafitinib	Exclude missing	18	2	2	64	0	26
Erdafitinib	Exclude missing	21	2	0	64	0	26
Erdafitinib	Exclude missing	24	2	0	64	0	26
Erdafitinib	Exclude missing	27	2	0	64	0	26
Erdafitinib	Exclude missing	30	0	0	64	1	27
Erdafitinib	Exclude missing	33	0	0	64	0	27
Erdafitinib	Exclude missing	36	0	0	65	0	27
Erdafitinib	Exclude missing	39	0	0	65	0	27
Chemotherapy	THOR ITT	0	130	0	0	0	0
Chemotherapy	THOR ITT	3	43	59	59	28	28
Chemotherapy	THOR ITT	6	23	15	74	5	33
Chemotherapy	THOR ITT	9	9	12	86	2	35
Chemotherapy	THOR ITT	12	4	3	89	2	37

Chemotherapy	THOR ITT	15	2	0	89	2	39
Chemotherapy	THOR ITT	18	2	0	89	0	39
Chemotherapy	THOR ITT	21	1	1	90	0	39
Chemotherapy	THOR ITT	24	1	0	90	0	39
Chemotherapy	THOR ITT	27	0	0	90	1	40
Chemotherapy	THOR ITT	30	0	0	90	0	40
Chemotherapy	THOR ITT	33	0	0	90	0	40
Chemotherapy	THOR ITT	36	0	0	90	0	40
Chemotherapy	THOR ITT	39	0	0	90	0	40
Erdafitinib	THOR ITT	0	136	0	0	0	0
Erdafitinib	THOR ITT	3	90	31	31	15	15
Erdafitinib	THOR ITT	6	39	43	74	8	23
Erdafitinib	THOR ITT	9	24	12	86	3	26
Erdafitinib	THOR ITT	12	12	7	93	5	31
Erdafitinib	THOR ITT	15	7	3	96	2	33
Erdafitinib	THOR ITT	18	3	4	100	0	33
Erdafitinib	THOR ITT	21	3	0	100	0	33
Erdafitinib	THOR ITT	24	3	0	100	0	33
Erdafitinib	THOR ITT	27	2	0	100	1	34
Erdafitinib	THOR ITT	30	1	0	100	1	35
Erdafitinib	THOR ITT	33	1	0	100	0	35
Erdafitinib	THOR ITT	36	0	1	101	0	35
Erdafitinib	THOR ITT	39	0	0	101	0	35

Table 6. Count of patients at risk, events, and number of patients censored during the interval for ATC-adjusted TTNT comparison for erdafitinib and chemotherapy

Treatment	**Scenario**	**Time (months)**	**Number at risk**	**Number of events**	**Cumulative number of events**	**Number censored**	**Cumulative number censored**
Chemotherapy	THOR ITT	0	112	0	0	0	0
Chemotherapy	THOR ITT	3	45	62	62	5	5
Chemotherapy	THOR ITT	6	21	23	85	1	6
Chemotherapy	THOR ITT	9	8	11	96	2	8

Chemotherapy	THOR ITT	12	3	5	101	0	8
Chemotherapy	THOR ITT	15	2	1	102	0	8
Chemotherapy	THOR ITT	18	1	0	102	1	9
Chemotherapy	THOR ITT	21	1	0	102	0	9
Chemotherapy	THOR ITT	24	1	0	102	0	9
Chemotherapy	THOR ITT	27	0	0	102	1	10
Chemotherapy	THOR ITT	30	0	0	102	0	10
Chemotherapy	THOR ITT	33	0	0	102	0	10
Chemotherapy	THOR ITT	36	0	0	102	0	10
Chemotherapy	THOR ITT	39	0	0	102	0	10
Erdafitinib	THOR ITT	0	135	0	0	0	0
Erdafitinib	THOR ITT	3	102	24	24	9	9
Erdafitinib	THOR ITT	6	53	43	67	6	15
Erdafitinib	THOR ITT	9	34	15	82	4	19
Erdafitinib	THOR ITT	12	21	9	91	4	23
Erdafitinib	THOR ITT	15	14	5	96	2	25
Erdafitinib	THOR ITT	18	9	4	100	1	26
Erdafitinib	THOR ITT	21	5	4	104	0	26
Erdafitinib	THOR ITT	24	4	1	105	0	26
Erdafitinib	THOR ITT	27	2	1	106	1	27
Erdafitinib	THOR ITT	30	1	0	106	1	28
Erdafitinib	THOR ITT	33	1	0	106	0	28
Erdafitinib	THOR ITT	36	1	0	106	0	28
Erdafitinib	THOR ITT	39	0	0	106	1	29
Erdafitinib	Base case	0	125	0	0	0	0
Erdafitinib	Base case	3	93	23	23	9	9
Erdafitinib	Base case	6	44	43	66	6	16
Erdafitinib	Base case	9	23	18	83	3	19
Erdafitinib	Base case	12	15	5	88	3	22
Erdafitinib	Base case	15	11	3	92	1	23
Erdafitinib	Base case	18	5	5	97	1	24
Erdafitinib	Base case	21	3	2	99	0	24
Erdafitinib	Base case	24	2	0	99	0	24
Erdafitinib	Base case	27	1	1	100	0	24
Erdafitinib	Base case	30	0	0	100	1	25
Erdafitinib	Base case	33	0	0	100	0	25
Erdafitinib	Base case	36	0	0	100	0	25
Erdafitinib	Base case	39	0	0	100	0	26
Erdafitinib	Exclude missing	0	92	0	0	0	0
Erdafitinib	Exclude missing	3	72	14	14	6	6
Erdafitinib	Exclude missing	6	42	27	41	3	9

Erdafitinib	Exclude missing	9	27	11	52	4	13
Erdafitinib	Exclude missing	12	18	4	56	4	17
Erdafitinib	Exclude missing	15	12	4	60	2	20
Erdafitinib	Exclude missing	18	7	5	65	0	20
Erdafitinib	Exclude missing	21	3	4	69	0	20
Erdafitinib	Exclude missing	24	3	0	69	0	20
Erdafitinib	Exclude missing	27	2	1	70	0	20
Erdafitinib	Exclude missing	30	0	0	70	1	22
Erdafitinib	Exclude missing	33	0	0	70	0	22
Erdafitinib	Exclude missing	36	0	0	70	0	22
Erdafitinib	Exclude missing	39	0	0	70	0	22

Section B: Clarification on cost-effectiveness data

Population

B1. Priority question. Table 28 from the CS summarises the THOR ATC-adjusted patient population characteristics that were used to inform the economic model.

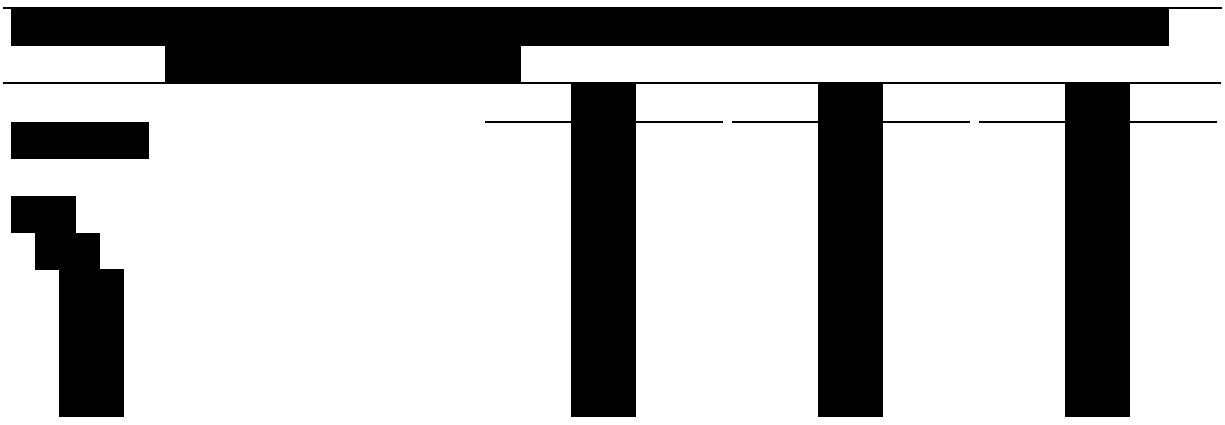
a. **The THOR trial was conducted in 23 countries, including the UK. Please provide the patient population characteristics for the UK participants in the THOR trial.**
b. **Please compare the UK patient characteristics with the patient characteristics used in the economic model (CS, table 28).**
c. **As per CS, the population characteristics *"were deemed generalisable and representative of the UK setting by UK-based clinicians.*" However, some of the clinical experts consulted by the company argued that most patients would be [redacted] than the starting age selected by the company (i.e., 66). In addition, the average UK weight and BSA for the population in this age group would be higher. Please comment on whether the patient characteristics currently used in the economic model are representative of UK clinical practice. Please discuss how this age difference might**

affect the safety profile and efficacy of erdafitinib in the UK population, considering that older patients may be frailer.

d. **Please provide scenario analysis using age, weight, and BSA that are more aligned with the UK setting.**
e. **A worst-case scenario approach was implemented to deal with missing data. In this scenario, patient with missing ECOG PS scores or tumour stage at diagnosis were assigned the less favourable patient outcome characteristics available (i.e., ECOG PS of 1-2, and tumour stage of 3-4). The company argued that this approach was conservative, as it upweighted the worst patients' characteristics in the analysis. However, this approach may lead to bias and can misrepresent the actual population that will use the technology. Please justify why the worst-case scenario approach was used over other imputation methods. Discuss the criteria considered (e.g., data missing at random) and the potential limitations of the worst-case method (e.g. bias and generalizability).**
f. **Please provide an overview of the percentage of missing data and provide overviews of the patterns of missingness. Please also comment on any potential associations between missing and observed data.**
g. **Please perform data imputation using a multiple imputation method and provide an updated economic model and scenario analysis using the multiple imputation method.**

a. The patient population characteristics for the UK participants in the THOR trial are presented in Table 7 and Table 8.

Table 7. Summary of demographics and baseline characteristics data: UK subjects



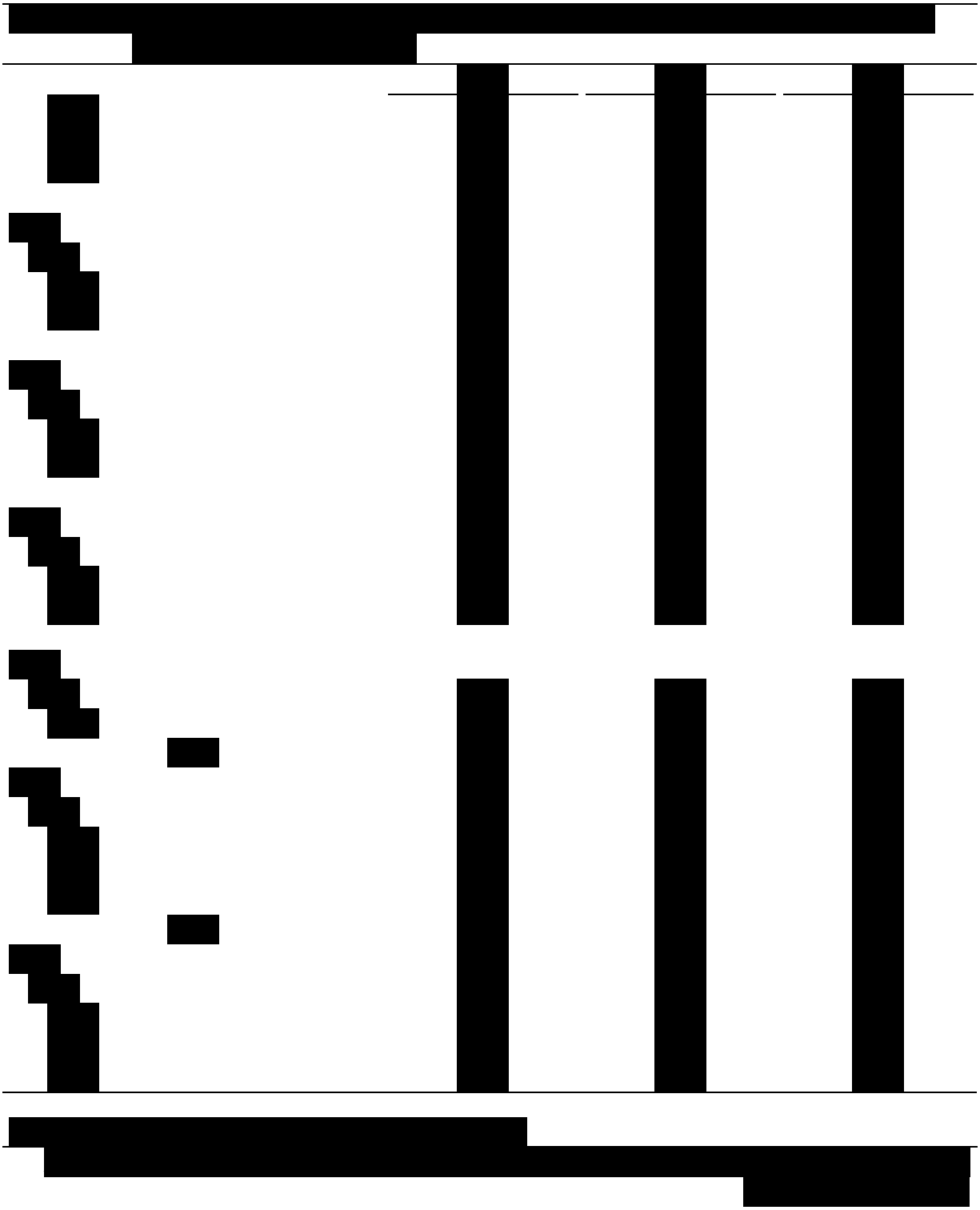
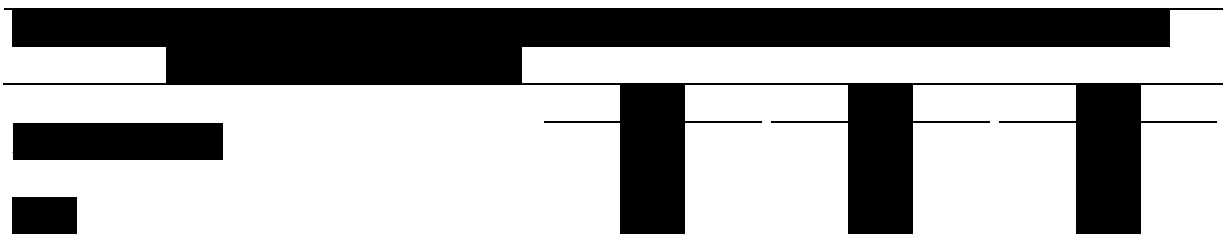
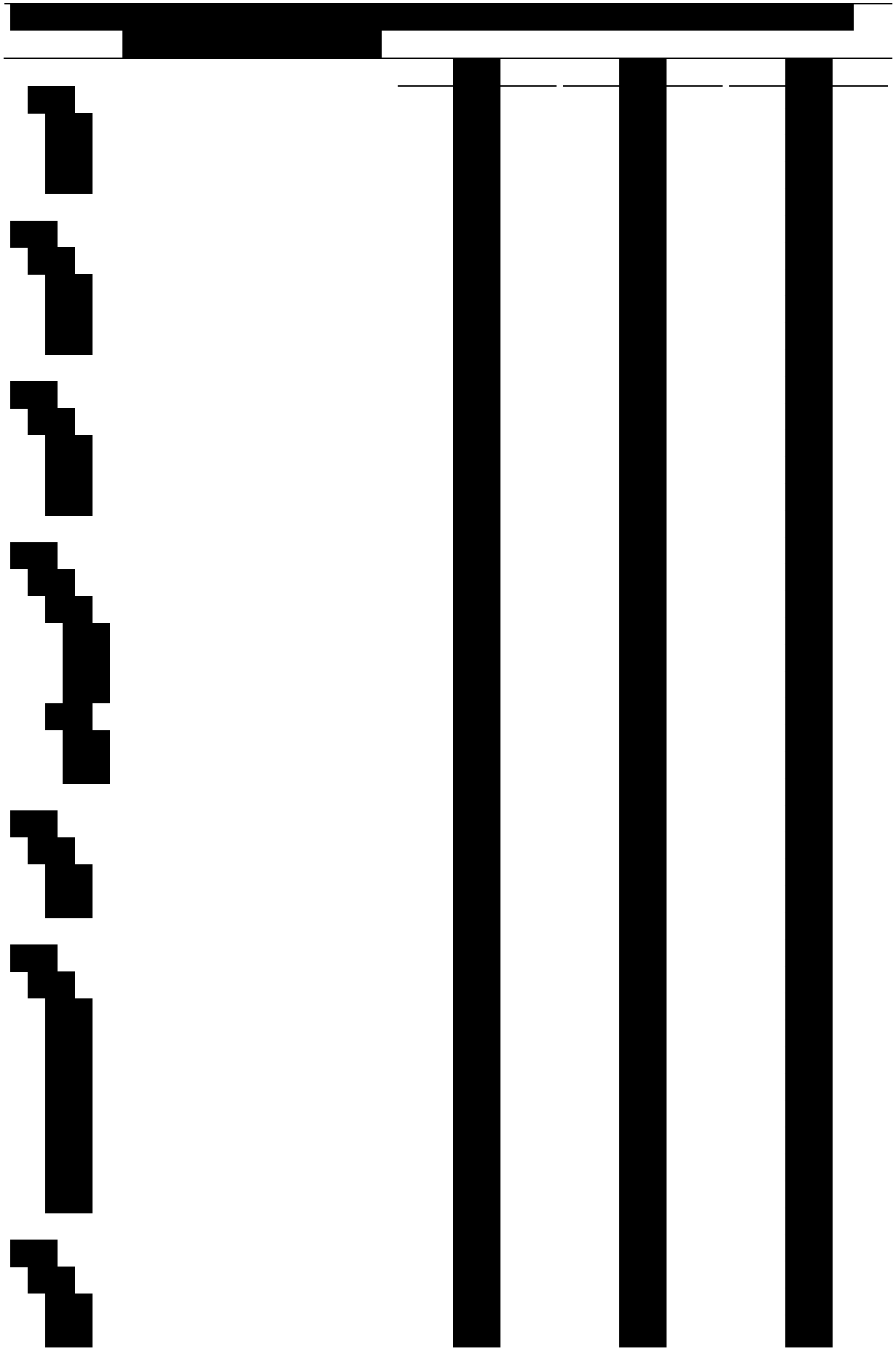
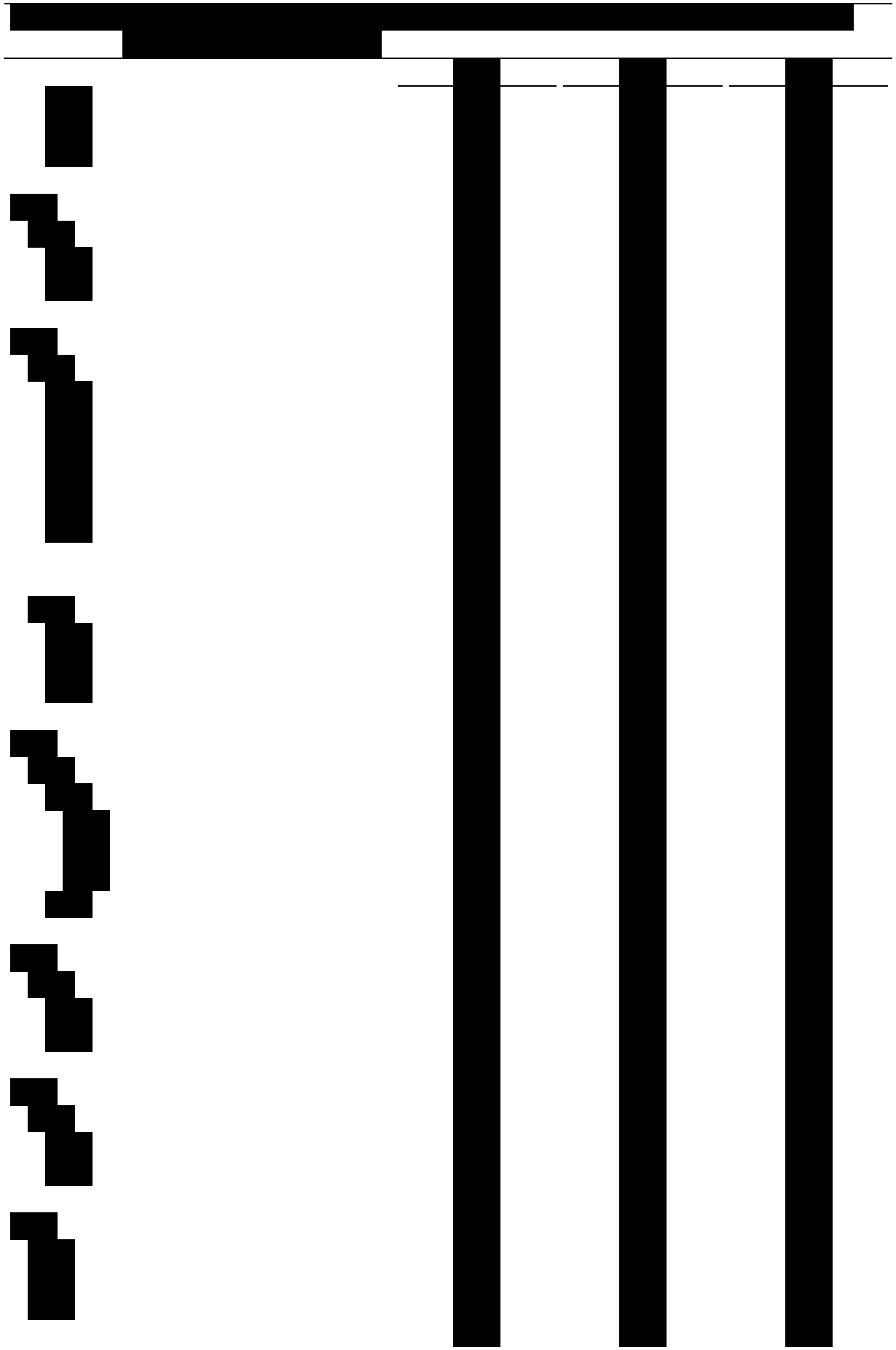
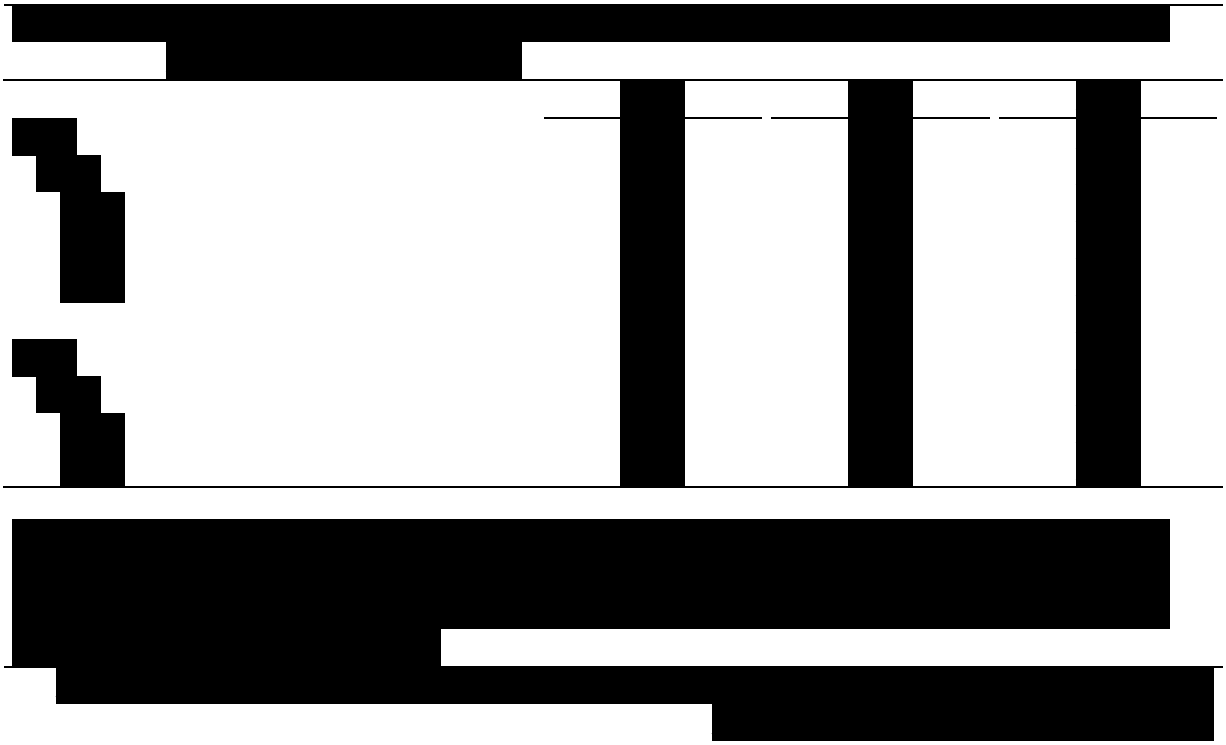


Table 8. Summary of disease characteristics at baseline: UK subjects









b. Comparison of the UK patient population with patient characteristics used in the economic model is shown in Table 9.

   It is important to acknowledge that the THOR trial had a small number of patients (12 patients) from the UK. Therefore, any comparisons or analyses requested specifically for this subgroup may yield limited information and should be interpreted with caution.

Table 9. Comparison of the UK patient population with patient characteristics used in the economic model.

	Economic model (n = 126)		**THOR UK subjects (n = 12)**	
Population characteristic	**Mean**	**Standard deviation**	**Mean**	**Standard deviation**
Age at model start	66.5	10.4	[redacted]	[redacted]
Average patient weight (kg)	75.0	20.6	[redacted]	[redacted]
Average body surface area (m²)	1.9	0.3	[redacted]	[redacted]
Average creatinine clearance (mL/min)	64.0	24.1	[redacted]	[redacted]
Proportion male	73.7%	N/A	[redacted]	[redacted]
Key: ATC, average treatment effect of the control; N/A, not applicable				

c. General perception is that clinical trial populations are younger than patients in real practice. However, clinicians agreed that the age ranges of patients in THOR and RW UK mUC study were similar[5], with a median age of 66.5 and 68.8, respectively. Additionally, the erdafitinib population was weighted to match the proportion of age categories (< 65 and ≥ 65) in NCRAS (a dataset that reflects UK clinical practice). A subgroup analysis of the erdafitinib arm in THOR showed a median survival of approximately 11 months for patients ≥ 65 years versus 14 months for patients < 65 years (Figure 4, CSR page 61). In addition, previous appraisals in mUC were based on IMvigor211 (TA525) and KEYNOTE-045 (TA692) trials which had median patient ages of 67.0 and 66.0 years, respectively, which were deemed generalisable to the UK patient population initiating second-line treatment.

d. The most appropriate values for the UK setting for patient baseline characteristics are from the UK RW mUC study. Reweighting the erdafitinib population in THOR to match the population witnessed in UK clinical practice is more suitable for decision making than using the twelve patients from the UK from the THOR trial. Therefore, no scenario analysis will be conducted, as the most appropriate values have been used in the base case analysis.

e. As shown in the report, the information on stage at diagnosis was missing in 27% of patients in the erdafitinib arm of the THOR trial but it was available in all patients from the UK RW mUC study. Conversely, data on ECOG PS was missing in 57% of patient from the UK RW mUC study whilst it was complete for the erdafitinib arm. We decided to overcome this issue by defining a base case in which patients with missing values are aggregated to the worst patient-outcome characteristic available. This approach was based on the following considerations:

    - First, initial exploratory analyses did not show any major difference in association with the outcome between the missing category and the other categories included. These analyses were performed by including a missing group category within the variables of interest (i.e. stage at diagnosis and ECOG PS) and run a univariate and multivariable Cox proportional hazard regression model.

- Second, we assumed that data was missing at random within each study. Specifically, missingness in stage at diagnosis does not depend on the treatment as patients were randomized in the trial, while exploratory analyses do not indicate that patients with missing ECOG present different characteristic.

- Third, other imputation approaches (e.g. multiple imputation) were not considered due to the limited number of variables available in UK RW mUC study compared to the percentage of missing data.

This approach presents some advantages. By assigning missing patients to another category, we can retain all the data available from both studies, increasing the sample size, reducing the uncertainty around the estimates, and providing more robust analyses. This approach is also conservative in assessing outcome differences between erdafitinib and comparator treatments from the UK RW mUC study. By assigning more patient to the more severe ECOG PS group and using a weighting approach that estimates the ATC, we will up-weight the less favourable patients in the erdafitinib group which will lead to more conservative estimates of the treatment-outcome association.

There are however some limitations that need to be highlighted. First, it is reasonable to assume that not all missing patients belong to the less-favourable group. Therefore, we are including a mix of more severe and less severe patients together, which can lead to bias in the estimates. However, as already mentioned, this bias is in disfavour of the erdafitinib arm as it likely shows a smaller relative risk compared to the RWE treatments. We also performed sensitivity analyses where we assigned patients with missing data to the more favourable group or excluded them from the analysis altogether and we observed comparable results. Second, the overproportion of patients with ECOG PS 1-2 in the RWE cohort can limit generalizability of the findings. However, inputs from clinical experts confirmed that patients in real-world practice are frailer and tend to be ECOG 2 or more, especially in these treated experienced patients. Finally, it could be that the pattern of missingness might be dependent on specific patients' characteristics in the RWE cohort which are not captured/available in the dataset. Unfortunately, this is an inherited

characteristic of RWE data, and it cannot be tackled in this analysis. However, the exploratory analyses with all important characteristics included in the dataset did not indicate any dependency with the missing values. Results of the 3 scenarios in Table 10.

Table 10. Results of ITC between THOR and UK RW mUC study

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		0.53 (0.37, 0.76)
Missing excluded		
No of patients	92	31
Median OS, months (95% CI)	13.9 (8.9, 19.4)	6.5 (2.5, 7.0)
Hazard ratio		0.22 (0.12, 0.39)
Median TTNT, months (95% CI)	10.9 (8.3, 15.7)	4.9 (2.4, 6.9)
Hazard ratio		0.34 (0.21, 0.58)
Best case		
No of patients	126	72
Median OS, months (95% CI)	15.7 (10.2, 19.4)	6.5 (4.9, 7.0)
Hazard ratio		0.35 (0.23, 0.52)
Median TTNT, months (95% CI)	10.2 (7.7, 14.7)	5.4 (3.7, 6.8)
Hazard ratio		0.38 0.25, 0.59)

f. The NCRAS dataset (RW UK mUC study) provides valuable information collected to investigate the factors influencing overall survival and time to next treatment. The dataset includes the following variables: number of prior treatments (1 or 2), age at diagnosis (<65 or 65+), sex (Male or Female), tumour location (Lower or Upper), ECOG performance status (0 or 1-2), stage at diagnosis (1-2 or 3-4), and cisplatin ineligibility (Yes or No).

g.

h.

i. Figure 5 visually presents the locations within the dataset where data is missing and the frequency of multiple variables being missing simultaneously, if applicable. This gives an overview of the missing data pattern. Additionally,

j.

k.

l. Figure 6, the missing values map, provides insights into the extent of missing data within each specific variable. It is worth noting that the ECOG performance status variable is the only variable in the RW UK mUC study that has missing values (nearly 57% have missing ECOG scores). This proportion of missing data in ECOG performance status should not be disregarded and must be considered during the analysis.

Figure 5. Counts of missing data by variable

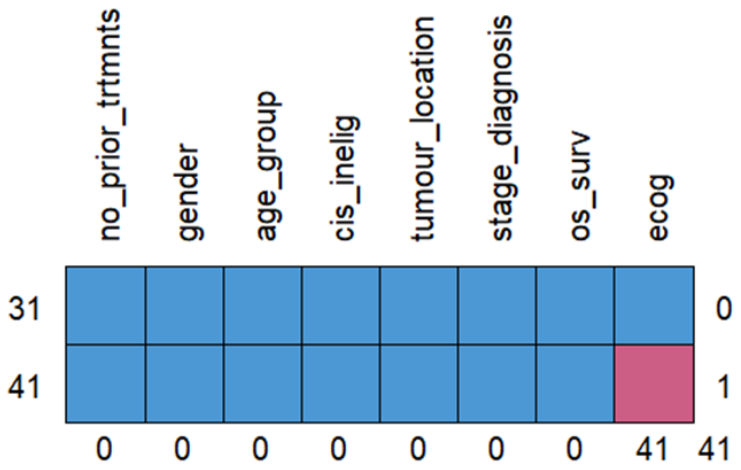


Figure 6. Map of missing values

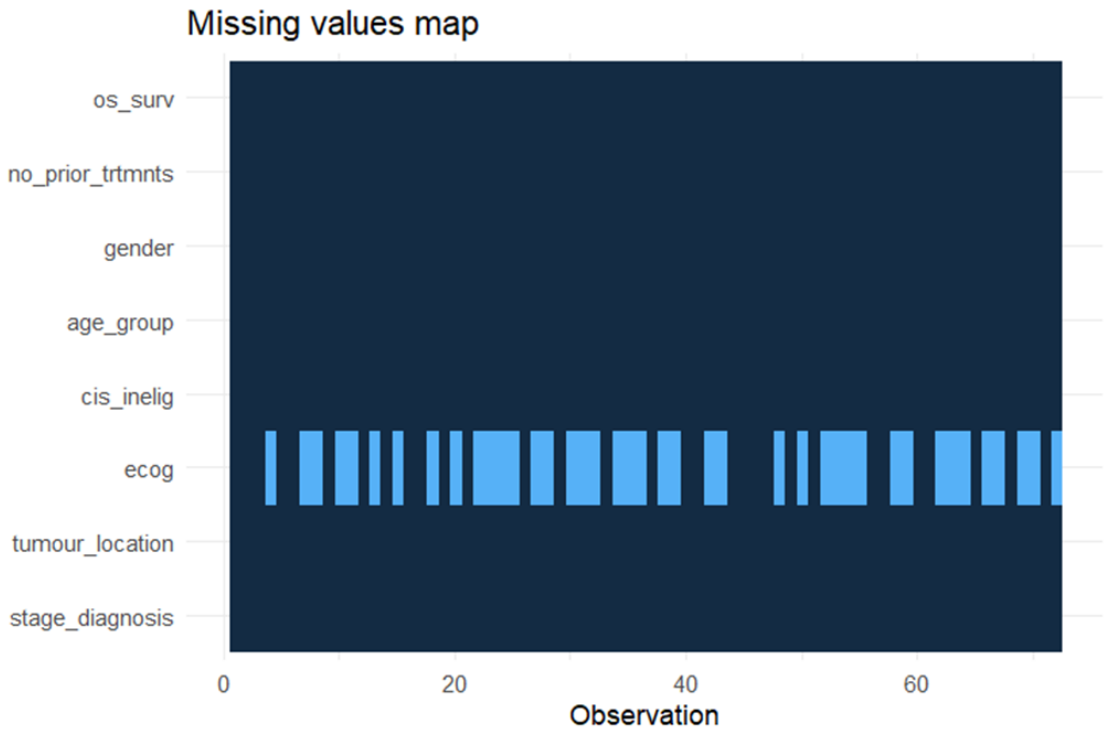


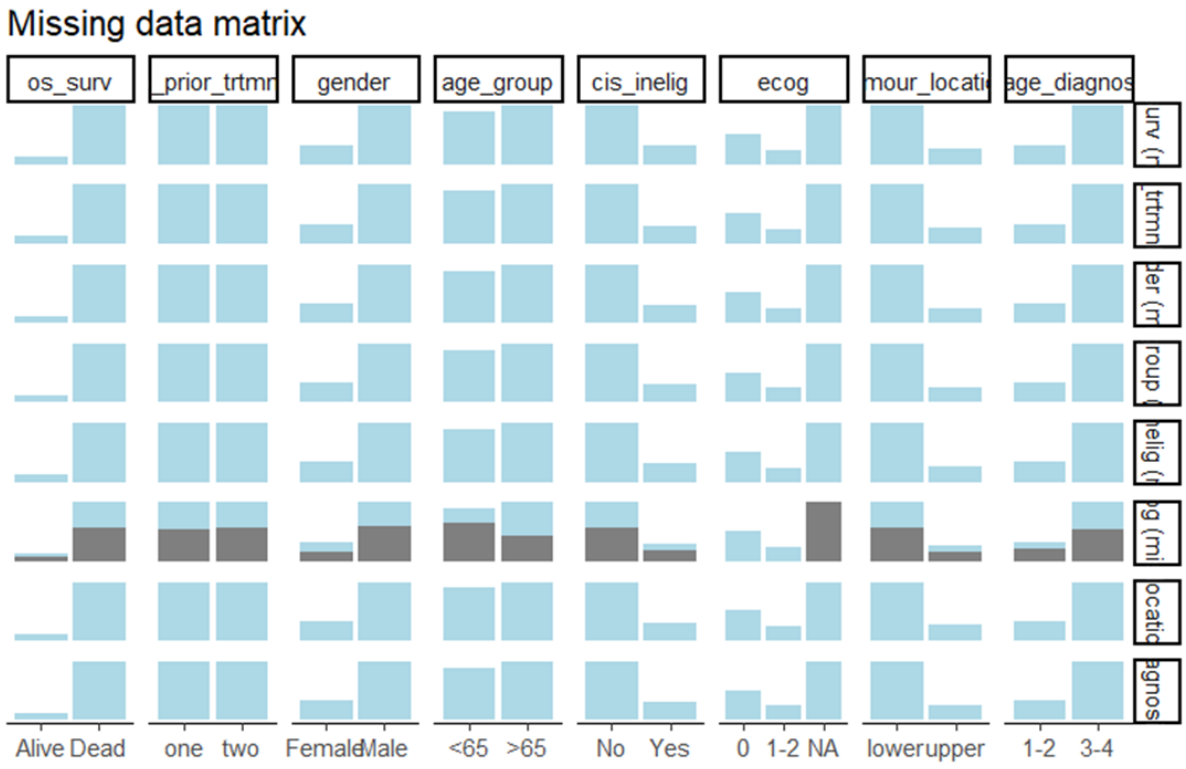
Figure 7 shows that missingness in ECOG PS differs by age category as age category <65 years has more missing data than patients 65+ years. We can now use *missing_compare* to check if the data can be considered missing completely at random (MCAR), missing at random (MAR), or missing not at random (MNAR). The output shown in Table 11 and

Figure 7 below clearly show that there is a significant difference in missingness between patients <65 years and those 65+ years old (p-value = 0.014) therefore the data is MNAR for this pair. The other pairwise comparisons show MCAR because there is no difference in the missingness of ECOG PS in other variables.

Table 11. Missing data analysis between ECOG PS and other variables

Missing data analysis: ECOG		**Not missing**	**Missing**	**p-value**
Number of prior treatments	1	16 (44.4)	20 (55.6)	1.00
	2	15 (41.7)	21 (58.3)	
Sex	Female	9 (50.0)	9 (50.0)	0.68
	Male	22 (40.7)	32 (59.3)	
Age category	<65	9 (26.5)	25 (73.5)	0.014
	>65	22 (57.9)	16 (42.1)	
Cisplatin ineligibility	No	24 (43.6)	31 (56.4)	1.00
	Yes	7 (41.2)	10 (58.8)	
Tumour Location	Lower	25 (43.9)	32 (56.1)	1.00
	Upper	6 (40.0)	9 (60.0)	
Cancer stage at diagnosis	1-2	7 (38.9)	11 (61.1)	0.891
	3-4	24 (44.4)	30 (55.6)	

Figure 7. Missing data matrix



m. The data on ECOG PS is missing for most patients of the UK RW mUC study (57%). At the same time, only a limited number of variables are available from the same study. Therefore, there is a limited information that can be used to properly imputed the missing values. Applying multiple imputation in this scenario might not lead to robust estimates as it might miss some important variables in the missing data mechanism.

Intervention and comparator

B2. Priority question. The final NICE scope mentions the following treatments as comparators: established clinical management without erdafitinib, including but not limited to: chemotherapy (including docetaxel, paclitaxel), atezolizumab,

and BSC. In the CS, the main comparator is a basket of paclitaxel ± carboplatin, modelled in a 3:1 ratio.

a. **Docetaxel was not incorporated in this appraisal as its "*use is restricted to clinical trials and is not current standard of care in England and Wales*". However, docetaxel was included as comparator in TA525 and TA530, in which was recognized as a relevant comparator next to paclitaxel and BSC. In addition, one of the six clinical experts consulted by the company agreed [redacted]. Please provide relevant information on docetaxel and justify why it was not considered a relevant comparator for this appraisal, given the above-mentioned arguments. Please provide evidence of the restricted use of docetaxel in this setting to support your critique.**
b. **Clinical experts agreed that "[redacted]". However, atezolizumab was not included as a comparator due to "lack of evidence on re-treating with a PD-L(1) inhibitor". Please justify why those already treated with anti-PD(L)1 therapy would not be treated with atezolizumab, and provide supporting evidence from available literature. If necessary, describe the mechanism of action of atezolizumab and how it may react to patients that had already received anti-PD(L)1 therapy.**
c. **One of the clinical experts consulted by the company stated that "[redacted]", when discussing their preferred 2L treatment. However, BSC was not included as a comparator, because there was no evidence available in patients after exposure to PD-L(1) therapy. Please provide further information on BSC for patients that did and did not receive PD-L(1) therapy and discuss the differences between the populations and BSC regimens.**
d. **Please comment on the appropriateness of the BSC used in TA525 and its generalizability for the population studied in this appraisal.**
e. **On the clinical advisory notes, [redacted]. However, it was**

omitted from the comparator list of this appraisal. Please provide a justification for not including carboplatin plus gemcitabine, despite being included in the NICE guideline [NG2] for UC, and being used in TA692, TA739, and TA674) as a comparator in the economic model.

f. **Please provide an updated economic model and scenario analyses including docetaxel, atezolizumab, carboplatin plus gemcitabine, and BSC, as comparators in the economic model.**

Before answering the questions in B2 a. – f., J&J would like to explain what has driven the rationale behind the chosen comparator. For J&J, the most important data sources are the RW UK mUC study, the clinical expert insights and the NICE guidelines. All these data sources combined led to our suggested base case and scenarios. From the RW UK mUC study, it became apparent that a variety of treatments were used after exposure to PD-(L)1 treatment. The 198 relevant patients have been captured, and the treatments they received are detailed in the below Table 12.

Table 12: Patients in the RW UK mUC study, treatments after PD-(L)1 treatment

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

*Gemcitabine + paclitaxel, abiraterone, carboplatin + etoposide, cyclophosphamide + doxorubicin + rituximab + vincristine, durvalumab, everolimus + lenvatinib, gemcitabine, MVAC dose dense methotrexate vinblastine doxorubicin and cisplatin one cycle every two weeks, MVAC methotrexate vinblastine doxorubicin and cisplatin one cycle every four weeks + carboplatin, Pazopanib, sorafenib, temozolomide

a. Treatment with docetaxel is very limited in clinical practice in England and it is not recommended in NICE guidelines. Point 1.7.7 of NG2 states *"Consider second-line chemotherapy with carboplatin in combination with paclitaxel or gemcitabine in combination with paclitaxel for people with incurable locally advanced or metastatic urothelial bladder cancer for whom cisplatin-based chemotherapy is not suitable, or who choose not to have it".*

   Whilst one clinician anecdotally stated they "would" use docetaxel over paclitaxel, no evidence was provided to support this rationale. The other five clinicians agreed paclitaxel is preferable to docetaxel with the latter only given during clinical trials. The evidence provided to rationalise this was the paclitaxel arm of the PLUTO study. This is also supported by the following RW UK mUC data which clearly shows the majority of clinicians choose paclitaxel not docetaxel:

   - Firstly, in the J&J UK RW mUC, only four (2.0%) patients received treatment with docetaxel at 2L or beyond following treatment with a PD-(L)1 inhibitor.
   - Secondly, two real-world publications have been incorporated which further suggest that docetaxel is not a relevant comparator. The first publication are results from a validated survey amongst urological oncologists. Restricted use of docetaxel is supported by this survey where zero respondents reported using docetaxel.[6] The survey showed paclitaxel is the most commonly used treatment in this setting in the UK. Clinicians would choose paclitaxel alone or in combination with platinum as their preferred choice of second-line regimen.
   - The second real-world publication presents the findings of a large UK-based retrospective cohort study that examined treatment patterns and survival outcomes in patients with locally advanced or metastatic

urothelial cancer, where the most common second-line of treatment received was single-agent paclitaxel.[7] Of the 200 patients (26.5%) who progressed on a first-line platinum-based chemotherapy treatment, single-agent paclitaxel was the most common second-line therapy used. No patient was treated with docetaxel. However, a limitation of this evidence is that this study span preceded the marketing authorisation of anti-PD-(L)1 treatments in England.

- Further, the British Uro-Oncology Group have commented that clinical experience is paramount, and practically all oncologists would favour paclitaxel. Two UK surveys have demonstrated that single agent paclitaxel is the agent most commonly in use in the second line setting therefore was adopted as the standard arm in the PLUTO study.[8]

b. Initially, it is essential to clarify that within the context of mUC in the UK, there are three relevant treatments categorized as PD-(L)1 inhibitors: avelumab, atezolizumab, and pembrolizumab. These agents share a common mechanism of action and are all classified as PD-(L)1 inhibitors. It is important to note that in the treatment of mUC, patients typically receive PD-(L)1 inhibitors until either disease progression or, in the case of atezolizumab, treatment should be discontinued after 2 years of uninterrupted treatment. Despite this, opting for a different PD-(L)1 inhibitor following progression with a previous PD-(L)1 inhibitor is considered clinically irrational due to the scarcity of evidence supporting the notion of retreating with either the same or alternative PD-(L)1 inhibitor.

   It is expected that an increased number of patients with mUC will have received treatment with immunotherapy agents. No prospective trials have investigated the re-treatment of such patients. Therefore, there is no evidence providing clinical rationale for re-treatment of patients who have received a PD-(L)1 inhibitor with atezolizumab and the clinical implications as to how patients may react are unknown.

   Re-treatment with a PD-(L)1 inhibitor is not recommended in NICE, EAU or ESMO guidelines. The latter recommends that rechallenge with a single-agent

PD-(L)1 inhibitor is not encouraged without further evidence. Additionally, UK-based clinicians outlined a treatment pathway for mUC, which did not include the re-treatment of a PD-(L)1 inhibitor, with all PD-(L)1 subsequent treatment being chemotherapy.[9]

However, in the RW UK mUC study, there is some use of PD-(L)1 treatment after patients are exposed to a PD-(L)1 treatment. The dataset available for comparison is small, with only 16 patients having been exposed to atezolizumab after PD-(L)1 treatment in the RW UK mUC study. With a lack of clinical rationale, support by clinical guidelines[10, 11] or clinical experts, J&J does not believe atezolizumab should be considered a valid comparator for this appraisal. Without a strong clinical rationale or a larger dataset, it is not appropriate to use this as a basis for comparison.

c. UK clinical experts advised that best supportive care (palliative care) may be given to patients that are not fit to receive chemotherapy or who may not accept chemotherapy due to patient choice. There is no clinical evidence to model health outcomes for the use of best supportive care in patients who have been previously treated with PD-L1 inhibitors. The data source for J&J RW UK mUC cohort study is the SACT dataset which details all NHS-funded systemic anti-cancer treatments administered to patients, therefore not being able to capture BSC data. As a result, accurately evaluating the cost-effectiveness of erdafitinib compared to best supportive care in this specific population is not feasible.

d. The patient population studied in appraisal TA525[12] did not have prior PD-(L)1 exposure, hence are out of scope of this appraisal population. Additionally, in the FAD from TA525 the following is mentioned: "*The committee recalled that best supportive care is included as a comparator in the NICE scope. It would have preferred to also see a comparison with best supportive care, but acknowledged that a lack of data would have made this difficult".* It is unknown if a comparison was shown and as discussed, it was deemed complex to compare. Nonetheless, there are several significant differences between the populations in TA525 and this appraisal and the BSC from TA525 is therefore not deemed or generalizable or appropriate.

e. NICE guidelines [NG2][13] recommends to offer carboplatin plus gemcitabine in eligible patients as a first-line option for patients who are ineligible for cisplatin plus gemcitabine. This combination, however, is not recommended as a second-line option. Point 1.7.7 of NG2 states *"Consider second-line chemotherapy with carboplatin in combination with paclitaxel or gemcitabine in combination with paclitaxel…"*. There is no evidence to support re-challenging patients in second-line or third-line with platinum-based chemotherapy. Both clinical experts and clinical guidelines do not endorse retreatment with platinum-based chemotherapy. As indicated in the RW UK mUC cohort study, only a limited number of patients (n=6, 3.0%) were being treated with carboplatin + gemcitabine in third-line. Second-line exposure to carboplatin + gemcitabine after PD-(L)1 treatment has been discarded by clinicians as not appropriate and its use was only seen as a result of the COVID-19 pandemic where PD-(L)1 use was advised for front-line treatment, instead of platinum-based chemotherapy.[5, 14]

   ESMO guidelines state rechallenge with platinum-based chemotherapy may be considered if progression occurred 12 months after the end of the previous platinum-based chemotherapy or 12 months after the end of previous platinum-based chemotherapy and maintenance avelumab. EAU guidelines strongly recommend single agent chemotherapy (including paclitaxel) as a second-line treatment after prior platinum-based chemotherapy +/- PD-(L)1 inhibitor with no recommendation for platinum-based chemotherapy rechallenge.[11]

   In addition, the target population in TA739 and TA674 was untreated PD-(L)1 positive, cisplatin unsuitable patients. Therefore, carboplatin + gemcitabine was an appropriate comparator in the first-line setting. The target population in TA692 was patients who have had received platinum-based chemotherapy in the first-line setting. Therefore, carboplatin + gemcitabine was not considered a comparator in this second-line setting.

f. As described in a.–e. J&J has provided information on the relevant UK comparators, which remains as paclitaxel ± carboplatin only.

B3. Priority question. The company considered paclitaxel ± carboplatin as the main comparator in the CS, which was modelled as a basket of paclitaxel monotherapy and paclitaxel in combination with carboplatin, weighted 3:1.

a. **The assumption of the 3:1 ratio for paclitaxel monotherapy and paclitaxel in combination with carboplatin was based on "*consensus from a UK advisory board, including six clinicians, and confirmed by the results from the UK RW mUC study conducted by Johnson and Johnson Innovative Medicine*". Please provide the exact statements of the clinical experts (dis)agreeing to that ratio and specify the number of clinicians that supported that ratio. Please justify how it was "*confirmed*" on the RW study and provide supporting evidence from published literature showing that this ratio is in line with UK clinical practice.**
b. **Please support the assumption that paclitaxel monotherapy is administered weekly, while, when in combination with carboplatin, it is administered every three weeks. Please provide evidence of weekly administration of paclitaxel monotherapy being standard of practice in the UK and refer to the NICE guidelines for mUC.**
c. **If applicable, please provide a scenario analysis assuming that paclitaxel monotherapy is administered every three weeks.**

a. The six advisors were asked which of the following patient groups from the J&J UK RW mUC cohort study would be the most relevant comparator for erdafitinib:

    a. Patients who received taxanes after anti PD-(L)1 therapy (at either first- or second-line) or
    b. Patients who received gemcitabine with carboplatin or cisplatin after anti PD-(L)1 therapy (at either first- or second-line).

    For the consensus and conclusion, J&J will present some snapshots of the discussion that led to the final recommendations. Advisors noted "it will be a small group of patients who have platinum-based chemotherapy second-line after anti PD-(L)1 therapy" and "some of the patients getting gemcitabine with

carboplatin or cisplatin after first-line immunotherapy are those who responded well and are being re-challenged". "It would be appropriate to use a basket comparator approach" and it was suggested "having group A as the main comparator, and not really targeting group B". "The comparator arm for erdafitinib would be those who had platinum, had IO, and are now going onto paclitaxel".

"Most clinicians will avoid first-line immunotherapy unless chemotherapy cannot be used". "If group B is important to target, the details in terms of which patients received first-line or second-line anti PD-(L)1 will need to be clarified". Advisors therefore recommended separating this group and describes why front-line PD-(L)1 monotherapy treatment, followed by platinum chemotherapy is illogical, rare and not in line with current clinical practice.

As suggested by advisors, we confirm only a limited number of patients (n = 6, 3.0%) were treated with carboplatin plus gemcitabine in third-line following anti-PD-(L)1 treatment in the UK RW mUC cohort study. This patient number is too small to make a comparison.

The relevant comparator for erdafitinib was suggested as Group A (those who had received anti PD-(L)1 followed by taxanes). In this group, practically all patients were treated with paclitaxel ± carboplatin. Since in the UK RW mUC study 75% of patients received paclitaxel monotherapy and 25% received paclitaxel + carboplatin, a 3:1 ratio was deemed the most appropriate comparator in this submission. Advisors suggested providing evidence using a basket of these 2 treatments, as described in one of the quotes above. No concerns were raised about the exact ratio of the treatments in the base case, but J&J has considered the potential impact of the different treatments by comparing the base case with paclitaxel monotherapy and paclitaxel in combination with carboplatin in B2.

The UK RW mUC cohort study is also supported by the UK clinical practice survey referred to in B2a where the majority of clinicians reported weekly

paclitaxel as an acceptable control arm for a randomised controlled trial of second line chemotherapy.

b. Weekly administration of paclitaxel monotherapy is not a licensed treatment, nor is it recommended by NICE guidelines. However, its weekly use in UK clinical practice is supported by in the recent Jones et al. 2024[9] oncologists' perspective review in addition to guidance provided in local systemic anticancer therapy protocols.[15-18]

   When utilised in combination with carboplatin, paclitaxel is administered every 3 weeks as supported by guidance in local SACT protocols.[19-21]

c. This scenario is not applicable as paclitaxel monotherapy is administered weekly for 3 weeks followed by 1 week off.

Treatment effectiveness

B7. Priority question: Although paclitaxel monotherapy (based on the PLUTO trial) and the chemotherapy arm of the THOR trial were included as comparators in the economic model, CS section B3.3 regarding the clinical data sources and outcomes in the economic model only considers erdafitinib and paclitaxel ± carboplatin. Please also provide detailed information about the clinical data sources and outcomes (i.e. overview of clinical data sources and outcomes, methods and inputs including time to event analyses of OS, TTNT, PFS and TTD) for paclitaxel monotherapy and the THOR chemotherapy arm.

The details of overall survival and progression-free survival for paclitaxel monotherapy (from PLUTO) are detailed in the Appendices, Sections Q.2.7 and Q.2.8, respectively. No data for TTNT and TTD was available for this trial. The THOR chemotherapy arm OS, PFS, and TTD are detailed in the Appendices, Sections R.4.2, R.4.3, and R.4.4, respectively. The rationale for the inclusion of these analyses were to assess the uncertainty around the choice of efficacy data for the relevant comparator, paclitaxel ± carboplatin. They were not used to provide primary evidence for this appraisal.

B8. Priority question: The company used conventional methods of parametric survival modelling as outlined in NICE DSU TSD14 for the extrapolation of survival estimates beyond the observed Kaplan Meier curves. Please provide, for OS, PFS, time to treatment discontinuation (TTD) and time to next treatment (TTNT) separately for the intervention and all comparators:

a. **Tables with numbers of patients at risk, in 3 month intervals (in line with question A7).**

b. **To examine the proportional hazard assumption, plot the scaled Schoenfeld residuals versus time (all survival curves)**

c. **Plot the smoothed hazards over time to examine the heuristics of the hazard function over time.**

d. **To examine diagnostics of parametric survival models (using the observed data):**

    a. **Plot the cumulative hazard versus time**

    b. **Plot the log smoothed hazard versus time**

    c. **Plot the standard normal quartiles versus log time**

    d. **Plot the log survival odds versus log time**

e. **In addition to separately fitted models, please provide scenario analysis including jointly fitted models assuming that the proportional hazards assumptions holds.**

f. **For all tables including long term (3, 5 and 10 years) estimates and goodness-of-fit statistics (i.e. CS tables 30-35), please also provide estimates of earlier time points (e.g. 3, 6, 9, 12, 18, 24, and 30 months) and provide the observed data estimates for these time points.**

g. **For erdafitinib, the standard parametric survival curves for the extrapolation of OS, PFS, TTD and TTNT do not seem to fit very well to the observed data (underestimation of the observed data in the first few months and overestimation thereafter). Please describe whether the use**

of spline-based models was explored. Please provide these analyses including 1 and 2 knot models (with default knot location) using the hazard, odds as wells as normal scales. Please elaborate on the appropriateness of these spline models and provide an updated economic model as well as scenario analyses enabling the use of these spline models.

h. **The validity of the extrapolations beyond the KM data for both intervention and the comparators was examined using clinical expert estimates at 3 years, 5 years and 10 years. Please also examine the validity of the extrapolations beyond the KM data with supporting evidence that the extrapolations are consistent with relevant external data.**

i. **Please justify the selection of the approaches to estimate and extrapolate OS, PFS, and TTD, taking into account the responses to the preceding questions as well as the "*Survival Model Selection Process Algorithm*" provided in NICE DSU TSD 14.**

a. Numbers of patients at risk in 3-month intervals are presented separately for each outcome in the Table 13, Table 14, Table 15 and Table 16. For ATC-adjusted groups, the numbers are rounded to nearest integer.

Table 13: Number at risk over time, overall survival

Time (months)	Erdafitinib, ATC (base case)	Erdafitinib, unadjusted	Erdafitinib, ATC, missing excl.	Paclitaxel ± carboplatin	Paclitaxel ± carboplatin, missing excl.	Chemotherapy (THOR)
0	126	136	92	72	31	130
3	111	118	85	51	20	89
6	89	98	74	36	15	67
9	65	75	47	15	5	44
12	40	47	32	12	4	31
15	31	36	24	8	4	19
18	23	26	19	5	2	14
21	16	18	13	3	0	10
24	15	16	11	2	0	9
27	12	10	10	2	0	4

30	8	6	4	2	0	3
33	7	4	2	2	0	3
36	7	4	2	0	0	2
39	6	3	1	0	0	0
42	6	3	1	0	0	0
45	6	3	1	0	0	0
48	5	2	1	0	0	0
51	0	0	0	0	0	0

Table 14: Number at risk over time, progression-free survival

Time (months)	Erdafitinib, ATC (base case)	Erdafitinib, unadjusted	Erdafitinib, ATC, missing excl.	Chemotherapy (THOR)
0	126	136	92	130
3	83	94	65	45
6	31	40	30	24
9	17	25	22	10
12	10	13	10	5
15	5	8	4	3
18	3	5	2	3
21	3	5	2	2
24	3	5	2	2
27	2	3	2	0
30	1	2	2	0
33	1	2	2	0
36	0	0	0	0

Table 15: Number at risk over time, time to next treatment

Time (months)	**Erdafitinib, ATC (base case)**	**Erdafitinib, ATC, missing excl.**	**Paclitaxel ± carboplatin**	**Paclitaxel ± carboplatin, missing excl.**
0	126	92	72	31
3	111	85	48	19
6	89	74	33	14
9	65	47	12	4
12	40	32	10	3
15	31	24	6	3
18	23	19	3	0
21	16	13	3	0
24	15	11	2	0
27	12	10	2	0
30	8	4	2	0
33	7	2	2	0
36	7	2	0	0
39	6	1	0	0

42	6	1	0	0
45	6	1	0	0
48	5	1	0	0
51	0	0	0	0

Table 16: Number at risk over time, time to treatment discontinuation

Time (months)	**Erdafitinib, ATC (base case)**	**Erdafitinib, unadjusted**	**Erdafitinib, ATC, missing excl.**	**Chemotherapy (THOR)**
0	125	135	91	112
3	94	103	73	46
6	48	54	43	22
9	24	35	28	9
12	16	22	19	4
15	12	15	13	3
18	5	10	7	2
21	4	6	5	2
24	3	5	3	2
27	2	3	2	0
30	1	2	2	0
33	1	2	2	0
36	1	2	2	0
39	0	0	0	0

b. The proportional hazards assumption is discussed below, separately for different comparisons.

Erdafitinib versus paclitaxel ± carboplatin

The scaled Schoenfeld residual plot and the associated statistical test for OS of erdafitinib (ATC-adjusted) versus paclitaxel ± carboplatin do not show strong evidence for lack of proportionality of hazards (

Figure 8). With TTNT, there is a stronger indication that the hazards are not proportional (p-value = 0.068) (Figure 9).

Figure 8. ATC-adjusted OS of erdafitinib vs paclitaxel ± carboplatin

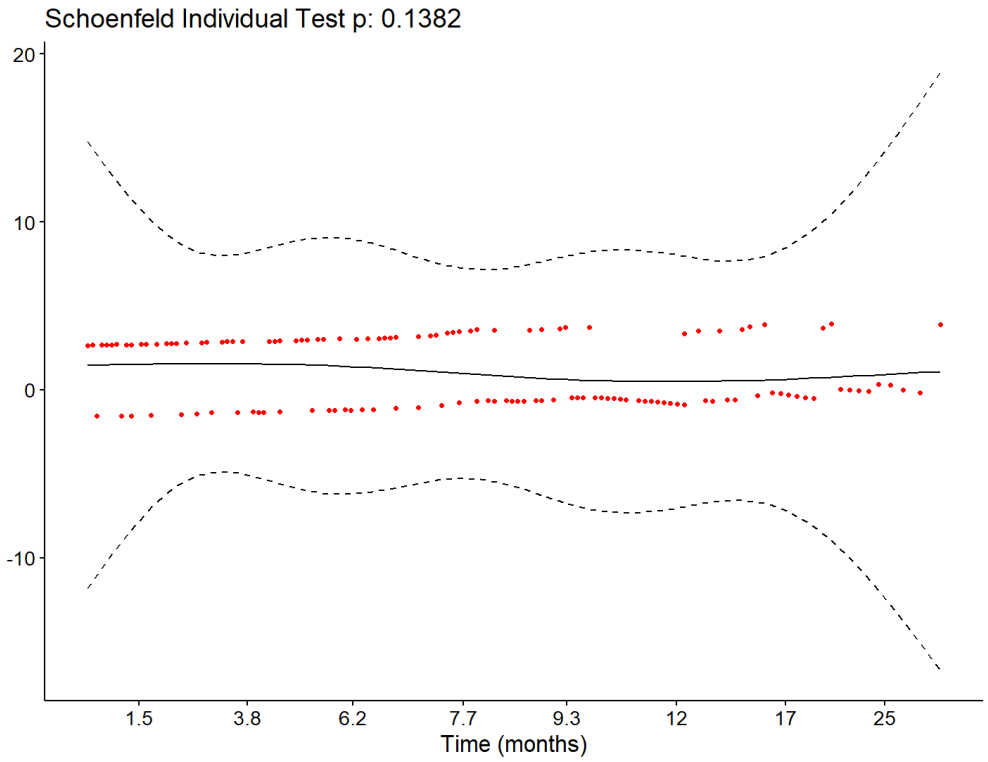
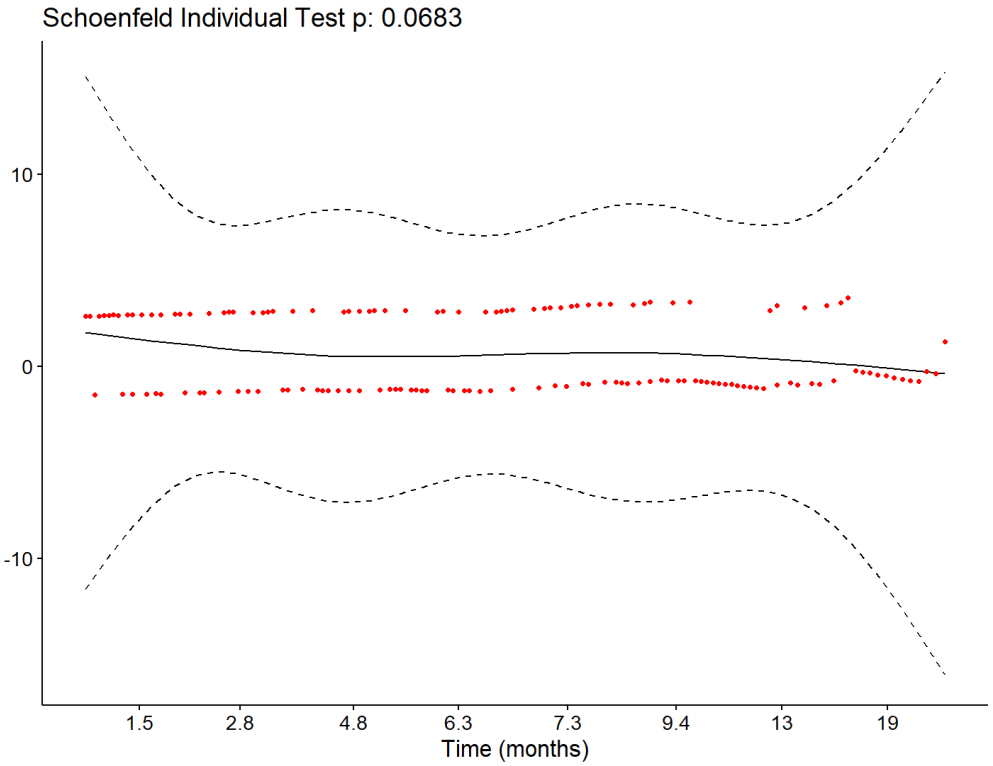


Figure 9. ATC-adjusted TTNT for erdafitinib vs paclitaxel ± carboplatin



Erdafitinib versus paclitaxel monotherapy (PLUTO)

The PH assumption was not violated. After re-weighting of the erdafitinib arm, the log-cumulative hazard curves were approximately parallel for OS (Figure 10). With PFS it is harder to tell since there is significant overlap (which is reflected in the HR being close to 1), but there is no obvious deviation either (Figure 11). In both cases the p-value of Schoenfeld residual-based test was very high, indicating no evidence of lack of proportionality. The HRs for OS and PFS derived in this analysis were used as to determine the OS and PFS extrapolations for paclitaxel in a scenario analysis. There was no time to treatment discontinuation (TTD) data reported in PLUTO, therefore it was decided that assuming TTD equal to PFS was a reasonable assumption as paclitaxel is administered until progression meaning TTD and PFS would be anticipated to be very similar.

Figure 10. OS Log Cumulative Hazard plot and Weighted Schoenfeld residual plots with Loess smoother for erdafitinib (THOR) versus paclitaxel (PLUTO)

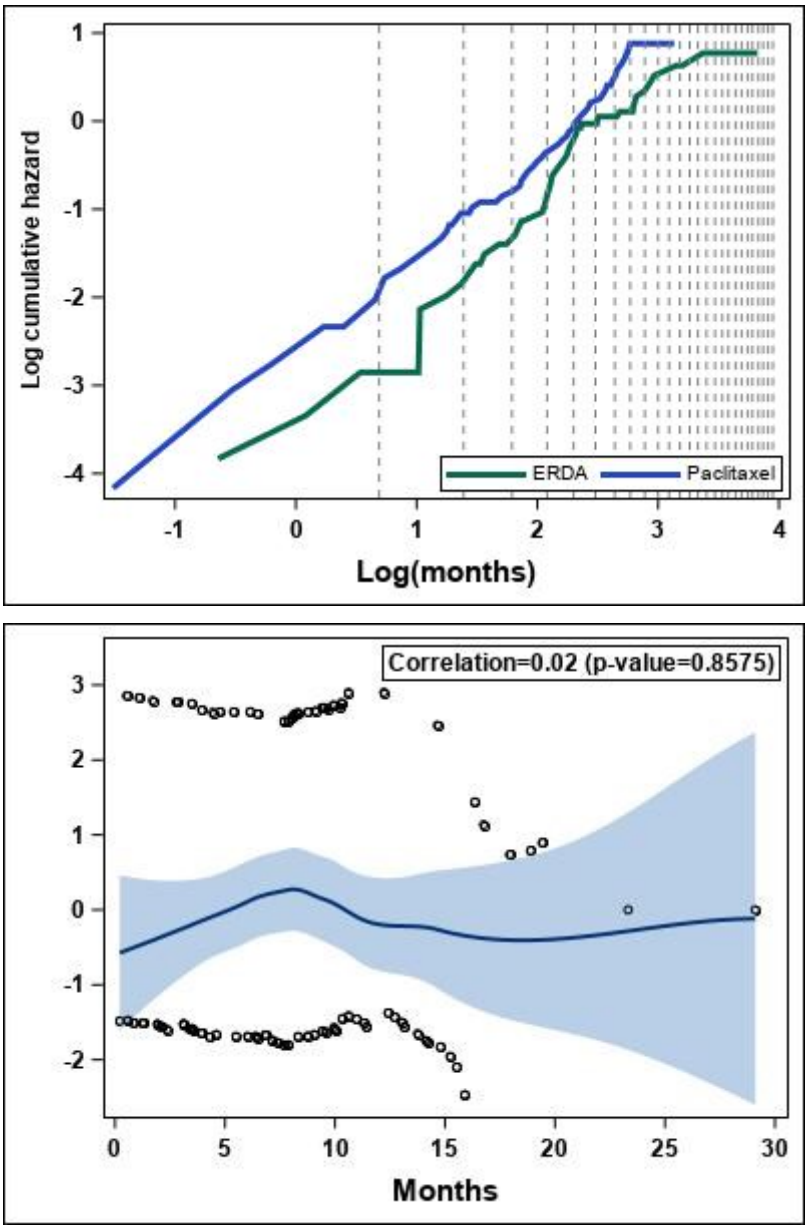
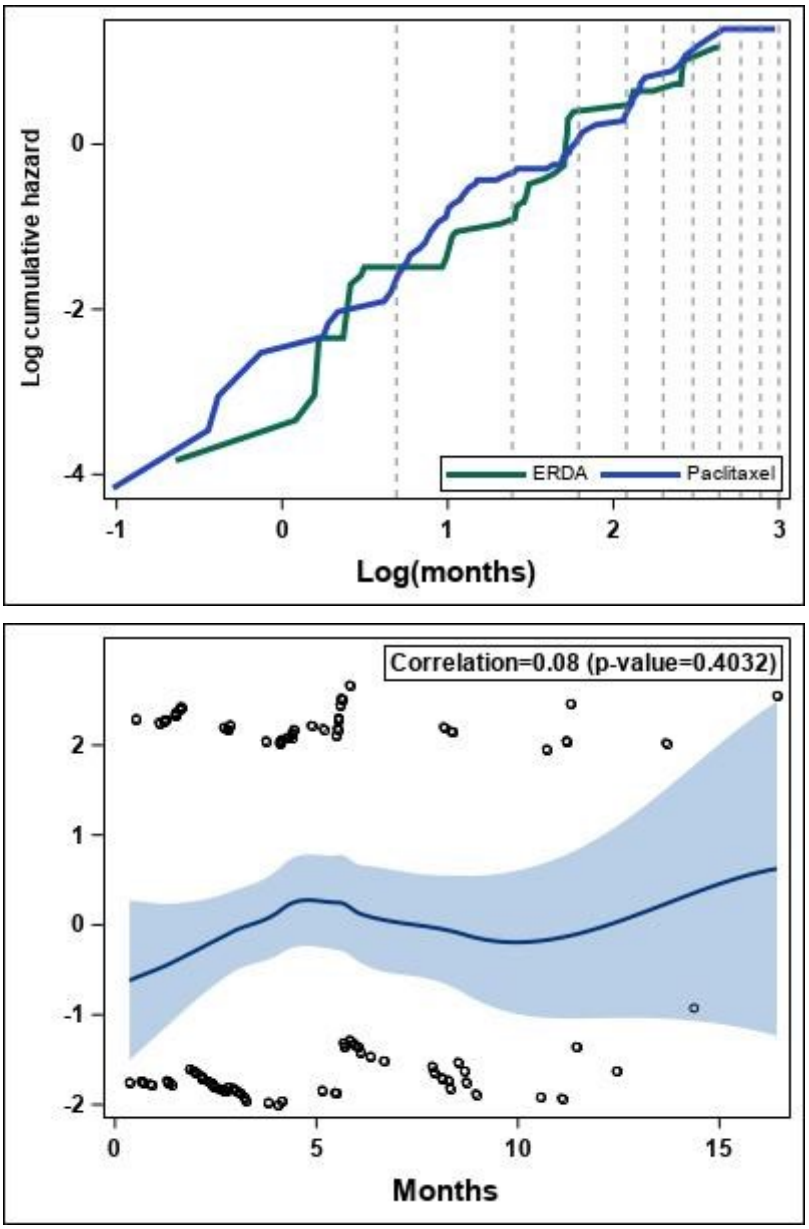


Figure 11. PFS Log Cumulative Hazard plot and Weighted Schoenfeld residual plots with Loess smoother for erdafitinib (THOR) versus paclitaxel (PLUTO)



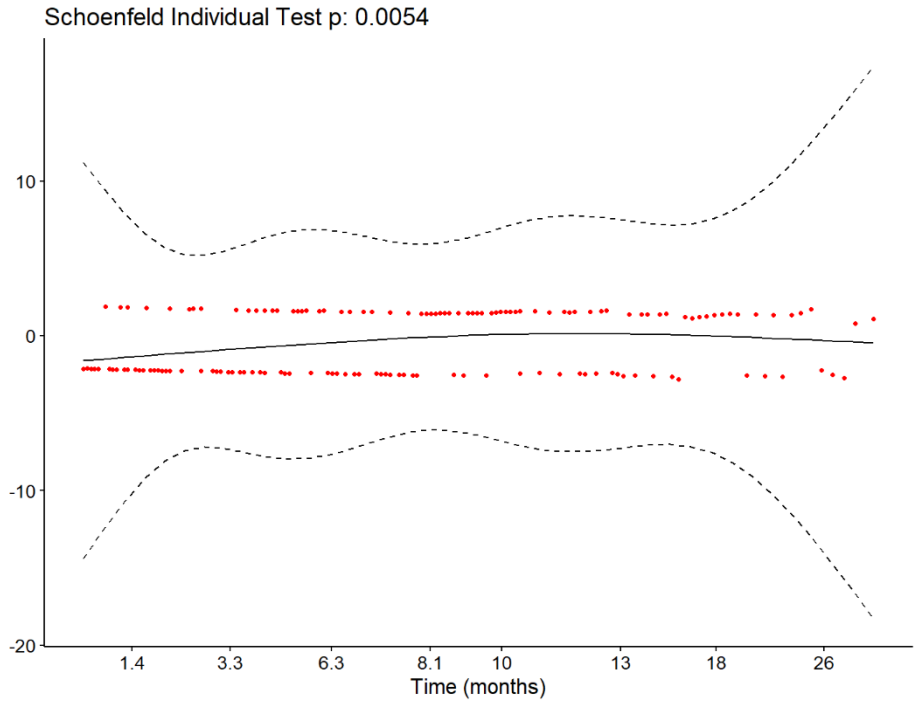
Erdafitinib versus chemotherapy (THOR)

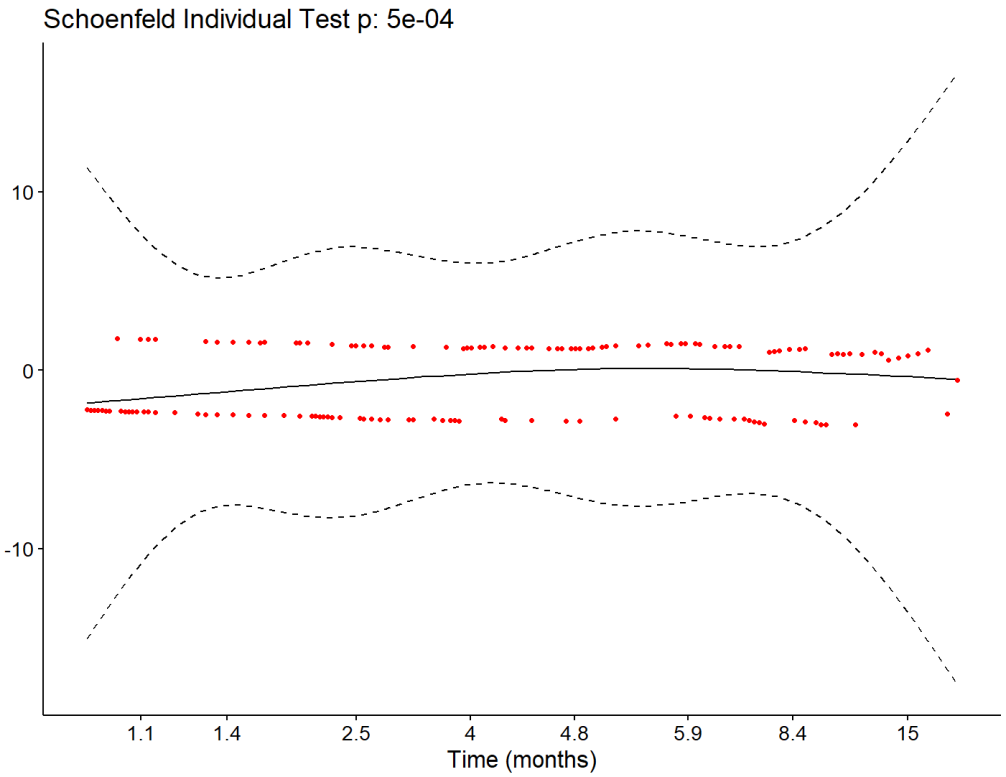
Based on the Schoenfeld residual plots and the associated tests, there is very strong evidence that OS and PFS hazards of erdafitinib and chemotherapy in THOR are not proportional (both p-values < 0.01) (

Figure 12 and Figure 13).

Figure 12: OS erdafitinib vs chemotherapy

Figure 13. PFS erdafitinib vs chemotherapy





c. Plot the smoothed hazards over time to examine the heuristics of the hazard function over time

This has been explored and examined in the appendices of the original submission under R.4.2 for OS.

d. Please see the requested diagnostic plots below.

a. Cumulative hazard over time

Figure 14. Cumulative hazard over time for OS of ATC-adjusted erdafitinib versus paclitaxel ± carboplatin

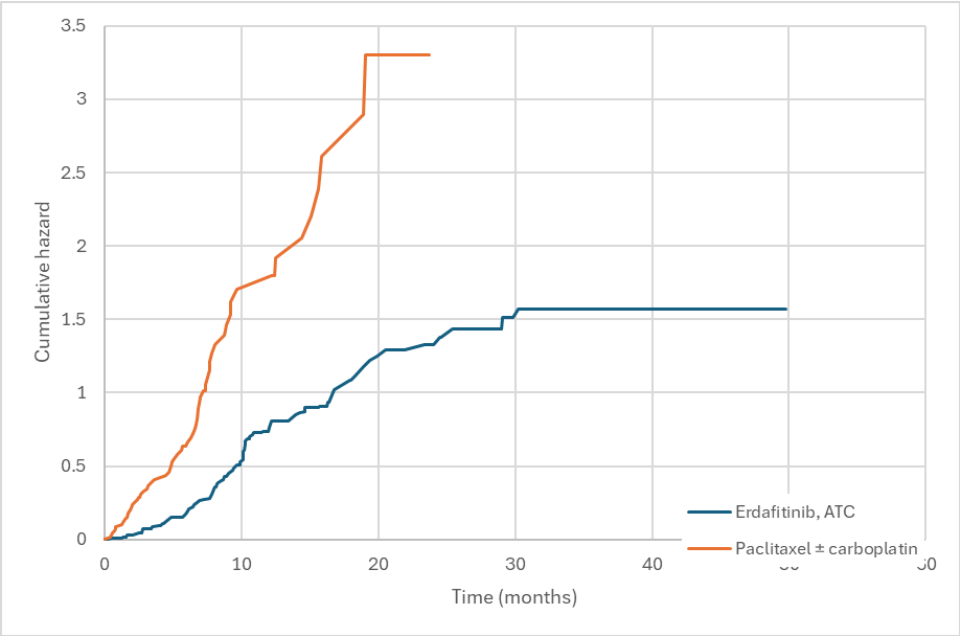


Figure 15. Cumulative hazard over time for OS of ATC-adjusted erdafitinib versus paclitaxel ± carboplatin, missing data excluded

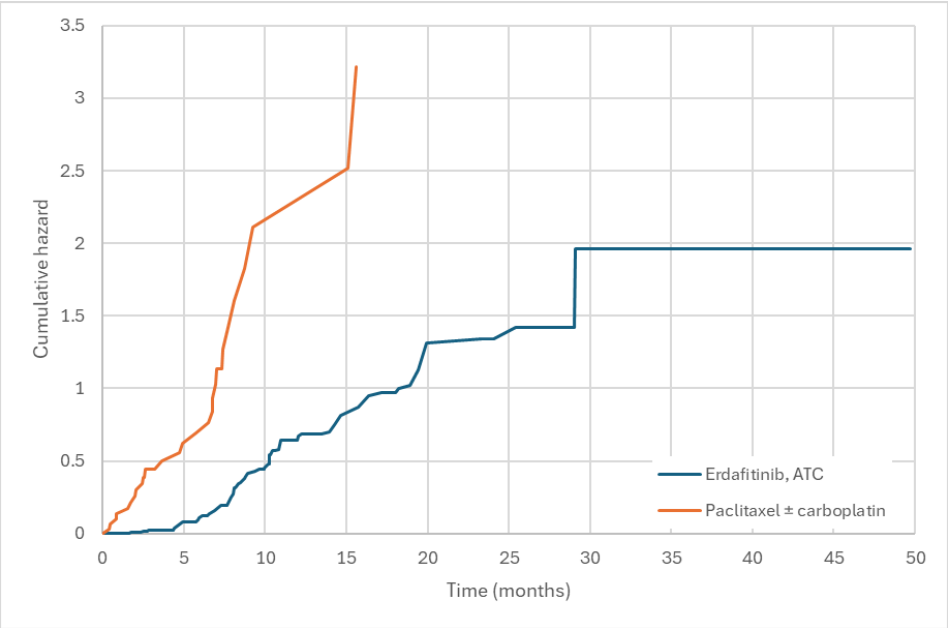


Figure 16. Cumulative hazard over time for OS of erdafitinib (unadjusted) versus chemotherapy (THOR)

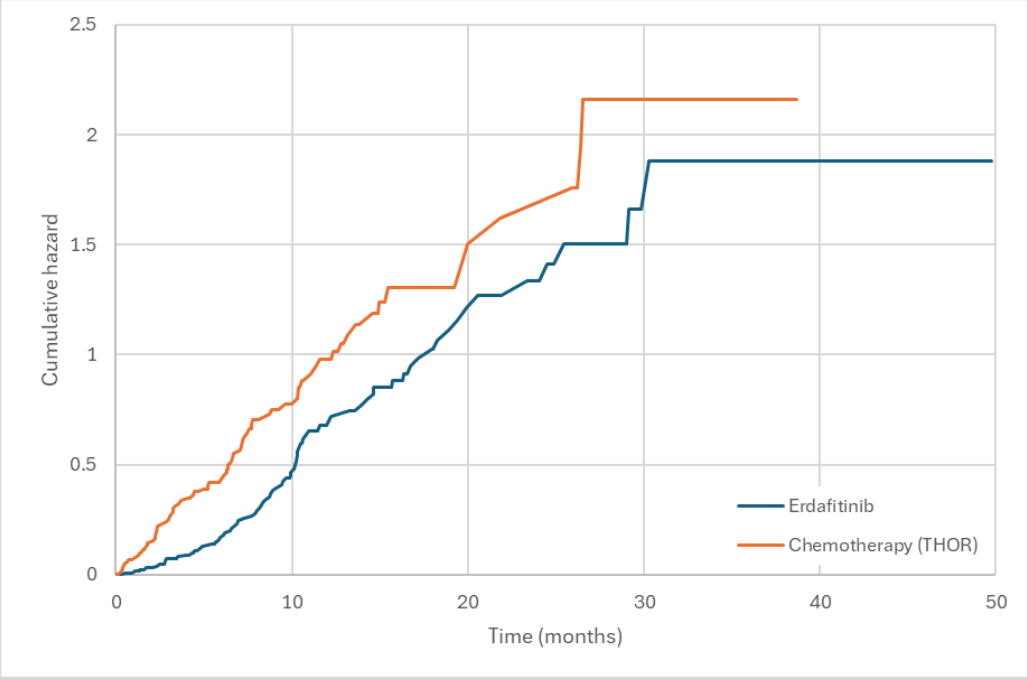


Figure 17. Cumulative hazard over time for PFS of ATC-adjusted erdafitinib

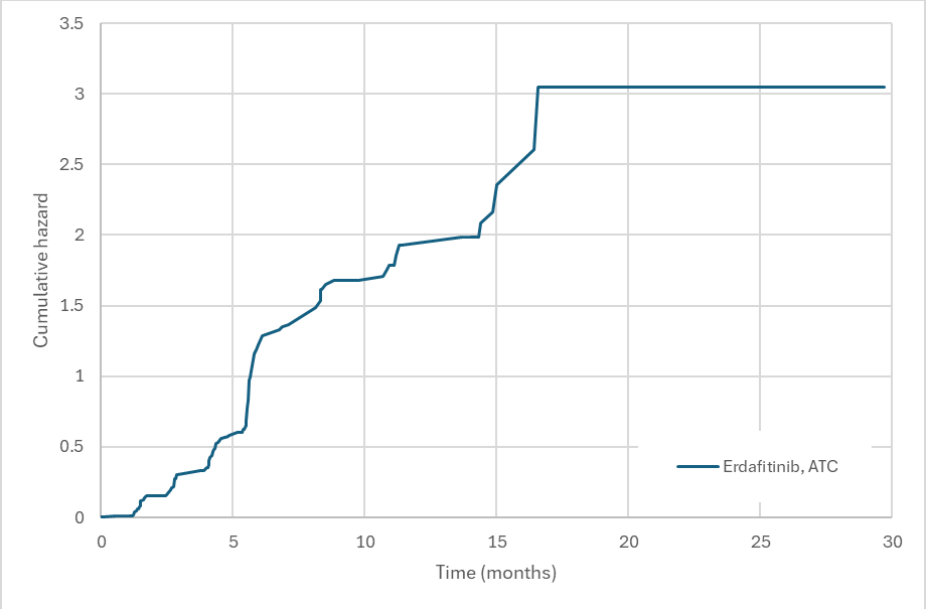


Figure 18. Cumulative hazard over time for PFS of ATC-adjusted erdafitinib, missing data excluded

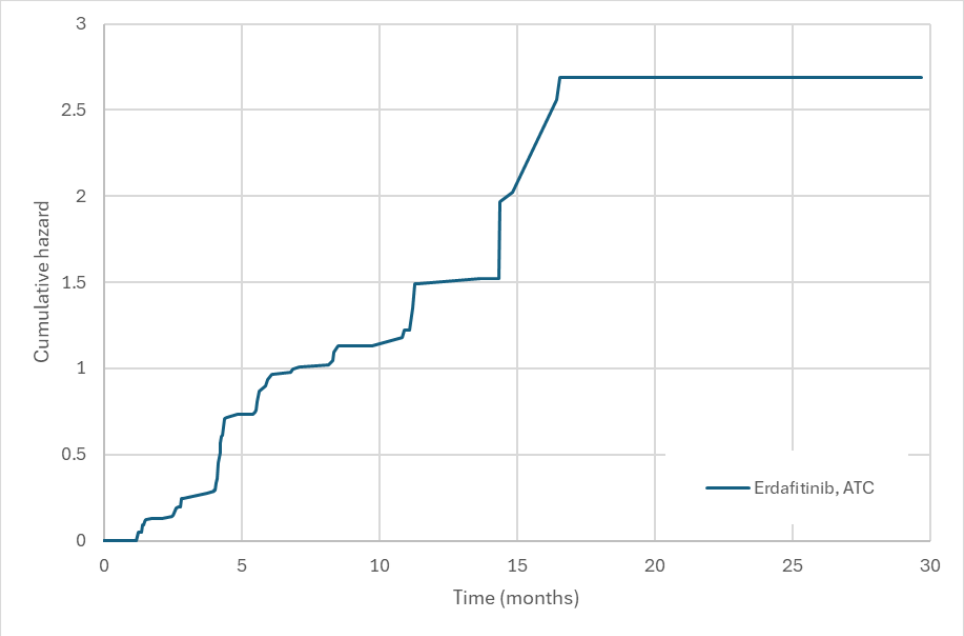


Figure 19. Cumulative hazard over time for PFS of erdafitinib (unadjusted) versus chemotherapy (THOR)

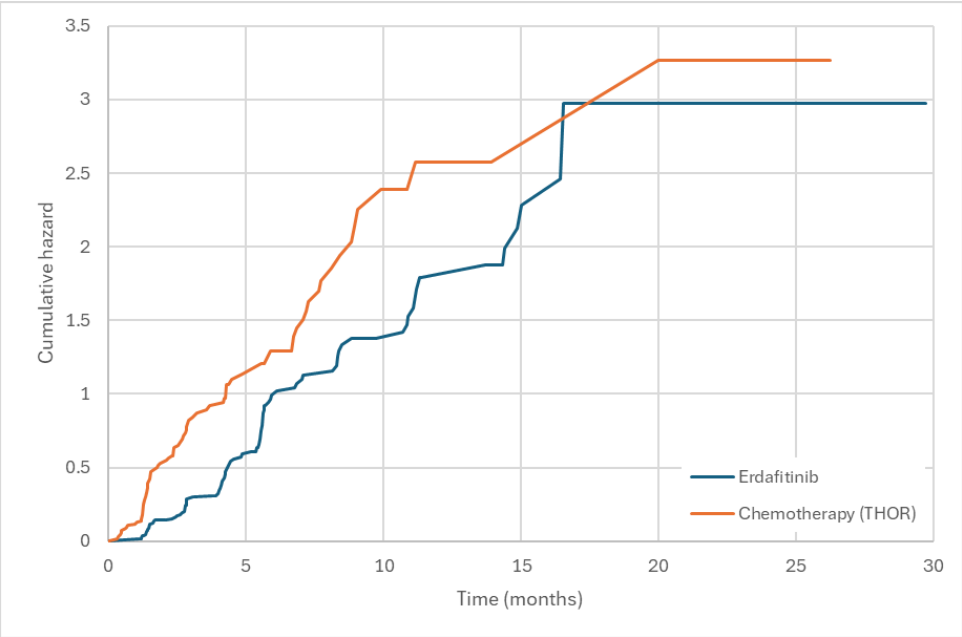


Figure 20. Cumulative hazard over time for TTD of ATC-adjusted erdafitinib

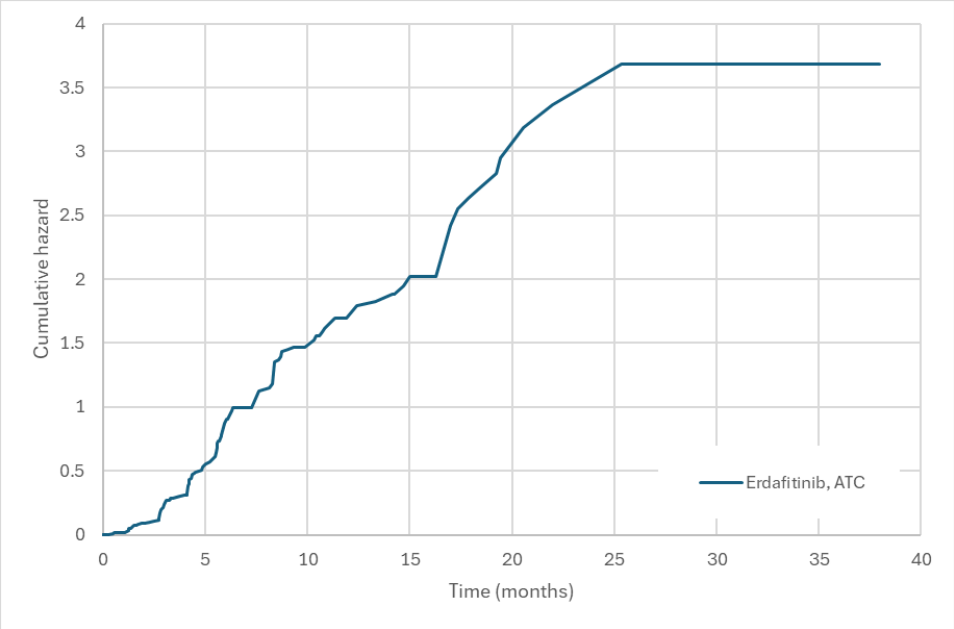


Figure 21. Cumulative hazard over time for TTD of ATC-adjusted erdafitinib, missing data excluded

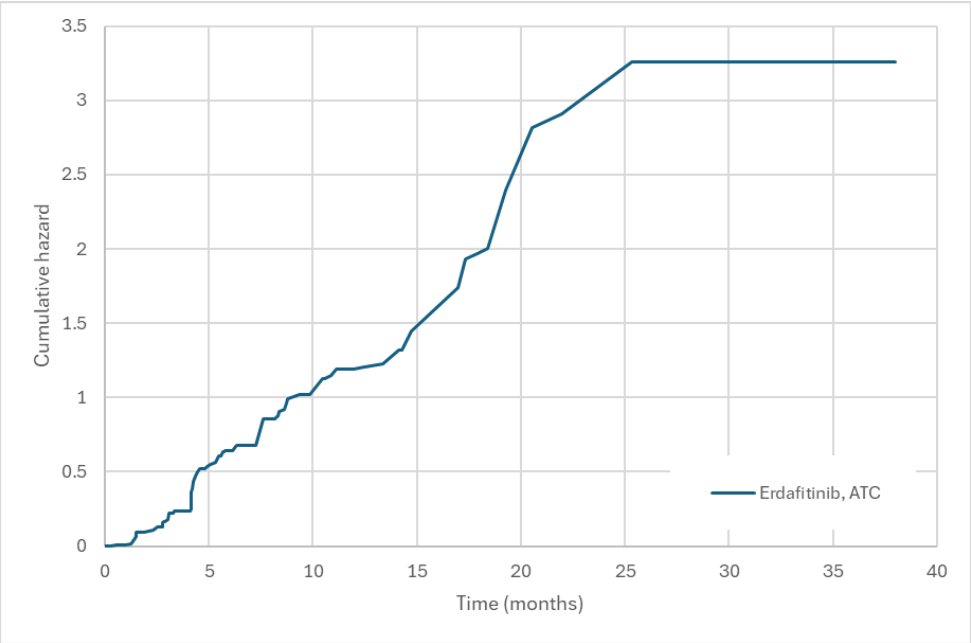
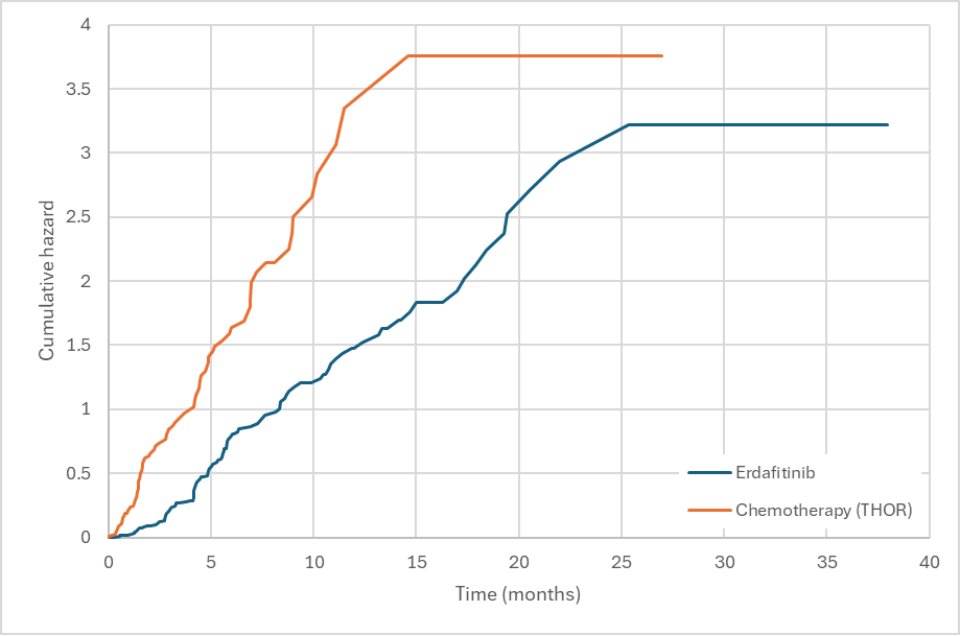


Figure 22. Cumulative hazard over time for TTD of erdafitinib (unadjusted) versus chemotherapy (THOR)



b. Log smoothed hazard over time

As standard smoothing methods do not account for weights applied to the observations, smoothed hazard or log hazards plots are not

informative when applied to ATC-adjusted curves. For this reason, we are including only log hazard plots for unadjusted curves.

Figure 23. Log smoothed hazard over time – OS, paclitaxel ± carboplatin

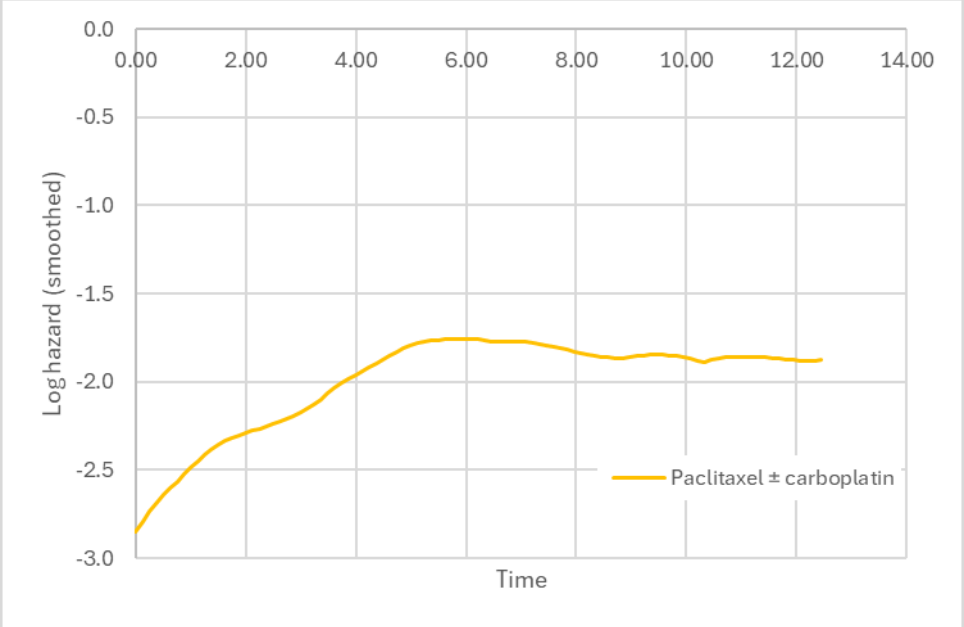


Figure 24. Log smoothed hazard over time – OS, paclitaxel ± carboplatin, missing data excluded

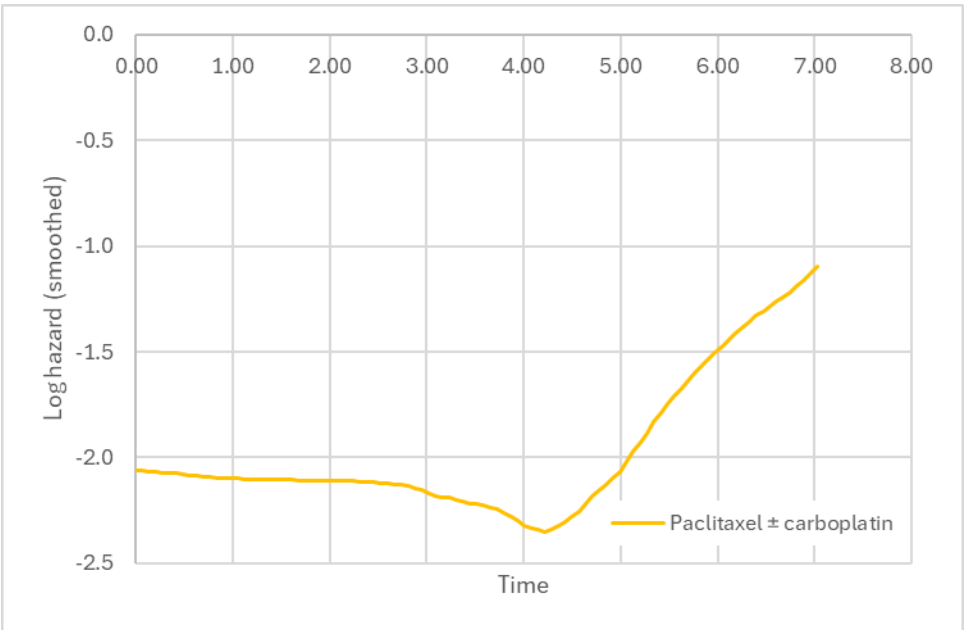


Figure 25. Log smoothed hazard over time – OS, erdafitinib (unadjusted) and chemotherapy (THOR)

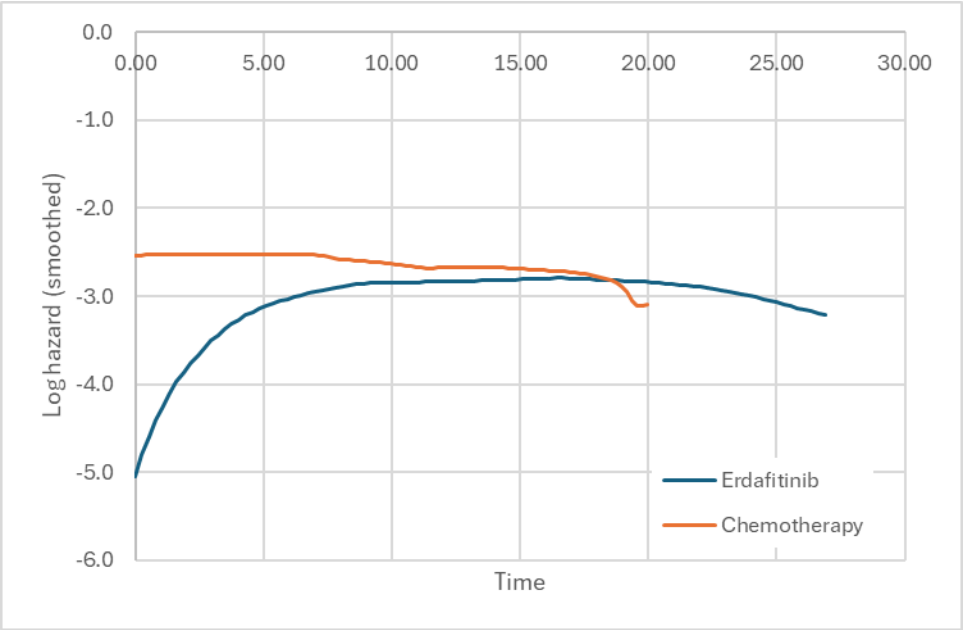


Figure 26. Log smoothed hazard over time – TTNT, paclitaxel ± carboplatin

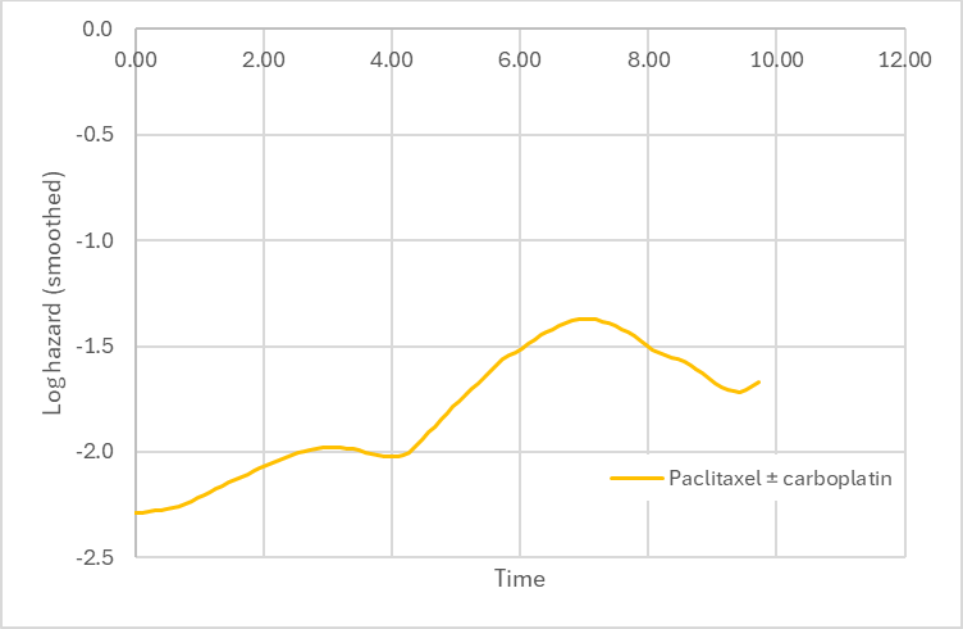


Figure 27. Log smoothed hazard over time – TTNT, paclitaxel ± carboplatin, missing data excluded

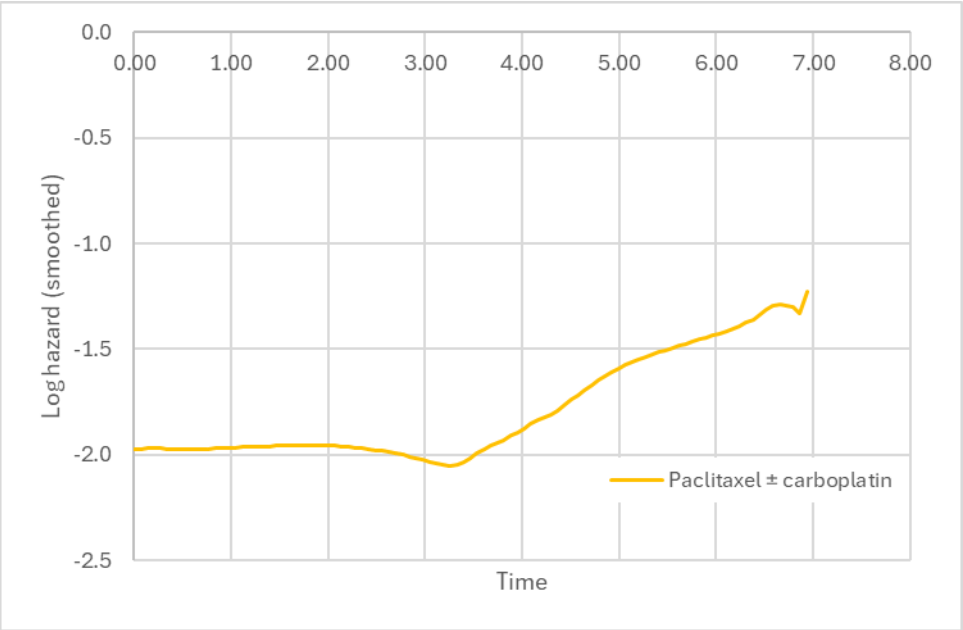


Figure 28. Log smoothed hazard over time – PFS, erdafitinib (unadjusted) and chemotherapy (THOR)

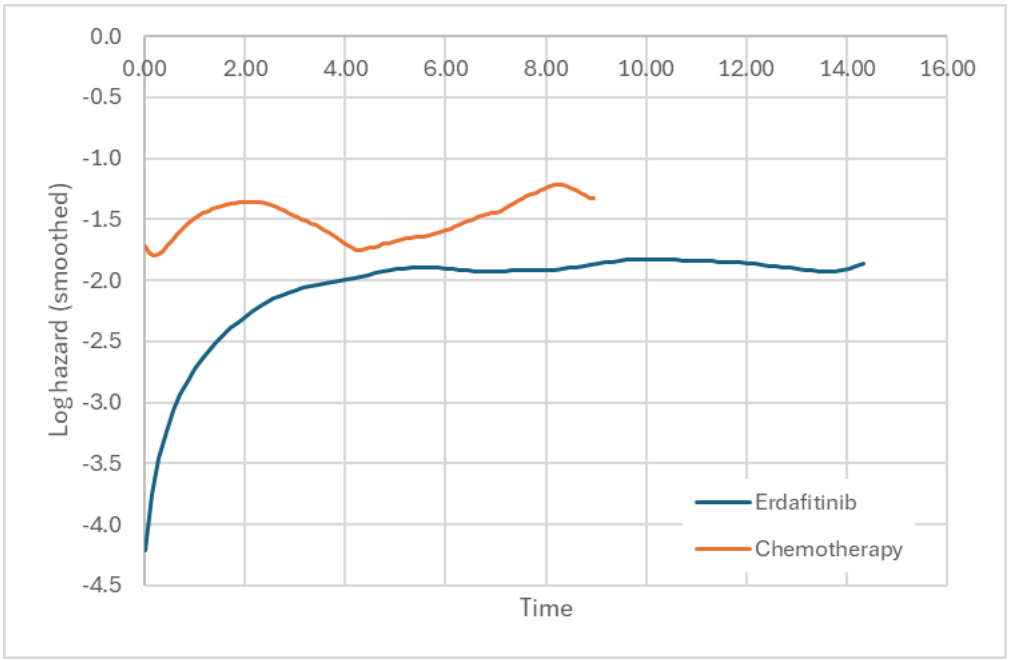
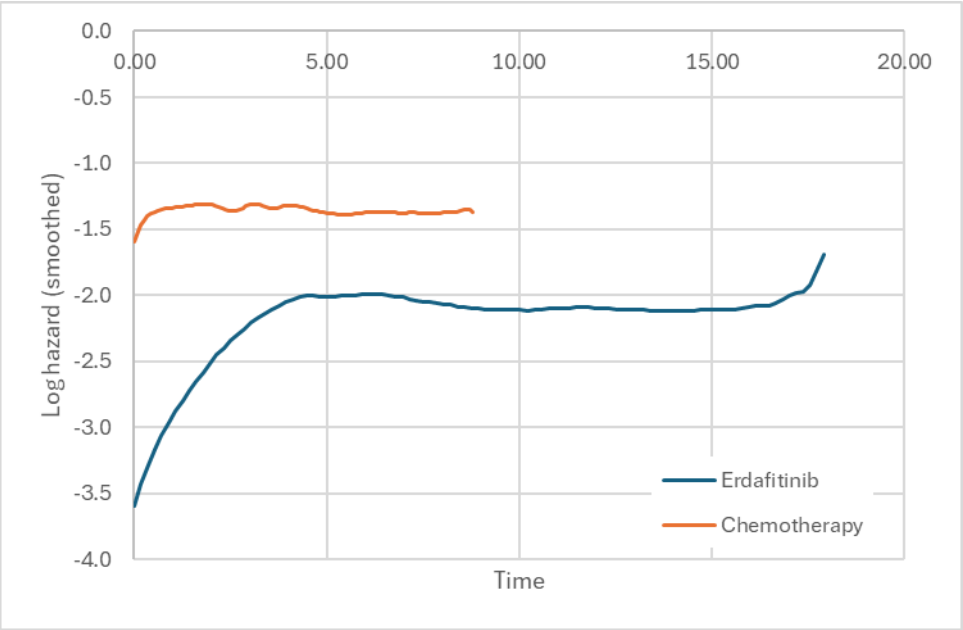


Figure 29. Log smoothed hazard over time – TTD, erdafitinib (unadjusted) and chemotherapy (THOR)



c. Standard normal quartiles over log time

Figure 30. Standard normal quantiles vs log time – OS, erdafitinib (ATC) and paclitaxel ± carboplatin

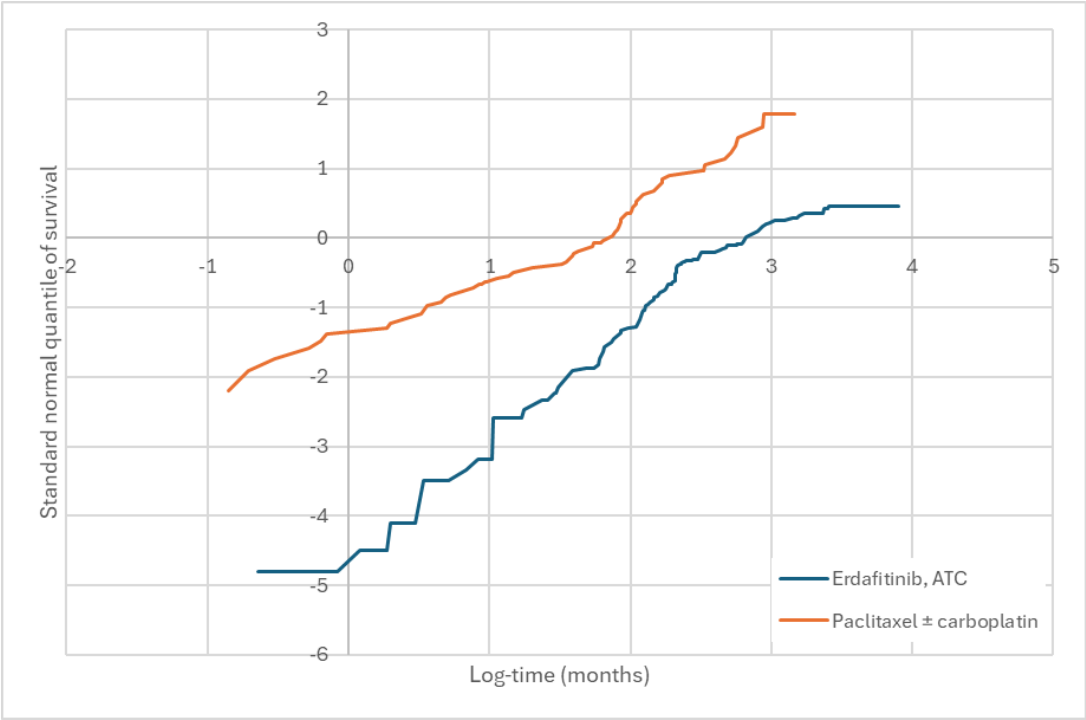


Figure 31. Standard normal quantiles vs log time – OS, erdafitinib (ATC) and paclitaxel ± carboplatin, missing data excluded

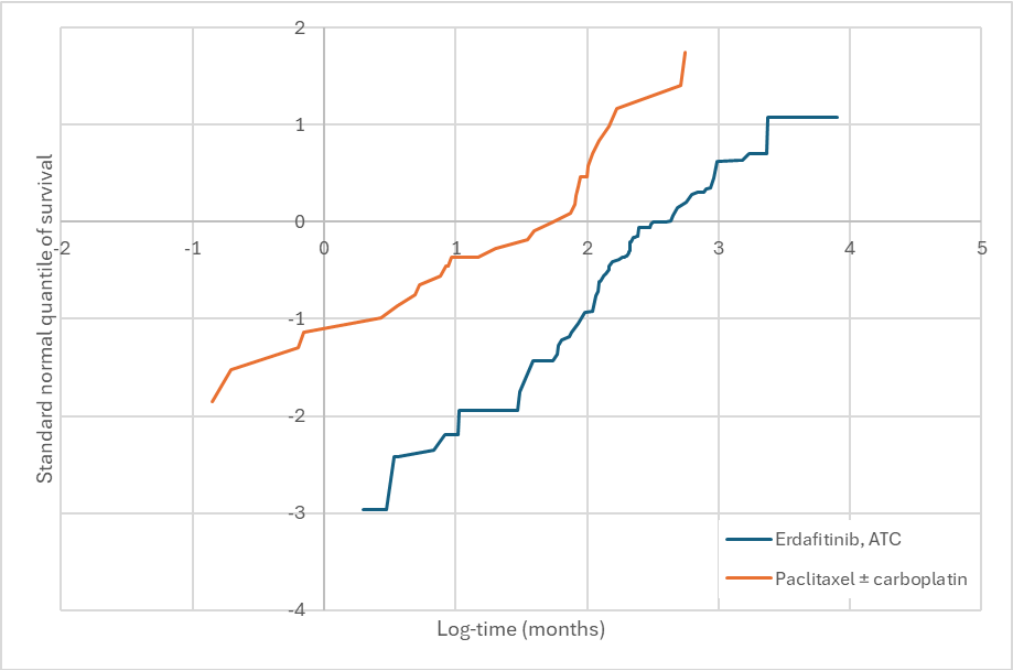


Figure 32. Standard normal quantiles vs log time – OS, erdafitinib (unadjusted) and chemotherapy (THOR)

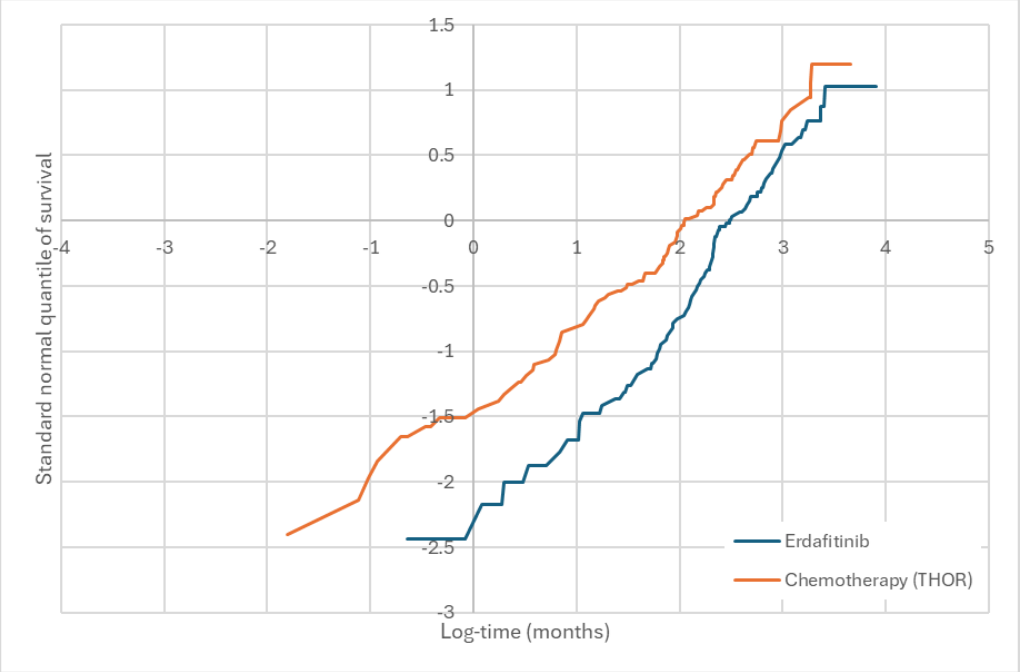


Figure 33. Standard normal quantiles vs log time – PFS, erdafitinib (ATC)

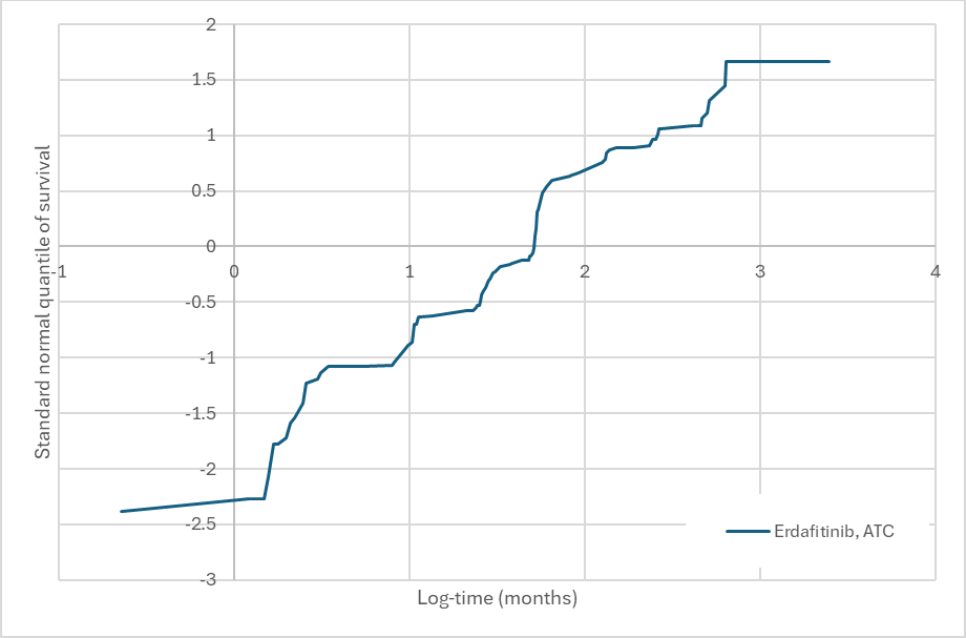


Figure 34. Standard normal quantiles vs log time – PFS, erdafitinib (ATC), missing data excluded

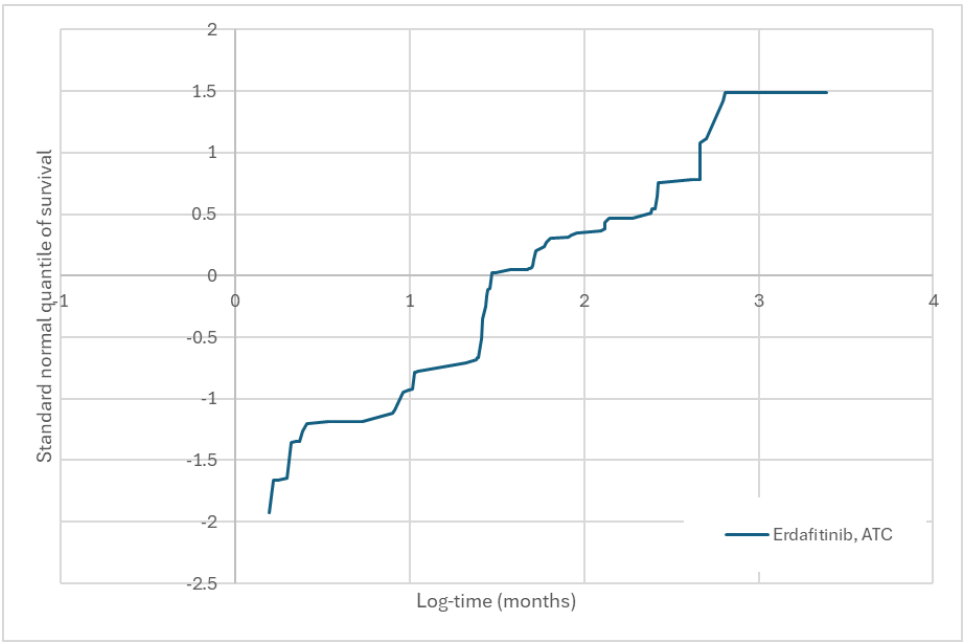


Figure 35. Standard normal quantiles vs log time – PFS, erdafitinib (unadjusted) and chemotherapy (THOR)

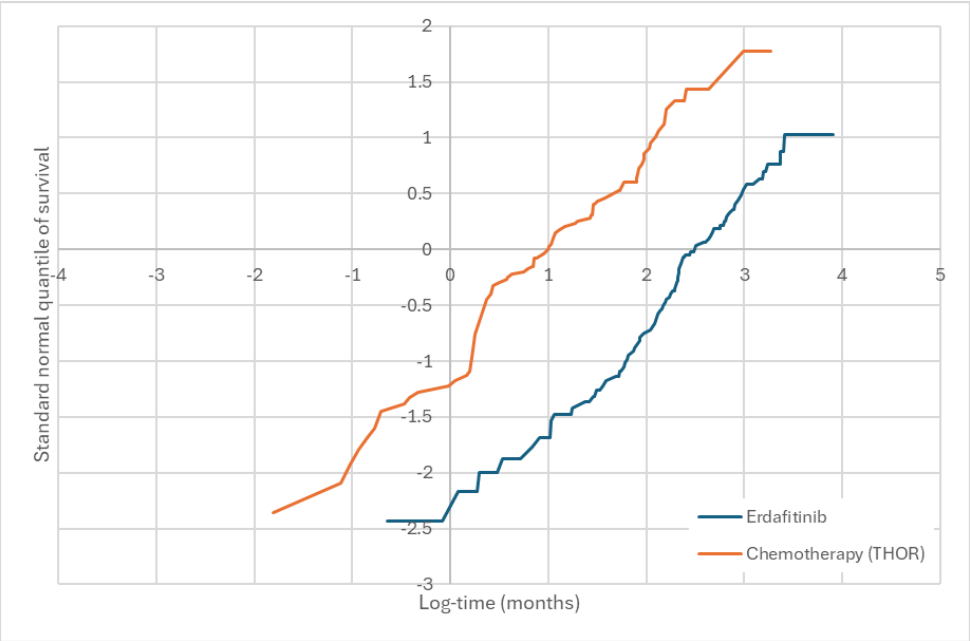


Figure 36. Standard normal quantiles vs log time – TTNT, erdafitinib (ATC) and paclitaxel ± carboplatin

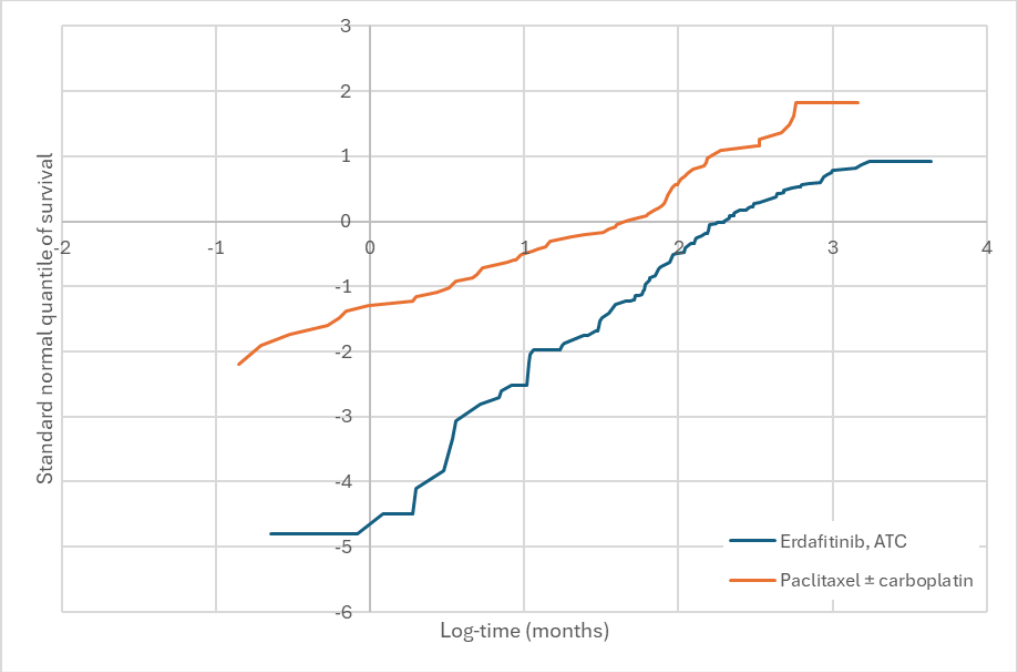


Figure 37. Standard normal quantiles vs log time – TTNT, erdafitinib (ATC) and paclitaxel ± carboplatin, missing data excluded

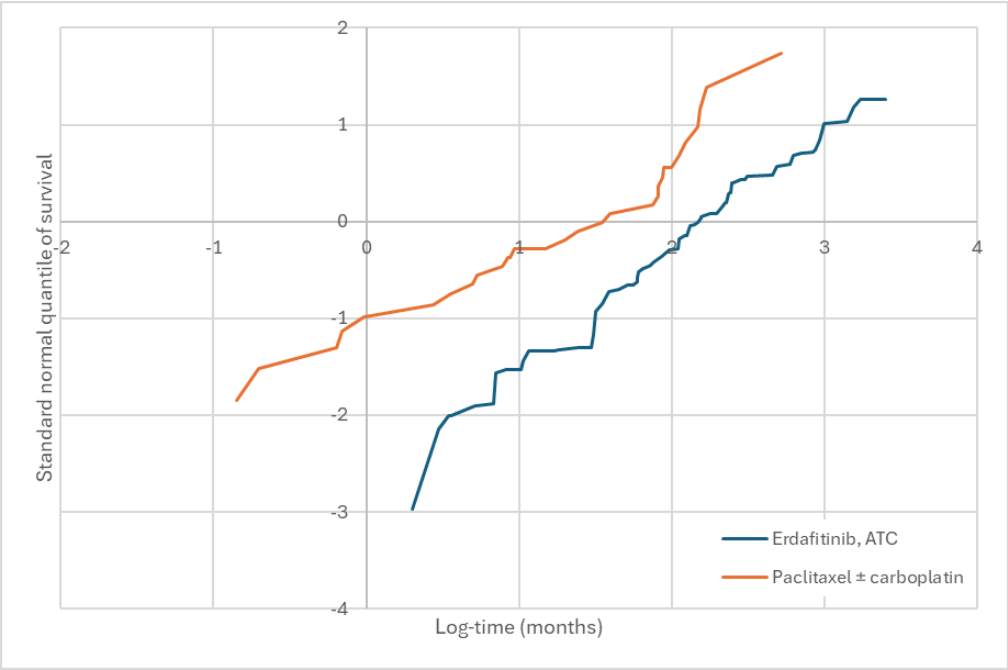


Figure 38. Standard normal quantiles vs log time – TTD, erdafitinib (ATC)

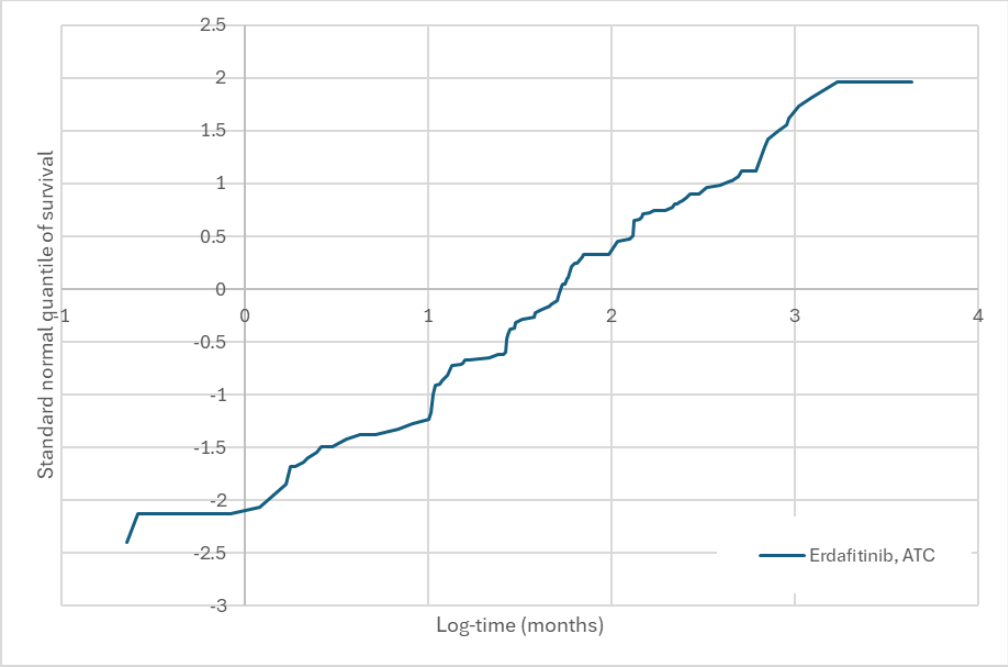


Figure 39. Standard normal quantiles vs log time – TTD, erdafitinib (ATC), missing data excluded

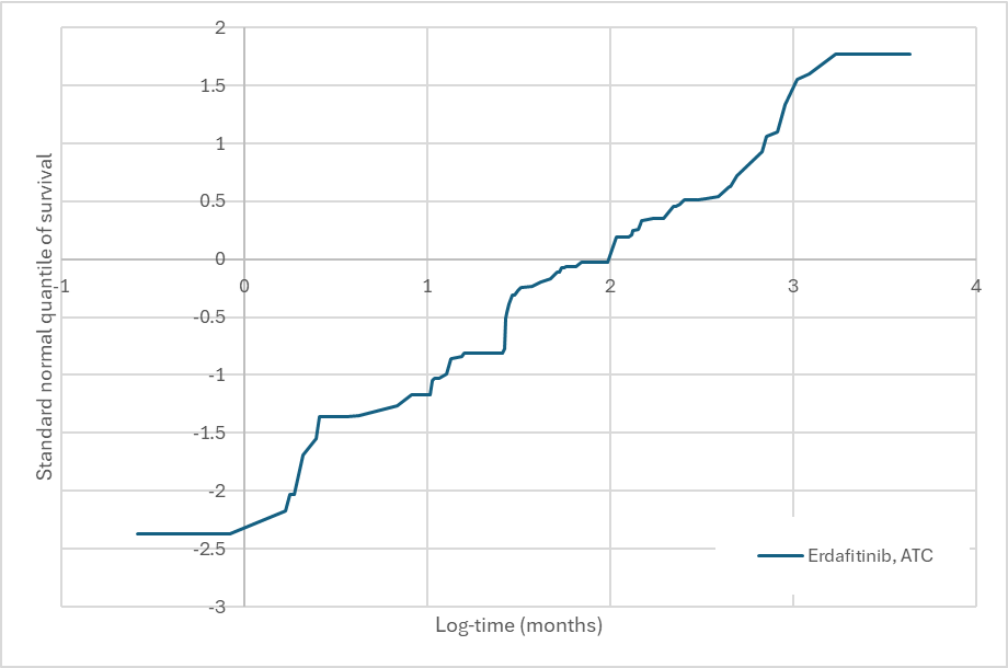
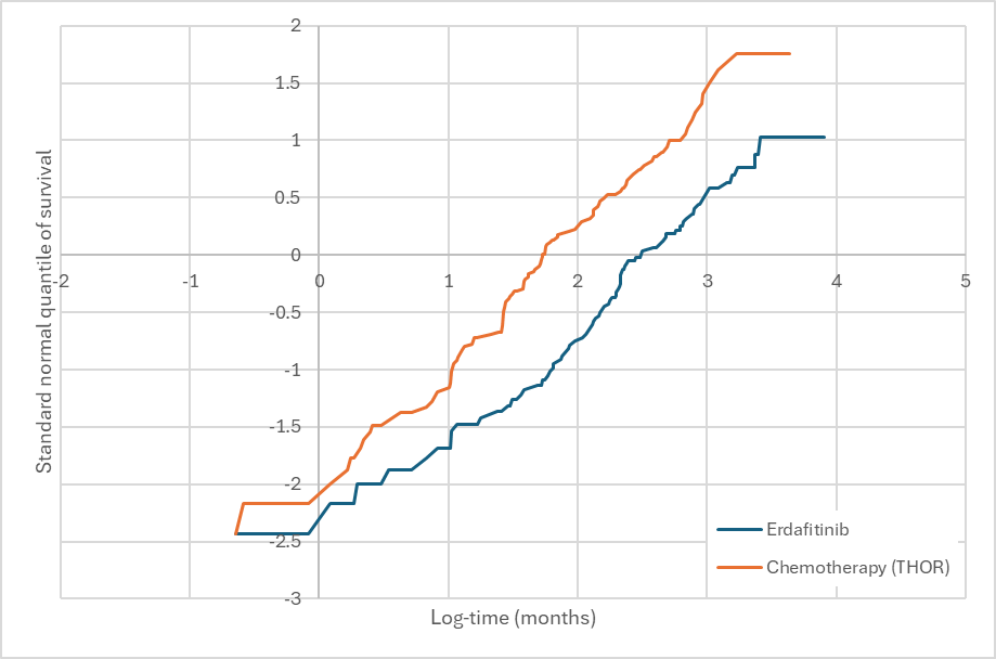


Figure 40. Standard normal quantiles vs log time – TTD, erdafitinib (unadjusted) and chemotherapy (THOR)



d. Log survival odds versus log time

Figure 41. Log survival odds vs log time – OS, erdafitinib (ATC) and paclitaxel ± carboplatin

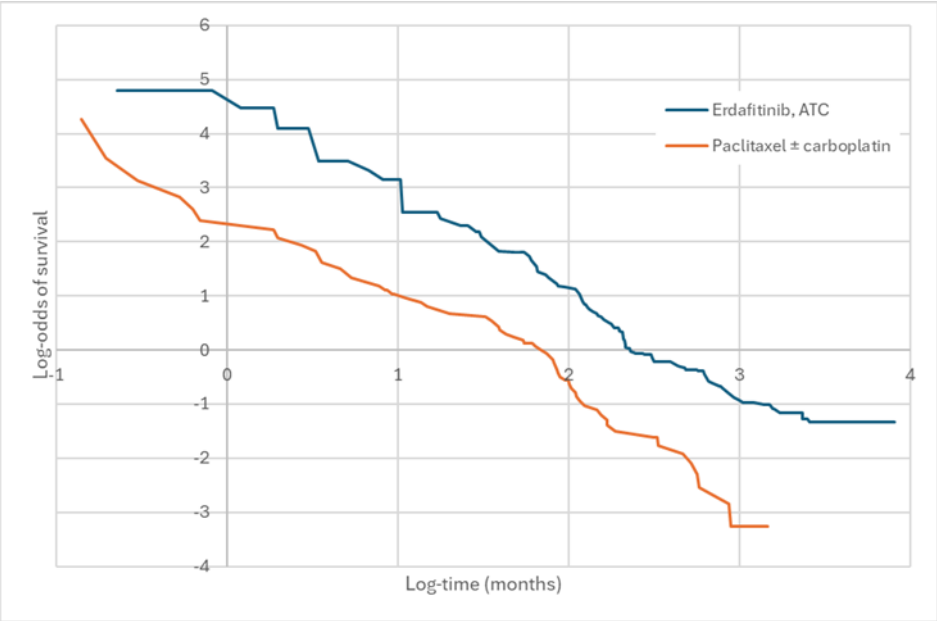


Figure 42. Log survival odds vs log time – OS, erdafitinib (ATC) and paclitaxel ± carboplatin, missing data excluded

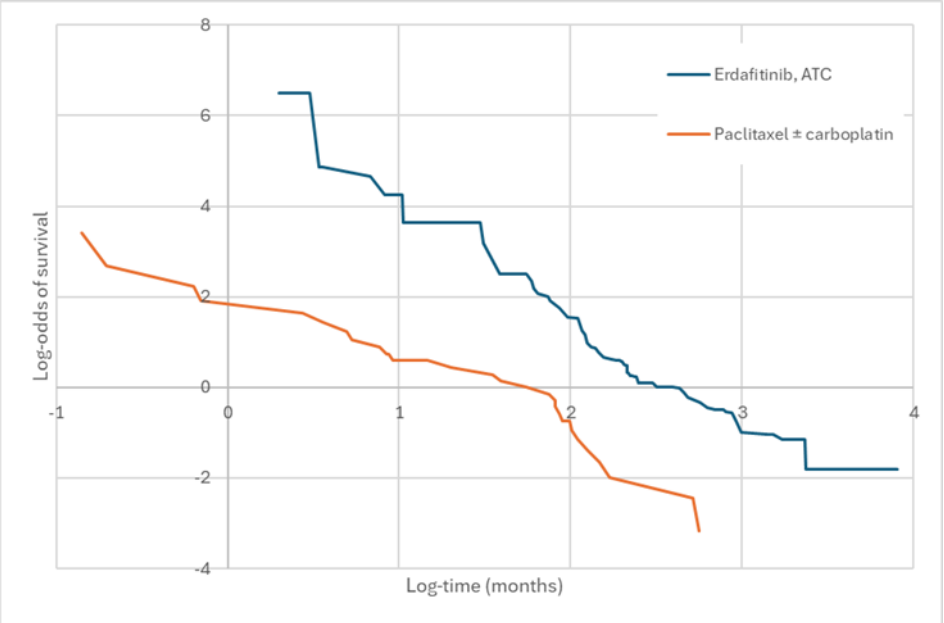


Figure 43. Log survival odds vs log time – OS, erdafitinib (unadjusted) and chemotherapy (THOR)

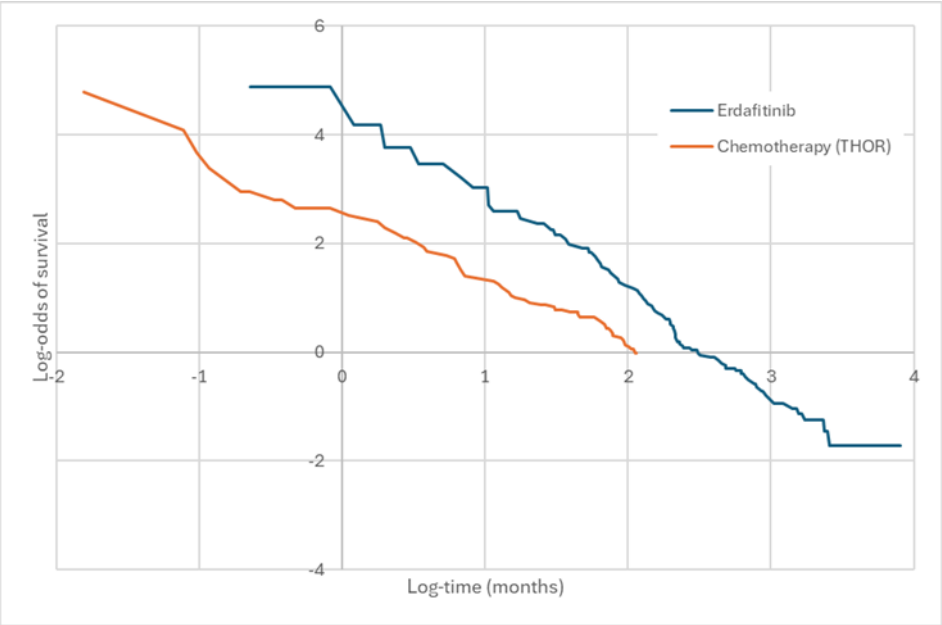


Figure 44. Log survival odds vs log time – PFS, erdafitinib (ATC)

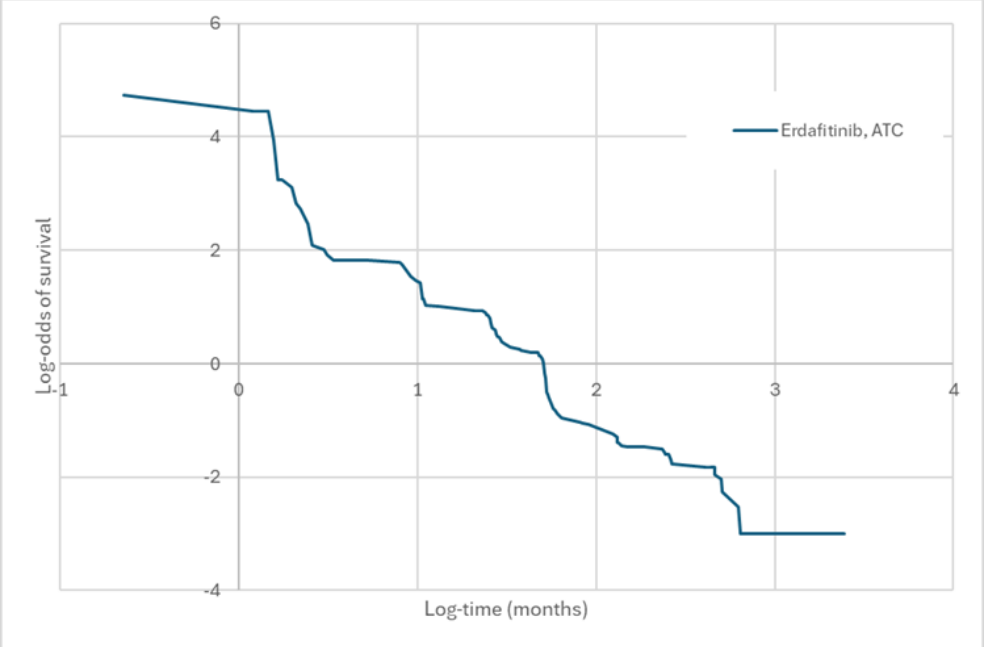


Figure 45. Log survival odds vs log time – PFS, erdafitinib (ATC), missing data excluded

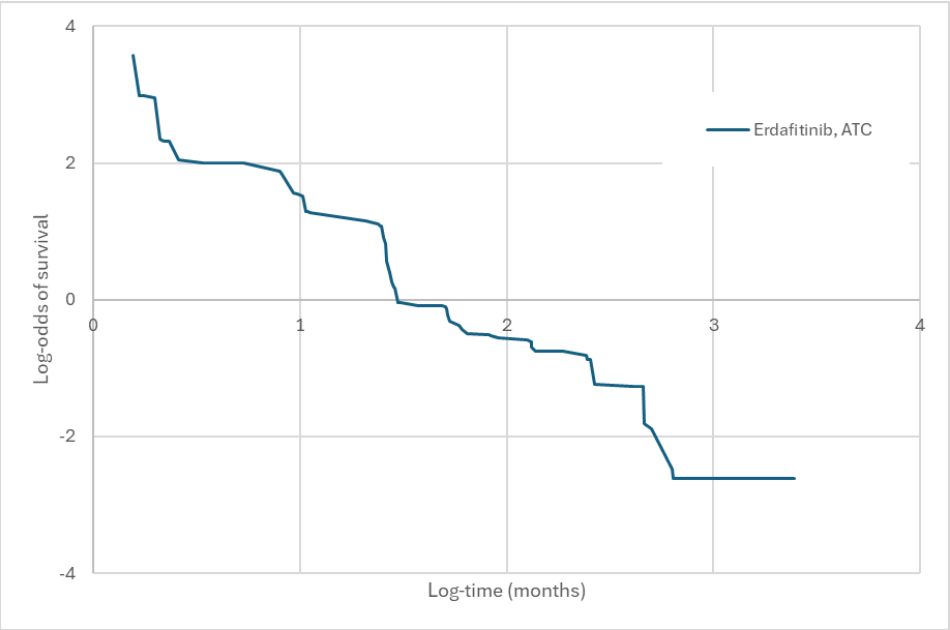


Figure 46. Log survival odds vs log time – PFS, erdafitinib (unadjusted) and chemotherapy (THOR)

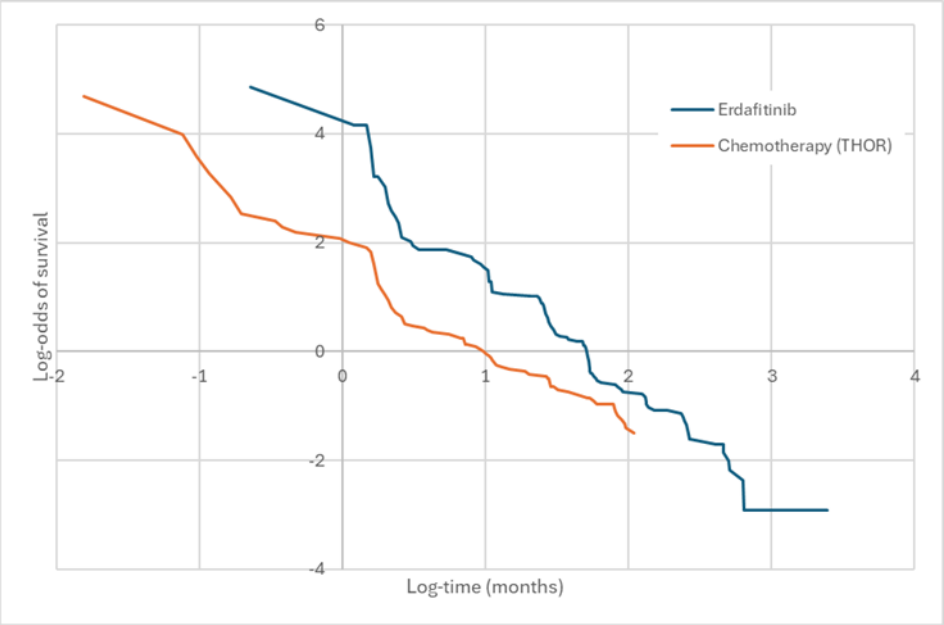


Figure 47. Log survival odds vs log time – TTNT, erdafitinib (ATC) and paclitaxel ± carboplatin

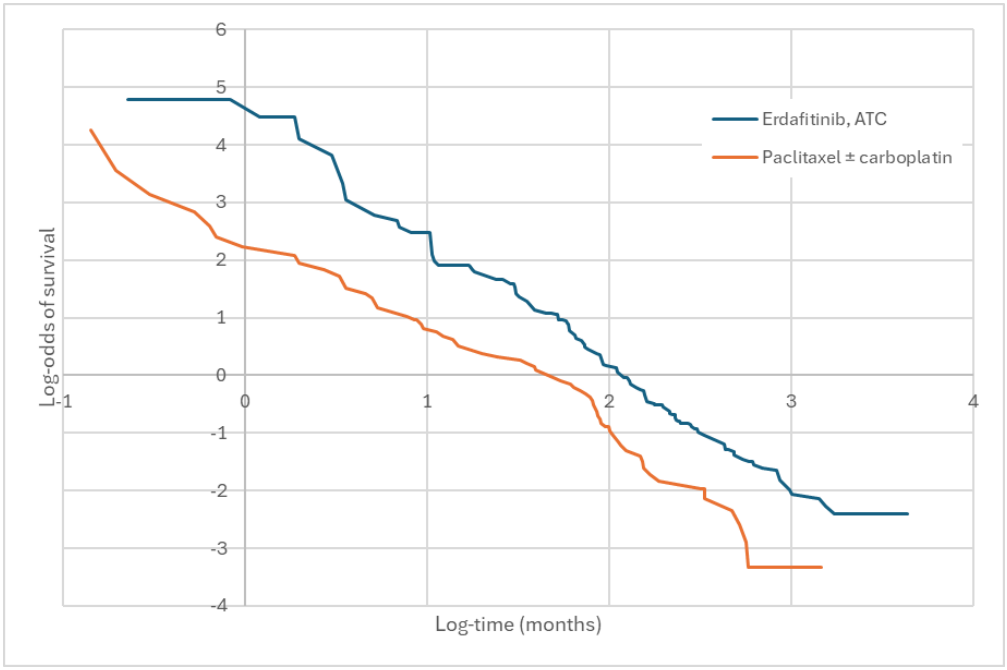


Figure 48. Log survival odds vs log time – TTNT, erdafitinib (ATC) and paclitaxel ± carboplatin, missing data excluded

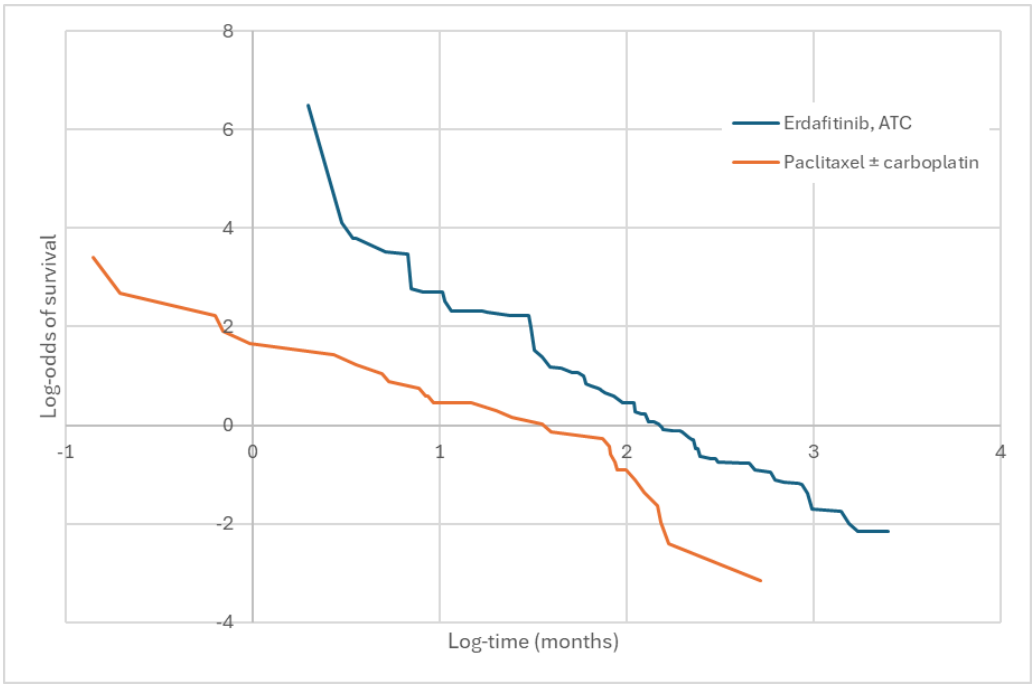


Figure 49. Log survival odds vs log time – TTD, erdafitinib (ATC)

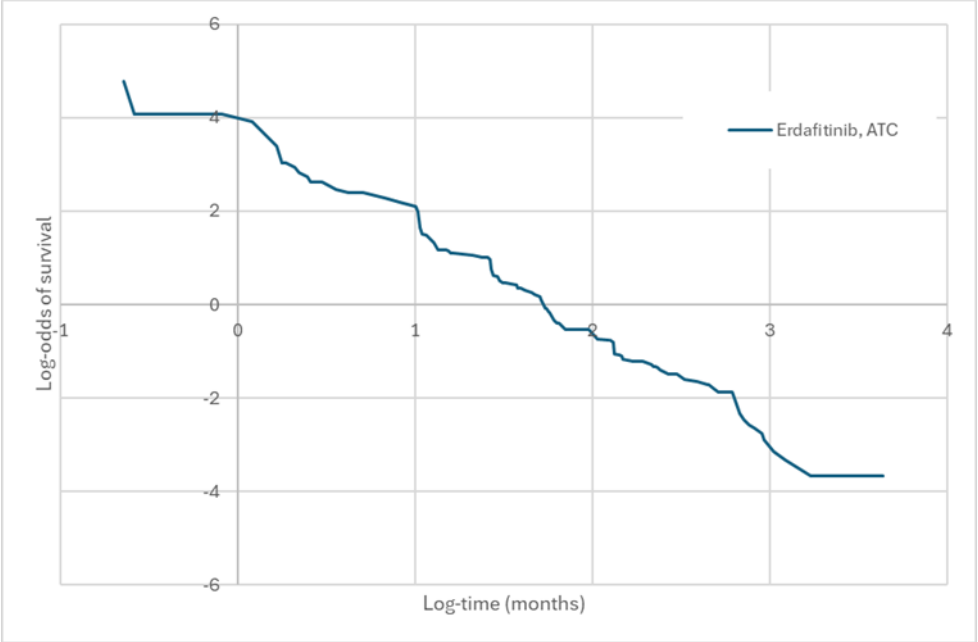


Figure 50. Log survival odds vs log time – TTD, erdafitinib (ATC), missing data excluded

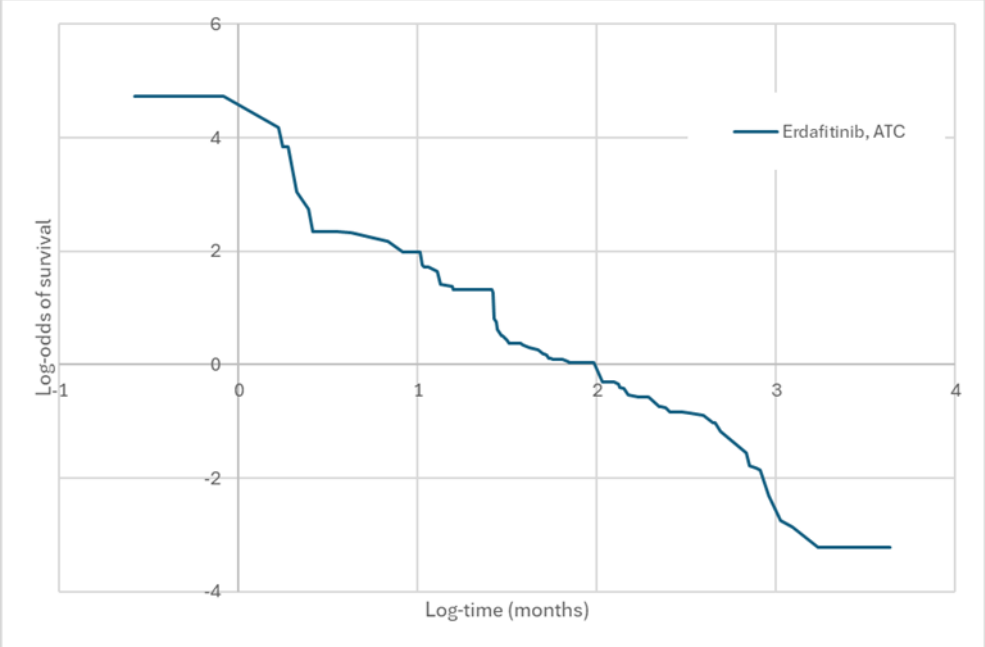
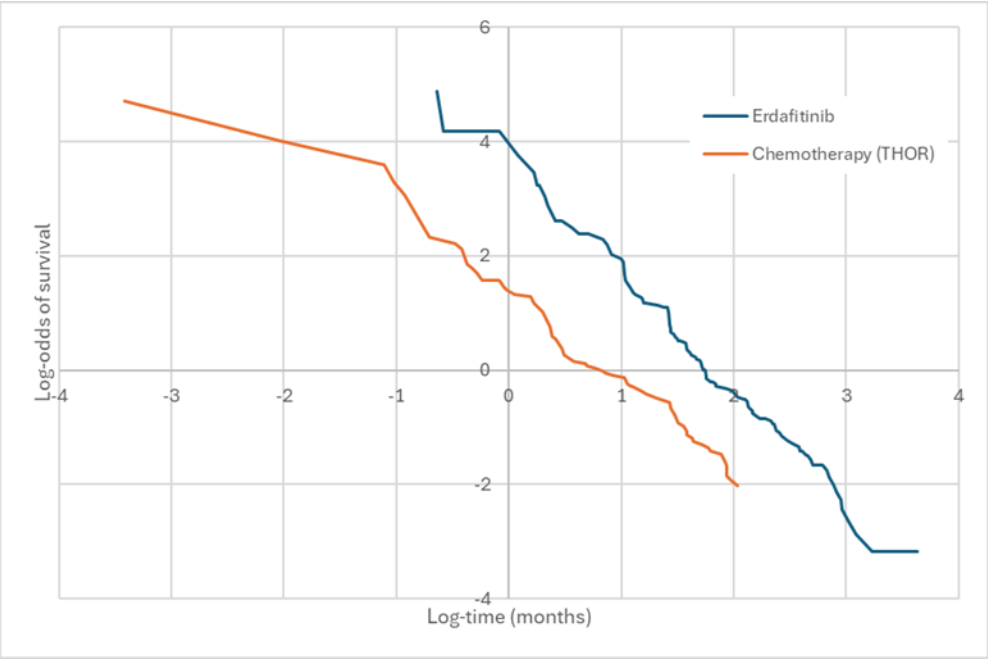


Figure 51. Log survival odds vs log time – TTD, erdafitinib (unadjusted) and chemotherapy (THOR)



e. While there is no strong evidence against the proportional hazards assumption in the case of OS of erdafitinib (ATC-adjusted) and paclitaxel ± carboplatin, the three parametric distributions that can model proportional hazards (exponential, Weibull and Gompertz) provide poor fits to the data even when fitted individually to each group, and it can be expected that placing an additional constraint on them in the form of a shared parameter would only worsen their fit. There is more evidence that the proportional hazards assumption could be violated in the case of TTNT, and it is clearly violated in the case of OS and PFS between erdafitinib and THOR chemotherapy.

   The remaining distributions (as well as the Weibull distribution under a different parametrization) are based on an accelerated failure time (AFT) rather than proportional hazards assumption. While in some cases AFT joint models could potentially provide good fits to both erdafitinib and the comparator, like with all joint models the required assumption of a constant treatment effect over time is very strong, and even small violations of that assumption can be meaningful in long-term extrapolations. We note the concern about treatment effect waning in question B11 and the suggestion to incorporate it in the economic model if

waning is indicated by trends in the data. We believe a more consistent approach is to not impose an assumption of constant treatment effects in the statistical models in the first place.

Due to limited time to respond, and as for the reasons explained above, we do not think additional analyses using joint fits would provide meaningful information, joint fits have not been implemented in the updated model. However, for transparency, we provide estimated parameters for joint OS and TTNT of erdafitinib (with base-case ATC adjustment) and paclitaxel ± carboplatin in Table 17 and Table 18 below.

Table 17. Joint fit for OS of ATC-adjusted erdafitinib and paclitaxel ± carboplatin

Distribution	**Parameter**	**Estimate**	**Information criteria**	**Predicted survival: 5 years (%)**	**Predicted survival: 10 years (%)**
Exponential	rate	−3.0379	AIC: 959.9 BIC: 966.5	Erda: 5.6 Pacli + carbo: 0.0	Erda: 0.3 Pacli + carbo: 0.0
	treatment: pacli ± carbo	1.0201			
Generalised gamma	mu	2.6751	AIC: 944.4 BIC: 957.5	Erda: 5.3 Pacli + carbo: 0.3	Erda: 0.8 Pacli + carbo: 0.0
	sigma	−0.0356			
	Q	0.2013			
	treatment: pacli ± carbo	−0.9629			
Gompertz	shape	−0.0021	AIC: 961.9 BIC: 971.7	Erda: 6.3 Pacli + carbo: 0.1	Erda: 0.6 Pacli + carbo: 0.0
	rate	−3.0161			
	treatment: pacli ± carbo	1.0106			
Log-logistic	shape	0.5826	AIC: 940.6 BIC: 950.5	Erda: 6.0 Pacli + carbo: 1.3	Erda: 1.8 Pacli + carbo: 0.4
	scale	2.5570			
	treatment: pacli ± carbo	−0.8807			
Log-normal	meanlog	2.5931	AIC: 943.1 BIC: 953.0	Erda: 6.6 Pacli + carbo: 0.7	Erda: 1.4 Pacli + carbo: 0.1
	sdlog	−0.0021			
	treatment: pacli ± carbo	−0.9724			
Weibull	shape	0.1822	AIC: 954.8	Erda: 2.5	Erda: 0.0

			BIC: 964.7		Pacli + carbo: 0.0	Pacli + carbo: 0.0
	scale	3.0049				
	treatment: pacli ± carbo	−0.9455				
Gamma	shape	0.3703	AIC: 950.6 BIC: 960.4		Erda: 2.4 Pacli + carbo: 0.0	Erda: 0.0 Pacli + carbo: 0.0
	rate	−2.5589				
	treatment: pacli ± carbo	−3.0379				

Key: Erda, erdafitinib; pacli ± carbo, paclitaxel ± carboplatin; AIC, Akaike information criterion; BIC, Bayesian information criterion

Table 18. Joint fit for TTNT of ATC-adjusted erdafitinib and paclitaxel ± carboplatin

Distribution	**Parameter**	**Estimate**	**Information criteria**		**Predicted survival: 5 years (%)**	**Predicted survival: 10 years (%)**
Exponential	rate	-2.4649	AIC: 1000.7 BIC: 1007.3		Erda: 0.6 Pacli + carbo: 0.0	Erda: 0.0 Pacli + carbo: 0.0
	treatment: pacli ± carbo	0.5890				
Generalised gamma	mu	2.1934	AIC: 973.1 BIC: 986.3		Erda: 0.6 Pacli + carbo: 0.0	Erda: 0.0 Pacli + carbo: 0.0
	sigma	-0.1554				
	Q	0.2232				
	treatment: pacli ± carbo	-0.6041				
Gompertz	shape	0.0182	AIC: 1000.5 BIC: 1010.4		Erda: 0.0 Pacli + carbo: 0.0	Erda: 0.0 Pacli + carbo: 0.0
	rate	-2.5940				
	treatment: pacli ± carbo	0.6119				
Log-logistic	shape	0.7047	AIC: 969.5 BIC: 979.4		Erda: 1.8 Pacli + carbo: 0.6	Erda: 0.4 Pacli + carbo: 0.1
	scale	2.1074				
	treatment: pacli ± carbo	-0.5756				
Log-normal	meanlog	2.1163	AIC: 972.3 BIC: 982.2		Erda: 1.2 Pacli + carbo: 0.2	Erda: 0.1 Pacli + carbo: 0.0
	sdlog	-0.1259				
	treatment: pacli ± carbo	-0.6365				
Weibull	shape	0.2625	AIC: 985.9 BIC: 995.8		Erda: 0.0 Pacli + carbo: 0.0	Erda: 0.0 Pacli + carbo: 0.0

	scale	2.4617				
	treatment: pacli ± carbo	-0.5080				
Gamma	shape	0.5251	AIC: 978.9 BIC: 988.7		Erda: 0.0 Pacli + carbo: 0.0	Erda: 0.0 Pacli + carbo: 0.0
	rate	-1.8569				
	treatment: pacli ± carbo	0.5259				

Key: Erda, erdafitinib; pacli ± carbo, paclitaxel ± carboplatin; AIC, Akaike information criterion; BIC, Bayesian information criterion

f. For all tables including long term (3, 5 and 10 years) estimates and goodness-of-fit statistics (i.e. CS tables 30-35), we provide estimates of earlier time points (e.g. 3, 6, 9, 12, 18, 24, and 30 months) and provide the observed data estimates for these time points. These are presented in Table 19, Table 20, Table 21, Table 22 and Table 23.

Table 19. Comparison of short and long-term erdafitinib OS survival and goodness-of-fit statistics (CS, Table 30)

Model	**3m**	**6m**	**9m**	**12m**	**18m**	**24m**	**30m**	**3-year**	**5-year**	**10-year**	**AIC**	**BIC**
Exponential	86.2%	74.7%	64.7%	56.1%	42.1%	31.6%	23.7%	17.8%	5.7%	0.3%	571.6	574.4
Weibull	89.8%	78.7%	68.0%	58.2%	41.7%	29.2%	20.1%	13.7%	2.6%	0.0%	570.2	575.9
Gompertz	85.2%	73.3%	63.3%	54.9%	41.7%	32.2%	25.2%	19.9%	8.8%	2.1%	573.1	578.8
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	557.2	562.9
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**554.8**	**560.5**
Gamma	91.5%	80.1%	68.7%	58.1%	40.5%	27.7%	18.6%	12.4%	2.3%	0.0%	567.0	572.6
Generalised gamma	92.7%	78.0%	64.7%	53.9%	38.5%	28.5%	21.8%	17.1%	7.7%	1.9%	559.1	567.6
Observed and advisory board consensus	92.7%	84.0%	64.9%	47.9%	33.7%	26.5%	22.0%	15% (5 – 25%)	5% (1 – 10%)	1% (0 – 5%)		

Table 20: Comparison of short and long-term paclitaxel ± carboplatin OS survival and goodness-of-fit statistics (CS, Table 31)

Model	**3m**	**6m**	**9m**	**12m**	**18m**	**24m**	**30m**	**3-year**	**5-year**	**10-year**	**AIC**	**BIC**
Exponential	66.2%	44.5%	29.9%	20.1%	9.1%	4.1%	1.9%	0.8%	0.0%	0.0%	388.3	390.6
Weibull	72.3%	47.9%	30.4%	18.6%	6.5%	2.1%	0.6%	0.2%	0.0%	0.0%	386.6	391.2
Gompertz	68.2%	46.3%	30.8%	20.1%	8.0%	2.9%	0.9%	0.3%	0.0%	0.0%	389.6	394.2
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	387.9	392.4
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**387.8**	**392.4**
Gamma	72.8%	47.3%	29.5%	18.0%	6.4%	2.2%	0.8%	0.3%	0.0%	0.0%	385.6	390.1
Generalised gamma	71.8%	45.5%	28.4%	17.9%	7.2%	3.1%	1.3%	0.6%	0.0%	0.0%	386.9	393.7
Observed and advisory board consensus	72.1%	53.0%	23.1%	18.2%	7.3%	3.7%	1.8%	3% (0 – 7%)	1% (0 – 3%)	0% (0 – 1%)		

Table 21. Comparison of short and long-term erdafitinib TTNT and goodness-of-fit statistics (CS, Table 32)

Model	3m	6m	9m	12m	18m	24m	30m	3-year	5-year	10-year	AIC	BIC
Exponential	83.0%	69.4%	58.0%	48.5%	34.1%	23.7%	16.5%	11.6%	2.8%	1.9%	674.9	677.8
Weibull	90.7%	78.2%	65.4%	53.5%	34.1%	20.1%	11.3%	6.1%	0.4%	1.9%	658.7	664.4
Gompertz	85.8%	73.3%	62.1%	52.1%	35.8%	23.0%	14.2%	8.2%	0.4%	1.9%	657.8	666.4
Log-normal	93.8%	77.3%	61.1%	48.0%	30.4%	19.6%	13.3%	9.2%	2.7%	1.9%	672.8	678.5
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**653.8**	**659.5**
Gamma	92.5%	79.4%	65.4%	52.5%	32.4%	18.7%	10.6%	5.9%	0.5%	1.9%	658.0	663.7
Generalised gamma	93.4%	78.5%	63.0%	49.7%	30.7%	18.7%	11.7%	7.4%	1.4%	1.9%	662.9	668.6
Observed data	92.7%	84.0%	64.1%	44.0%	27.6%	18.6%	14.5%					

Table 22. Comparison of short and long-term paclitaxel ± carboplatin TTNT and goodness-of-fit statistics (CS, Table 33)

Model	3m	6m	9m	12m	18m	24m	30m	3-year	5-year	10-year	AIC	BIC
Exponential	62.2%	39.3%	24.9%	15.7%	6.3%	2.5%	1.0%	0.4%	0.0%	0.0%	387.4	389.6
Weibull	67.8%	41.9%	24.7%	14.1%	4.2%	1.2%	0.3%	0.1%	0.0%	0.0%	386.0	390.6
Gompertz	63.1%	40.1%	25.2%	15.6%	5.8%	2.1%	0.7%	0.2%	0.0%	0.0%	389.2	393.8
Log-normal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**383.8**	**388.3**
Log-logistic	67.4%	37.5%	22.3%	14.5%	7.5%	4.6%	3.1%	2.2%	0.9%	0.2%	384.3	388.9
Gamma	68.7%	41.4%	23.8%	13.4%	4.0%	1.2%	0.3%	0.1%	0.0%	0.0%	384.4	388.9
Generalised gamma	66.6%	38.5%	22.5%	13.6%	5.3%	2.3%	1.0%	0.5%	0.0%	0.0%	384.3	391.1
Observed data	66.6%	46.4%	16.8%	13.7%	3.5%	3.5%	3.5%					

Table 23. Comparison of short and long-term erdafitinib PFS and goodness-of-fit statistics (CS, Table 34)

Model	3m	6m	9m	12m	18m	24m	30m	3-year	5-year	10-year	AIC	BIC
Exponential	63.0%	43.0%	28.4%	18.7%	8.2%	3.6%	1.6%	0.7%	0.0%	0.0%	559.6	562.4
Weibull	71.0%	46.3%	26.8%	14.5%	3.6%	0.8%	0.1%	0.0%	0.0%	0.0%	548.6	554.3
Gompertz	64.4%	43.9%	28.5%	18.2%	6.9%	2.4%	0.8%	0.2%	0.0%	0.0%	561.0	566.7
Log-normal	70.3%	41.2%	23.4%	14.0%	5.6%	2.6%	1.3%	0.7%	0.1%	0.0%	530.0	535.7
Log-logistic	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**528.0**	**533.7**
Gamma	72.8%	45.3%	24.8%	12.9%	3.1%	0.7%	0.2%	0.0%	0.0%	0.0%	541.1	546.8
Generalised gamma	69.7%	40.6%	23.5%	14.5%	6.3%	3.2%	1.8%	1.0%	0.2%	0.0%	531.7	540.3
Observed data	73.6%	29.5%	18.7%	14.5%	4.8%	4.8%	4.8%					

g. For erdafitinib, the standard parametric survival curves for the extrapolation of OS, PFS, TTD and TTNT do not seem to fit very well to the observed data (underestimation of the observed data in the first few months and overestimation thereafter).

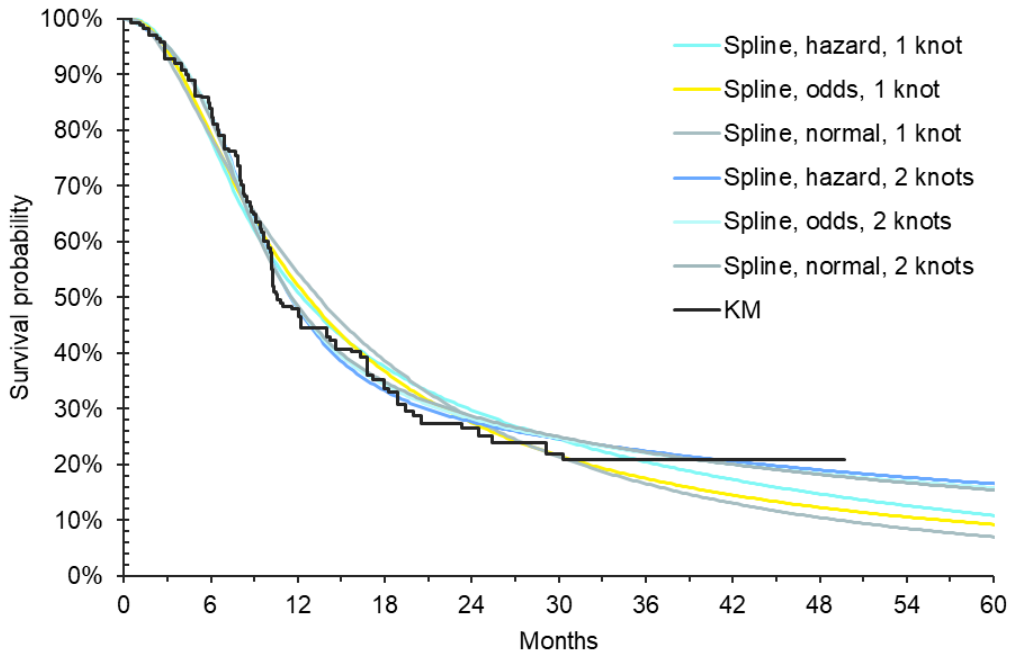
Despite these shortcomings, the use of spline-based models was not explored as we deemed the tail to be the main driver of the cost-effectiveness results.

We have now conducted the analysis.

Overall survival

Erdafitinib

Figure 52. Erdafitinib OS and fitted spline models



Comparison of the 6 spline models fitted to the erdafitinib OS data based on statistical fits and long-term estimates, is given in Table 24.

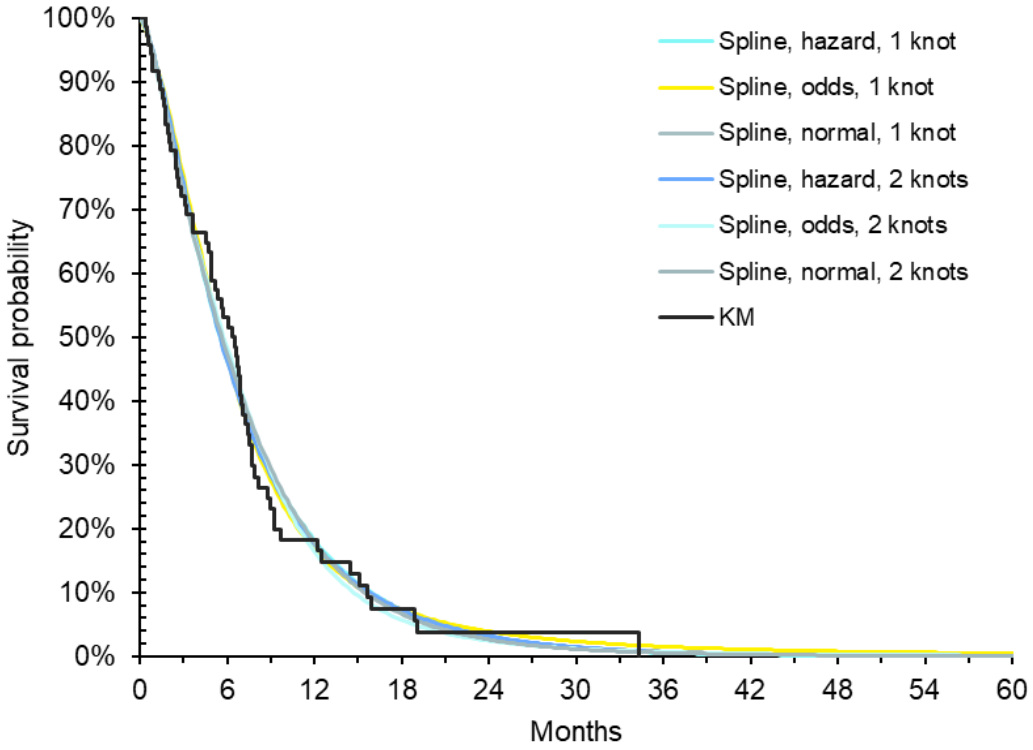
Table 24. Spline models' statistical fits and long-term extrapolations for erdafitinib OS

Model	3m	6m	9m	12m	18m	24m	30m	3-year	5-year	10-year	AIC	BIC
Spline: hazard scale, 1 knot	94.3%	77.7%	61.8%	50.7%	37.4%	29.7%	24.5%	20.5%	10.9%	3.0%	556.4	564.9
Spline: odds scale, 1 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**554.9**	**563.4**
Spline: normal scale, 1 knot	92.6%	78.2%	65.0%	54.1%	38.5%	28.3%	21.4%	16.6%	7.0%	1.6%	559.2	567.7
Spline: hazard scale, 2 knots	94.7%	82.2%	63.3%	47.6%	33.2%	27.6%	24.6%	22.4%	16.6%	9.9%	548.8	560.1
Spline: odds scale, 2 knots	94.9%	82.1%	62.8%	47.9%	34.2%	28.2%	24.7%	22.1%	15.9%	9.8%	549.3	560.6
Spline: normal scale, 2 knots	94.9%	81.3%	62.2%	48.1%	34.7%	28.7%	25.0%	22.2%	15.4%	0.0%	549.9	561.3
Observed data (and long-term estimates at 3, 5 and 10 years)	92.7%	84.0%	64.9%	47.9%	33.7%	26.5%	22.0%	15% (5 – 25%)	5% (1 – 10%)	1% (0 – 5%)		

The hazard scale, 2 knots is the best fitting model, however it predicts long-term survival estimates that are greater than the upper plausible values. Similarly, the next best fitting models odds scale, 2 knots and normal scale, 2 knots give implausible long-term estimates. The odds scale, 1 knot and normal scale 1 knot give realistic long-term estimates, therefore the odds scale, 1 knot is selected based on better AIC and BIC when compared to the normal scale, 1 knot.

Paclitaxel ± carboplatin

Figure 53. Paclitaxel ± carboplatin OS and fitted spline models



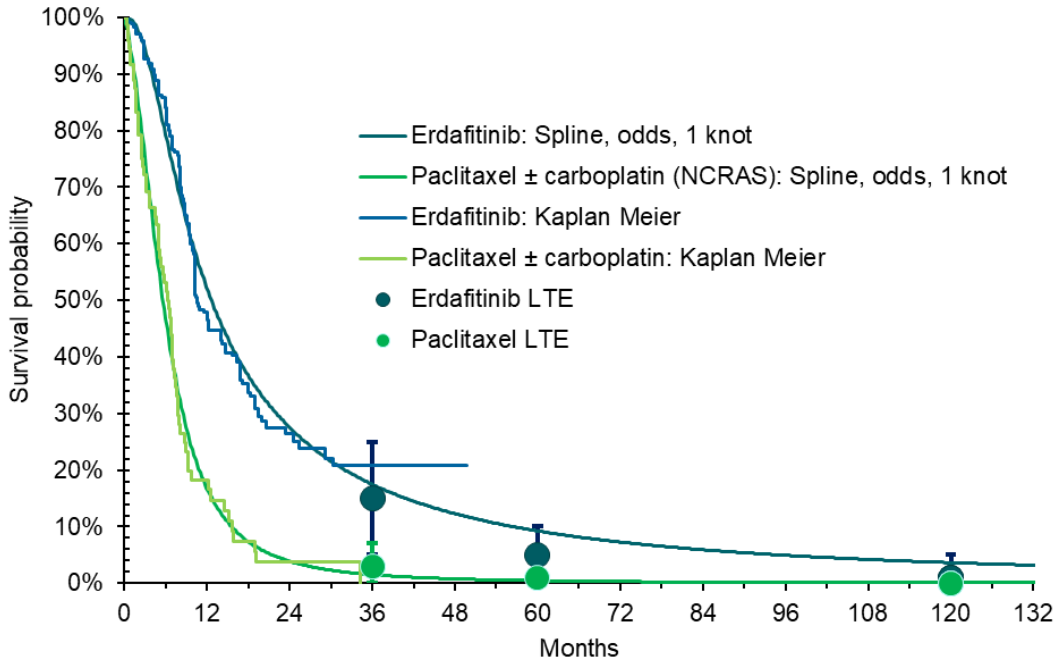
A comparison of the 5 spline curves fitted to the paclitaxel ± carboplatin OS curve is presented in Table 25.

Table 25. Statistical fits and long-term extrapolations for paclitaxel ± carboplatin OS

Model	3m	6m	9m	12m	18m	24m	30m	3-year	5-year	10-year	AIC	BIC
Spline: hazard scale, 1 knot	72.0%	45.7%	28.6%	18.0%	7.2%	2.9%	1.2%	0.5%	0.0%	0.0%	387.3	394.1
Spline: odds scale, 1 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**387.2**	**394.1**
Spline: normal scale, 1 knot	72.3%	45.8%	28.1%	17.3%	6.9%	3.0%	1.4%	0.7%	0.1%	0.0%	386.2	393.0
Spline: hazard scale, 2 knots	72.9%	45.5%	27.9%	17.5%	7.2%	3.2%	1.4%	0.7%	0.0%	0.0%	389.1	398.2
Spline: odds scale, 2 knots	71.5%	47.6%	28.5%	16.2%	5.7%	2.4%	1.2%	0.6%	0.1%	0.0%	387.6	396.7
Spline: normal scale, 2 knots	71.5%	46.7%	29.1%	17.6%	6.6%	2.6%	1.1%	0.5%	0.0%	0.0%	388.0	397.1
Observed data (and long-term estimates at 3, 5 and 10 years)	72.1%	53.0%	23.1%	18.2%	7.3%	3.7%	1.8%	3% (0 – 7%)	1% (0 – 3%)	0% (0 – 1%)		

The best fitting curve is the normal scale, 1 knot, however it predicts very low long-term estimates although within the range deemed appropriate by clinicians. As a conservative assumption, we select odds scale, 1 knot as it predicts higher long-term estimates of survival in patients receiving paclitaxel ± carboplatin.

Figure 54. Overlay of selected OS curves for erdafitinib and paclitaxel ± carboplatin



Time to next treatment

Erdafitinib: Comparison given in Table 26.

Figure 55. Erdafitinib TTNT and fitted spline models

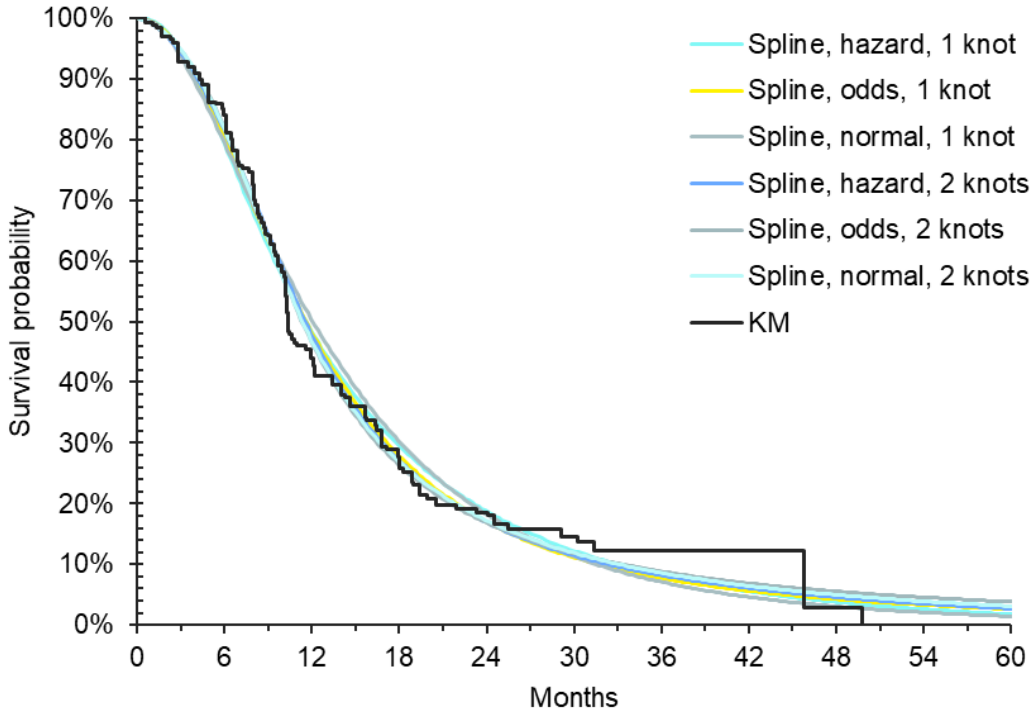


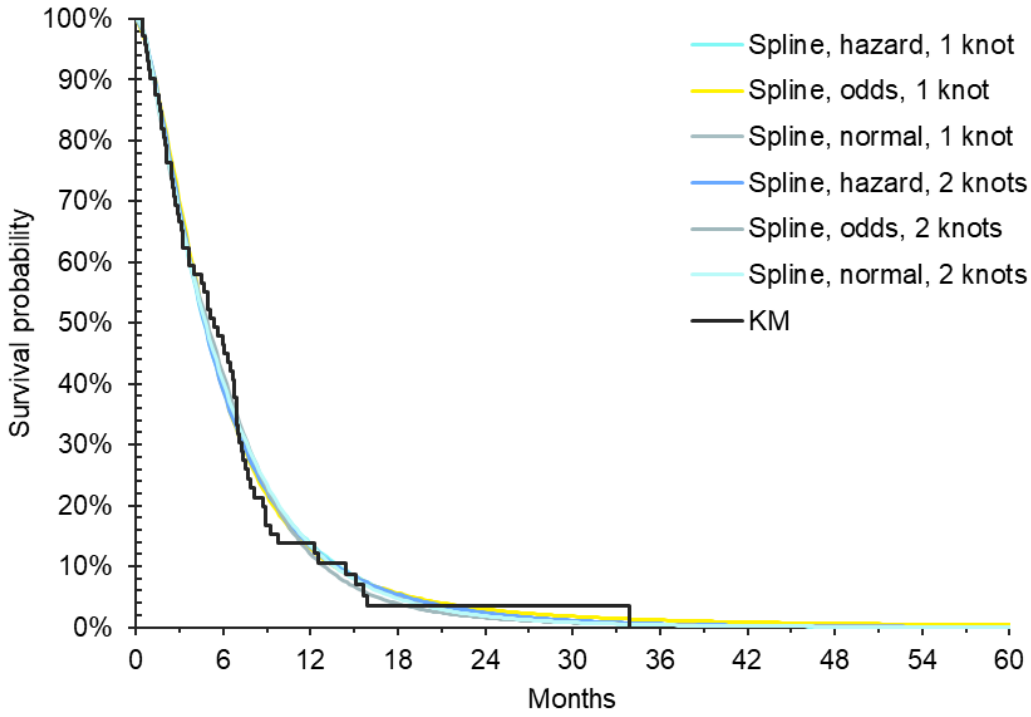
Table 26. Statistical fits for erdafitinib TTNT

Model	3m	6m	9m	12m	18m	24m	30m	3-year	5-year	10-year	AIC	BIC
Spline: hazard scale, 1 knot	94.2%	78.6%	61.9%	48.0%	29.7%	18.7%	12.2%	8.2%	1.8%	0.0%	656.1	664.6
Spline: odds scale, 1 knot	94.1%	79.8%	62.9%	47.9%	28.0%	17.0%	11.1%	7.7%	2.6%	0.6%	655.7	664.2
Spline: normal scale, 1 knot	93.3%	78.8%	63.5%	50.0%	30.4%	18.2%	11.2%	7.1%	1.4%	0.1%	657.7	666.2
Spline: hazard scale, 2 knots	93.9%	80.8%	63.8%	47.5%	27.2%	16.9%	11.5%	8.2%	2.7%	0.3%	655.3	666.6
Spline: odds scale, 2 knots	94.4%	81.3%	63.2%	46.2%	26.5%	16.8%	11.8%	8.8%	3.8%	1.2%	656.0	667.3
Spline: normal scale, 2 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**655.1**	**666.4**
Observed data	92.7%	84.0%	64.1%	44.0%	27.6%	18.6%	14.5%					

The best fitting spline Is normal scale, 2 knots based on statistical fits.

Paclitaxel ± carboplatin

Figure 56. Paclitaxel ± carboplatin TTNT and fitted spline models



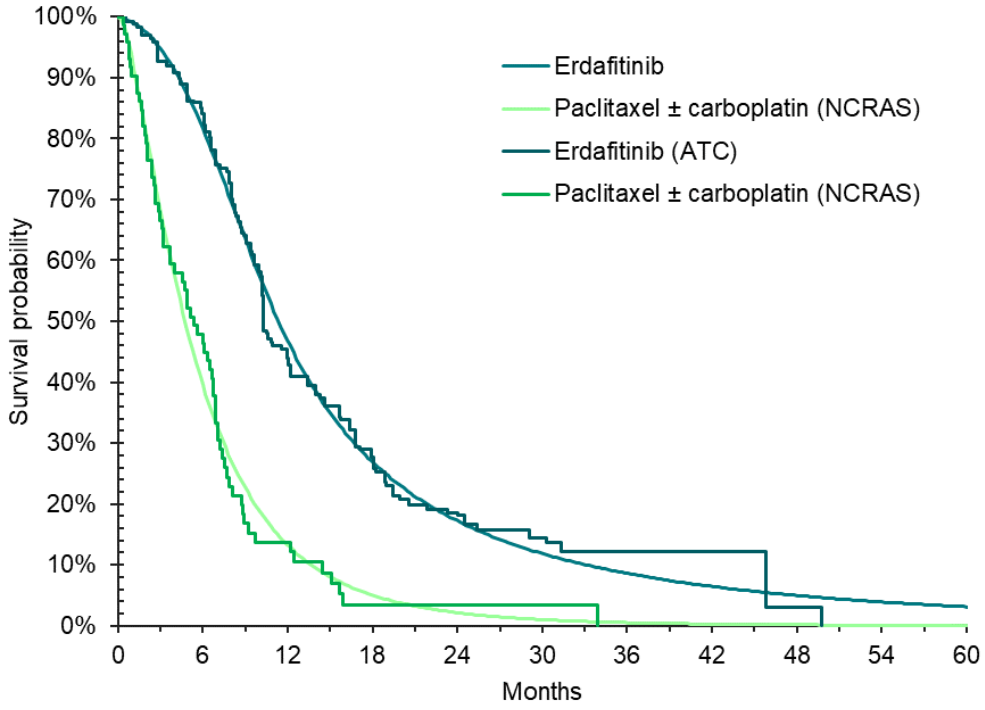
A comparison of the 6 fitted spline curves for paclitaxel ± carboplatin TTNT is presented in Table 27.

Table 27. Statistical fits for paclitaxel ± carboplatin TTNT

Model	3m	6m	9m	12m	18m	24m	30m	3-year	5-year	10-year	AIC	BIC
Spline: hazard scale, 1 knot	67.0%	38.5%	22.5%	13.6%	5.3%	2.2%	0.9%	0.4%	0.0%	0.0%	385.0	391.8
Spline: odds scale, 1 knot	68.8%	38.4%	21.3%	12.7%	5.6%	2.9%	1.8%	1.2%	0.4%	0.1%	384.7	391.5
Spline: normal scale, 1 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**383.7**	**390.5**
Spline: hazard scale, 2 knots	67.6%	38.2%	22.0%	13.3%	5.4%	2.4%	1.1%	0.5%	0.0%	0.0%	386.7	395.8
Spline: odds scale, 2 knots	66.5%	40.8%	22.4%	11.9%	3.8%	1.5%	0.7%	0.4%	0.1%	0.0%	384.7	393.8
Spline: normal scale, 2 knots	66.5%	39.6%	23.0%	13.3%	4.7%	1.8%	0.8%	0.4%	0.0%	0.0%	385.6	394.7
Observed data	66.6%	46.4%	16.8%	13.7%	3.5%	3.5%	3.5%					

The best fitting model is the normal scale, 1 knot based AIC and BIC statistics.

Figure 57. Overlay of selected TTNT curves for erdafitinib (normal scale, 2 knots) and paclitaxel ± carboplatin (normal scale, 1 knot)



Progression free survival

Erdafitinib: Model comparison is presented in Table 28.

Figure 58. Erdafitinib PFS and fitted spline models

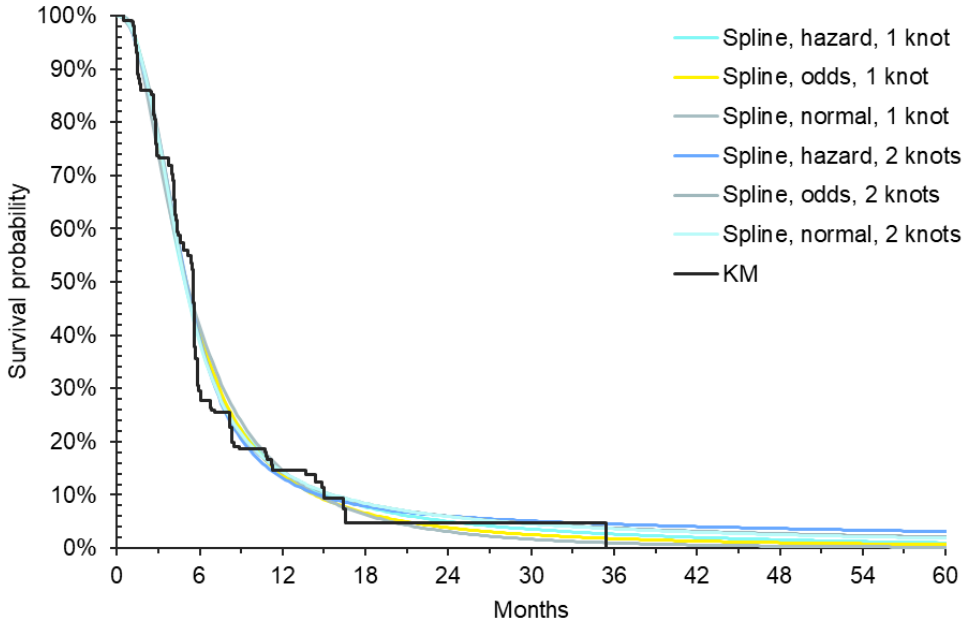
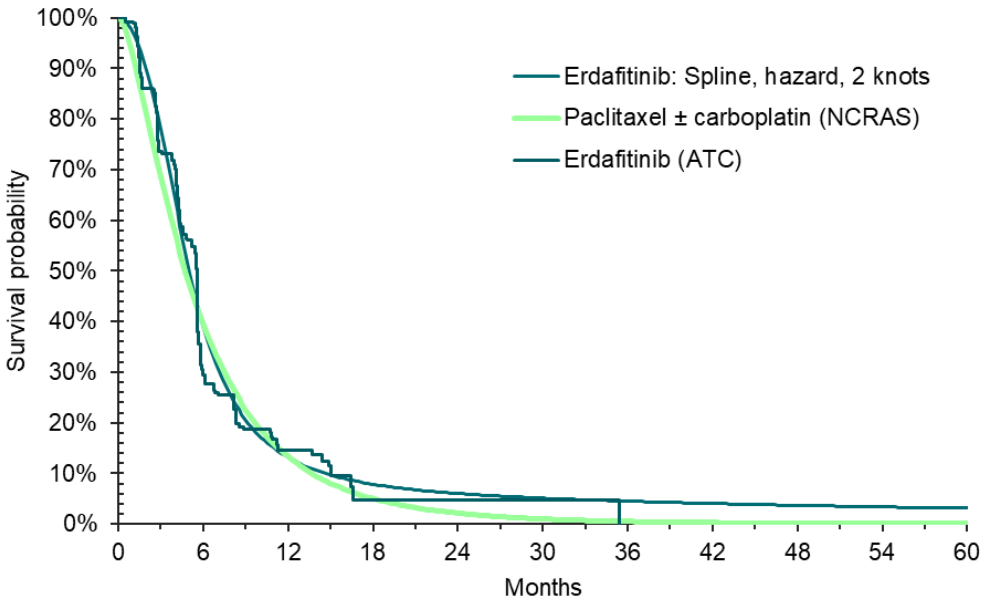


Table 28. Statistical fits for erdafitinib PFS

Model	3m	6m	9m	12m	18m	24m	30m	3-year	5-year	10-year	AIC	BIC
Spline: hazard scale, 1 knot	70.7%	38.7%	22.1%	14.3%	7.7%	5.0%	3.5%	2.6%	1.0%	0.2%	529.7	538.2
Spline: odds scale, 1 knot	71.5%	39.6%	22.0%	13.6%	6.6%	3.8%	2.5%	1.8%	0.7%	0.2%	529.6	538.2
Spline: normal scale, 1 knot	69.8%	40.7%	23.5%	14.4%	6.2%	3.1%	1.7%	1.0%	0.2%	0.0%	531.9	540.4
Spline: hazard scale, 2 knots	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	528.6	539.9
Spline: odds scale, 2 knots	73.5%	37.9%	21.1%	14.1%	8.4%	6.0%	4.6%	3.8%	2.1%	0.9%	529.5	540.9
Spline: normal scale, 2 knots	72.5%	37.6%	21.2%	14.2%	8.4%	5.9%	4.5%	3.6%	1.9%	0.7%	528.9	540.2
Observed data	73.6%	29.5%	18.7%	14.5%	4.8%	4.8%	4.8%					

The best fitting model is the hazard scale, 2 knots based on AIC/BIC statistics. Note that all fits had similar AIC/BIC which suggests that any of the curve can be relied upon.

Figure 59. Overlay of selected PFS curves for erdafitinib and paclitaxel ± carboplatin



PFS for paclitaxel ± carboplatin is assumed to be equivalent to TTNT.

Time to treatment discontinuation

Erdafitinib. Comparison presented in Table 29.

Figure 60. Erdafitinib TTD and fitted spline models

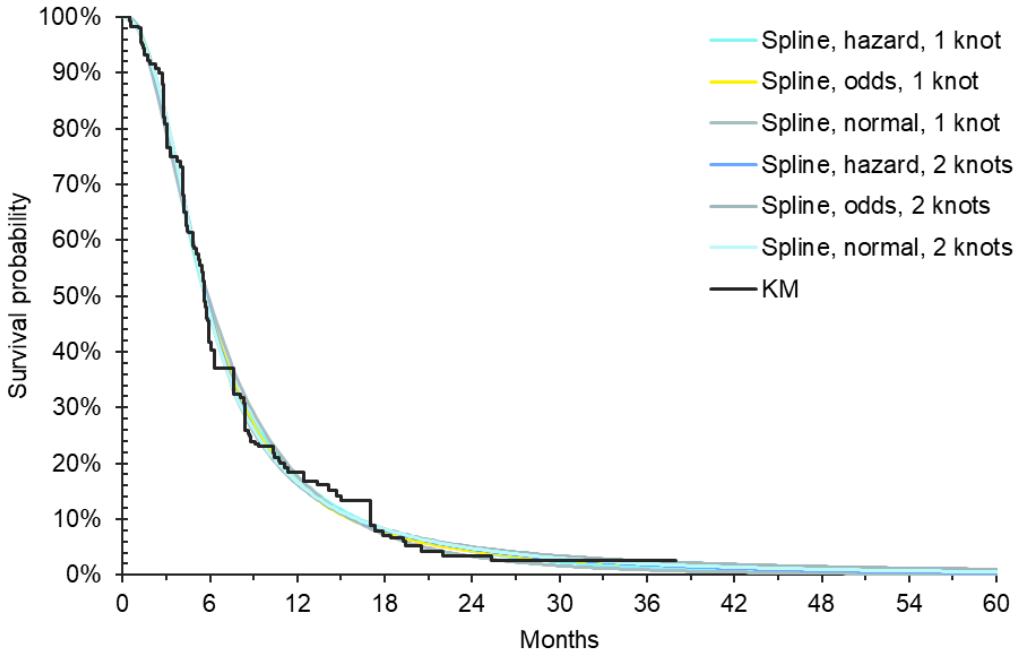
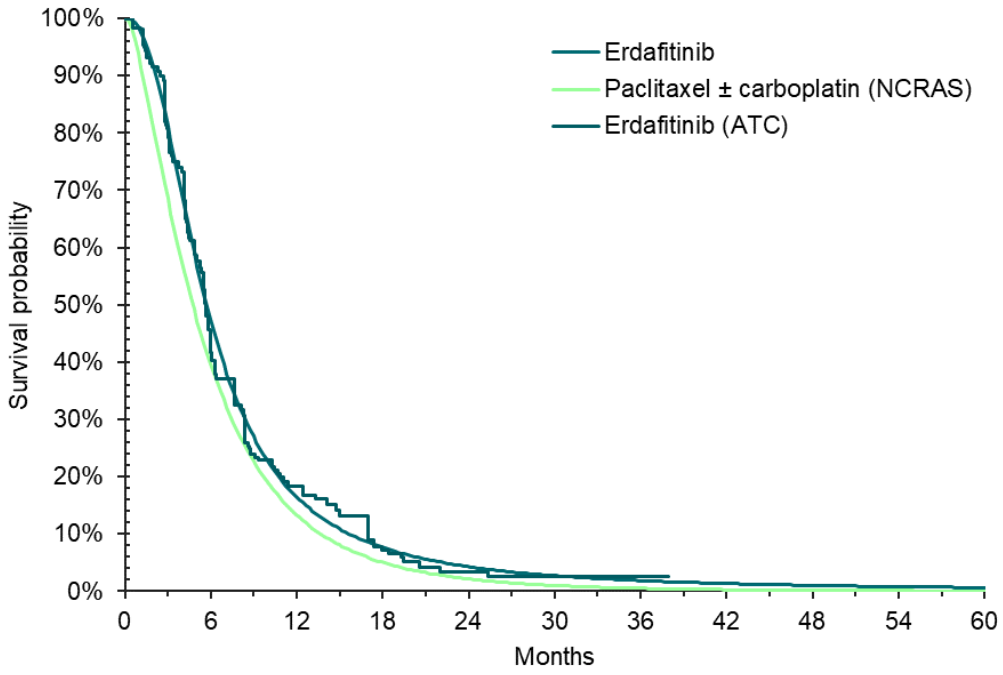


Table 29. Statistical fits for erdafitinib TTD

Model	3m	6m	9m	12m	18m	24m	30m	3-year	5-year	10-year	AIC	BIC
Spline: hazard scale, 1 knot	79.2%	46.0%	27.3%	17.3%	8.1%	4.2%	2.3%	1.3%	0.1%	0.0%	591.7	600.2
Spline: odds scale, 1 knot	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**591.0**	**599.5**
Spline: normal scale, 1 knot	78.3%	48.0%	28.7%	17.6%	7.2%	3.3%	1.6%	0.9%	0.1%	0.0%	593.7	602.2
Spline: hazard scale, 2 knots	80.6%	46.1%	25.8%	16.2%	8.0%	4.6%	2.9%	1.8%	0.4%	0.0%	592.2	603.5
Spline: odds scale, 2 knots	81.0%	45.4%	25.4%	16.1%	8.2%	5.0%	3.4%	2.5%	1.0%	0.3%	592.1	603.4
Spline: normal scale, 2 knots	80.9%	45.4%	25.7%	16.3%	8.2%	4.7%	3.0%	2.0%	0.6%	0.1%	591.5	602.8
Observed data	80.8%	41.7%	23.8%	18.3%	7.1%	3.5%	2.5%					

Based on AIC and BIC statistics, the best fitting curve is the odds scale, 1 knot.

Figure 61. Overlay of selected TTD curves for erdafitinib and paclitaxel ± carboplatin



TTD for paclitaxel ± carboplatin is assumed to be equivalent to the selected PFS curve.

The spline models fit the data well and even better than the standard parametric curves, however some of best fitting curves either overestimate or underestimate long-term estimates based on clinical feedback. We have updated the economic model and provided scenario analyses based on spline models.

Table 30. Company base case assumptions based on spline models

Treatment arm	OS	TTNT	PFS	TTD
Erdafitinib	Odds, 1 knot	Normal, 2 knots	Hazard, 2 knots	Odds, 1 knot
Justification	Gives plausible long-term estimates. 2 knots model gives best stats but not clinically plausible long-term estimates.	Best fitting spline	Best fitting spline	Best fitting spline although all curves are very close
Paclitaxel ± carboplatin (NCRAS)	Odds, 1 knot	Normal, 1 knot	Based on literature, Vaishampayan et al. 2005	Same as PFS

Justification	Gives plausible long-term estimates. All curves very close to each other	Best fitting curve	Based on the best data available	Best

Based on these model choices, the cost-effectiveness results are as shown in Table 31.

Table 31. Cost-effectiveness results based on spline models

	Total outcomes by treatment			**Incremental outcomes**			
	LYs	**QALYs**	**Costs**	**LYs**	**QALYs**	**Costs**	**ICER**
Erdafitinib	1.95	[redacted]	[redacted]				
Paclitaxel ± carboplatin	0.64	0.75	[redacted]	1.31	[redacted]	[redacted]	£21,443

h. The validity of the extrapolations beyond the KM data for both intervention and the comparators was examined using clinical expert estimates at 3 years, 5 years and 10 years. Please also examine the validity of the extrapolations beyond the KM data with supporting evidence that the extrapolations are consistent with relevant external data.

Although no external data suitable for validation is available, we have utilised long-term estimations from prior assessments for chemotherapy and immunotherapies, as well as insights from experts consulted in this appraisal, and experts consulted in prior appraisals. We compare the current predictions generated by the model for erdafitinib and the predictions accepted by the committee from TA692 and TA525, both of which are immunotherapies positioned as second-line treatments for mUC. Table 32 illustrates that the model's projections indicate higher estimates of survival when compared to the two immunotherapies at one year.

This discrepancy aligns with the higher median overall survival observed in the THOR trial, which reported a median overall survival of 12.1 months. All the

long-term projections are consistent with the clinical consensus from clinical experts for the current submission and also clinical experts who provided estimates in previous appraisals. Furthermore, beyond the initial year, the model predicts lower survival estimates. This aligns with the assessment made by clinicians that the prolonged survival tail typically observed with immunotherapies may not be present with erdafitinib. Furthermore, it is worth mentioning that the patients included in our submission have likely undergone more extensive prior treatments and are situated further along the treatment pathway, as they have already received immunotherapy. In contrast, the patients included in TA525 and TA692 would have only received chemotherapy and not been exposed to any form of immunotherapy.

Table 32. Erdafitinib versus immunotherapies from previous appraisals

	1yr	**2yrs**	**3yrs**	**5yrs**	**10yrs**	**20yrs**	**30yrs**	**35yrs**
Erdafitinib (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pembrolizumab (TA692)	44.5%	27.9%	20.2%	10.6%	4.4%	1.9%	1.1%	0.9%
Atezolizumab (TA525)	36.9%	20.7%	13.1%	7.7%	2.7%	0.7%		
Expert opinion (TA525)			10-20%	5-10%	0-5%			
Erdafitinib expert opinion			15% (5-25)	5% (1-10)	1% (0-5)			

J&J also assess the plausibility of our comparator estimates using the two taxanes (docetaxel and paclitaxel) from TA692 and TA525 (

Table 33). Long-term estimates are in line with expert opinion for this appraisal and previous appraisal experts' opinions. Our model estimates lower estimates compared to those obtained in the two appraisals since the patients included in our analysis are presumably at a more advanced stage in the treatment pathway. It is certain that our patients have already received immunotherapy, whereas the patients in the other submissions have only undergone chemotherapy and have not been exposed to any form of immunotherapy.

Table 33. Paclitaxel ± carboplatin versus chemotherapies in previous appraisals

	1yr	2yrs	3yrs	5yrs	10yrs	20yrs	30yrs	35yrs
Paclitaxel ± carboplatin (log-logistic)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Taxanes (TA692)	24.6%	10.4%	6.2%	3.3%	1.4%	0.6%	0.4%	0.3%
Taxanes (TA525)	28.9%	9.8%	5.2%	2.0%				
Expert opinion (TA530)				2-3%	1-2%			
Erdafitinib expert opinion			3% (0-7)	1% (1- 3)	0% (0-1)			

Taxanes: Docetaxel and paclitaxel

i. Although the standard parametric curves show a lesser degree of conformity with the observed data when compared to the spline curves, they still provide adequate forecasts for long-term survival. The cost-effectiveness findings are primarily influenced by the tail end of the distribution. Model selection was guided by factors including hazard functions, statistical fits, visual inspection, and, importantly, the long-term estimates. In the case of the comparator arm, particular attention is placed on clinical plausibility, as numerous well-fitting models yield lower survival probabilities for both spline and parametric curve fitting.

B9. Priority question: Due to the absence of PFS data for paclitaxel ± carboplatin in the UK RW mUC study, the company used the ratio of PFS to TTNT per cycle for erdafitinib to derive a PFS extrapolation for paclitaxel ± carboplatin. In addition, as TTD for paclitaxel ± carboplatin was also not available from the UK RW mUC study, a simplifying assumption was made that TTD for paclitaxel ± carboplatin would be equivalent to the generated PFS.

a. Please define PFS, TTNT and TTD and provide details of how these endpoints were used to inform the economic model.

b. Please justify why the ratio of PFS to TTNT per cycle for erdafitinib was used to derive the PFS extrapolation for paclitaxel ± carboplatin, elaborate on the appropriateness and potential implications of this assumption, supported by comprehensive references and literature.

c. Please elaborate on how the estimated PFS for paclitaxel ± carboplatin using the current approach (ratio of PFS to TTNT per cycle for erdafitinib) compares to the PFS of paclitaxel monotherapy from the PLUTO trial and the PFS of the chemotherapy arm from the THOR trial (i.e. comment on the plausibility that PFS for paclitaxel monotherapy (PLUTO) and vinflunine and docetaxel (THOR) are better than paclitaxel ± carboplatin PFS in the company's base-case.

d. Please provide alternative scenario analyses, as well as an updated economic model, to inform PFS for paclitaxel ± carboplatin, at least including:

i. Using paclitaxel ± carboplatin TTNT as a proxy for paclitaxel ± carboplatin PFS.

ii. using external data to inform paclitaxel ± carboplatin PFS.

e. Please comment on the suitability of the analyses provided in d) compared to the current approach in the company base-case.

f. Please justify the assumption that TTD for paclitaxel ± carboplatin would be equivalent to the generated PFS, elaborate on appropriateness and potential implications of this assumption, supported by comprehensive references and literature.

g. Please provide alternative scenario analyses, as well as an updated economic model, to inform TTD for paclitaxel ± carboplatin, at least including:

i. Assuming similar TTD for erdafitinib and paclitaxel ± carboplatin.

ii. Using external data to inform paclitaxel ± carboplatin TTD.

h. Please comment on the suitability of the analyses provided in g) compared to the current approach in the company base-case.

a. PFS was defined according to the THOR trial protocol as the duration from the date of randomisation to the date of disease progression (or relapse from

complete response) assessed per RECIST v1.1 by the investigator or death, whichever is reported first. It was used in the model to determine the proportion of the cohort remaining in the progression-free health state over time in the model. It was also used to inform the proportion of the cohort remaining on treatment for comparators for which TTD data were not available.

TTNT was defined as the time from randomisation (THOR) or initiation of treatment (NCRAS) to the earliest of death, movement to a new line of therapy, censoring or the end of the study period. It was used in the model to approximate the PFS of paclitaxel ± carboplatin by assuming the relationship between PFS risk and TTNT risk of paclitaxel ± carboplatin would be the same as that of erdafitinib. In the updated model, an option to set PFS equal to TTNT has also been added.

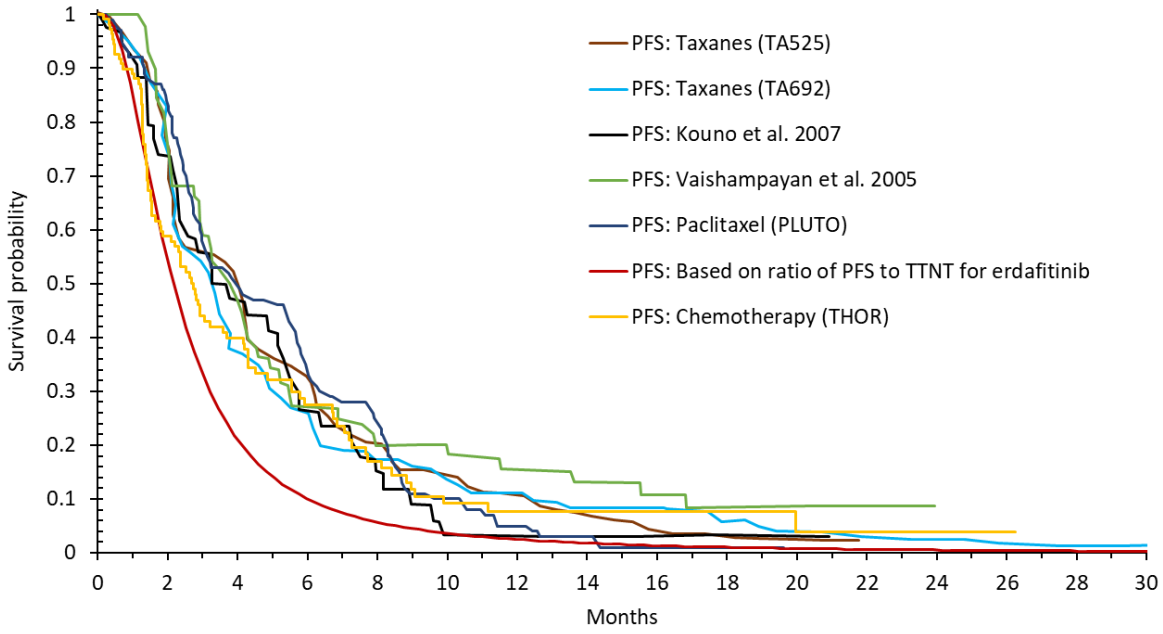
TTD was defined as the duration from the date of randomisation to the date of decision to discontinue treatment or death, whichever is reported first. It was used to inform the proportion of the cohort remaining on treatment over time in the model.

b. Given that the TTNT curves for both erdafitinib and paclitaxel ± carboplatin were close to the OS curves, we deemed it inappropriate to use TTNT as a proxy for PFS for paclitaxel ± carboplatin, as the median TTNT was also higher than the median PFS for erdafitinib. Therefore, a simplifying assumption was made to use the ratio of PFS to TTNT risk per cycle for erdafitinib to derive a PFS extrapolation for paclitaxel ± carboplatin. The median PFS from the derived curve is about 1.5 months which is lower than the median PFS of 4 months observed in some trials. This was a reasonable choice as we deemed non-trial patient population to be less fit and therefore progressing quicker than patients recruited in clinical trials.

c. The comparison of PFS curves for paclitaxel ± carboplatin (based on the ratio of PFS to TTNT per cycle for erdafitinib), literature curves, paclitaxel monotherapy (PLUTO) and vinflunine and docetaxel (THOR) are shown in Figure 62. These results show consistency in the curves from clinical studies. From a visual inspection, the chosen option is reasonable but clearly an outlier.

There is no evidence to justify its selection apart from being a more conservative approach leading to shorter treatment times in the population.

Figure 62. PFS curves for paclitaxel ± carboplatin (based on the ratio of PFS to TTNT per cycle for erdafitinib), paclitaxel monotherapy (PLUTO), chemotherapy (THOR) and literature curves



Taxanes: docetaxel and paclitaxel

Clinical evidence sourced from literature shows that the median PFS is about 4 months in trial settings (Table 34).

Table 34. PFS for paclitaxel monotherapy or in combination with carboplatin clinical trials

Study	Study design	Comparator	Patients randomised	Overall survival, Months (95% CI)	Progression-free survival, Months (95% CI)
Sridhar et al., 2020[22]	OL, randomized, phase 2 study	Paclitaxel	100	8.8 (6.1 – 10.6)	3.0 (2.1 – 4.4)
Jones et al., 2017[23] (PLUTO)	OL, randomized, phase 2 study. (PLUTO)	Paclitaxel	65	8.0 (6.9 – 9.7)[#]	4.1 (3.0 – 5.6)[#]
Lee et al., 2012[24]	OL, randomised, phase 2 study	Paclitaxel	37	6.5 (5.0 – 8.0)	2.7 (0.9 – 4.6)
Kouno et al. 2007[25]	Single arm phase 2 study	Paclitaxel ± carboplatin	35	5.0	3.8

Vaishampayan et al. 2005[26]	Single arm phase 2 study	Paclitaxel ± carboplatin	44	6.0 (5.0 – 8.0)	4.0 (3.0 – 5.0)
Matsubara et al., 2023[27]	OL, group sequential, phase 3 study (EV-301)	Docetaxel, Paclitaxel	50	10.6 (7.8 – 11.8)	5.4 (NR)
Bellmunt et al., 2017[28] and TA692[29 28]	OL, randomized, phase 3 study (KEYNOTE-045)	Docetaxel, Paclitaxel	182	7.0 (5.5 – 8.7)	3.3 (2.3 – 3.5)
Powles et al., 2018[30] and TA525[12, 30]	OL, randomized, phase 3 study (IMvigor211)	Docetaxel, Paclitaxel	214	7.5 (6.7 – 8.6)	3.7 (2.2 – 4.1)

#80% confidence interval (CI); NR: not reported

d. Please provide alternative scenario analyses, as well as an updated economic model, to inform PFS for paclitaxel ± carboplatin, at least including:

i. We use the paclitaxel ± carboplatin TTNT as a proxy for paclitaxel ± carboplatin PFS (Table 35).

Table 35. PFS for paclitaxel ± carboplatin given by paclitaxel ± carboplatin TTNT

	Total outcomes by treatment			**Incremental outcomes**			
	LYs	**QALYs**	**Costs**	**LYs**	**QALYs**	**Costs**	**ICER**
Erdafitinib	1.66	[redacted]	[redacted]				
Paclitaxel ± carboplatin	0.73	0.85	[redacted]	0.93	[redacted]	[redacted]	£27,156

ii. We use the PFS for paclitaxel ± carboplatin from Vaishampayan et al. 2005[26] as a scenario and also the PFS for paclitaxel monotherapy from the PLUTO trial as a proxy for PFS for paclitaxel ± carboplatin (NCRAS).[23] Note that TTD for paclitaxel ± carboplatin will be assumed to the same as the respective PFS curve chosen. The results are presented in Table 36 and Table 37, respectively.

Table 36. PFS for paclitaxel ± carboplatin given by Vaishampayan et al. 2005[26]

	Total outcomes by treatment	**Incremental outcomes**

	LYs	QALYs	Costs	LYs	QALYs	Costs	ICER
Erdafitinib	1.66	[redacted]	[redacted]				
Paclitaxel ± carboplatin	0.73	0.85	[redacted]	0.93	[redacted]	[redacted]	£26,490

Table 37. PFS for paclitaxel ± carboplatin given by paclitaxel monotherapy (PLUTO)

	Total outcomes by treatment			Incremental outcomes			
	LYs	QALYs	Costs	LYs	QALYs	Costs	ICER
Erdafitinib	1.66	[redacted]	[redacted]				
Paclitaxel ± carboplatin	0.73	0.85	[redacted]	0.93	[redacted]	[redacted]	£27,440

e. The choice of the PFS from literature is plausible, especially PFS for paclitaxel ± carboplatin from Vaishampayan et al. 2005[26]. The company base case of assuming the ratio of PFS to TTNT for erdafitinib (giving a median PFS of 1.5 months which is lower than 4.0 months observed from clinical studies) is more reasonable and may not reflect reality, therefore we propose to change the selection of PFS for paclitaxel ± carboplatin to the curve derived from literature.

f. TTD of paclitaxel ± carboplatin was based on its respective PFS curve because it was assumed that treatment would continue until disease progression or unacceptable toxicity. In TA530, treatment with paclitaxel was assumed to stop after 24 weeks (if treatment was not discontinued yet), which was deemed to represent the clinical use of paclitaxel in the UK.[23] In TA692, treatment durations of the platinum agents were limited to 6 cycles (5 months).

g. Please provide alternative scenario analyses, as well as an updated economic model, to inform TTD for paclitaxel ± carboplatin, at least including:

    i. Assuming similar TTD for erdafitinib and paclitaxel ± carboplatin.

Table 38. Similar TTD for erdafitinib and paclitaxel ± carboplatin

	Total outcomes by treatment			Incremental outcomes			
	LYs	**QALYs**	**Costs**	**Lys**	**QALYs**	**Costs**	**ICER**
Erdafitinib	1.66	[redacted]	[redacted]				
Paclitaxel ± carboplatin	0.73	0.86	[redacted]	0.93	[redacted]	[redacted]	£26,036

ii. Using external data to inform paclitaxel ± carboplatin TTD (TA525[12]).

Table 39. Data from TA525 to inform paclitaxel ± carboplatin TTD

	Total outcomes by treatment			Incremental outcomes			
	LYs	**QALYs**	**Costs**	**LYs**	**QALYs**	**Costs**	**ICER**
Erdafitinib	1.66	[redacted]	[redacted]				
Paclitaxel ± carboplatin	0.73	0.86	[redacted]	0.93	[redacted]	[redacted]	£30,676

h. Assuming equivalence of PFS and TTD is plausible given that treatment continue until disease progression or unacceptable toxicity. This can be improved by including a hard stop at 24 weeks if patients are still on treatment to align with UK clinical practice.

B10. Priority question: Paclitaxel ± carboplatin was modelled as a basket of paclitaxel monotherapy and paclitaxel in combination with carboplatin, weighted 3:1, respectively, in line with NCRAS estimates. Outcomes for this basket were reported in section 3.3 of the CS. Please also provide the outcomes (i.e. OS, PFS, TTD, TTNT) separately for paclitaxel monotherapy and paclitaxel in combination with carboplatin.

Outlined below are the outcomes of treatment with paclitaxel monotherapy and paclitaxel + carboplatin. Individually, each treatment option has a relatively small sample size, especially for paclitaxel + carboplatin alone which explores just 18

patients. Therefore, the base case incorporated a weighted approach to maximise the sample size and provide the most robust analyses. Whilst the hazard ratios differ between the two treatments, the weighted approach provides the best quality evidence for decision making for this appraisal.

Overall survival – Paclitaxel monotherapy

Table 40. Paclitaxel monotherapy baseline characteristics

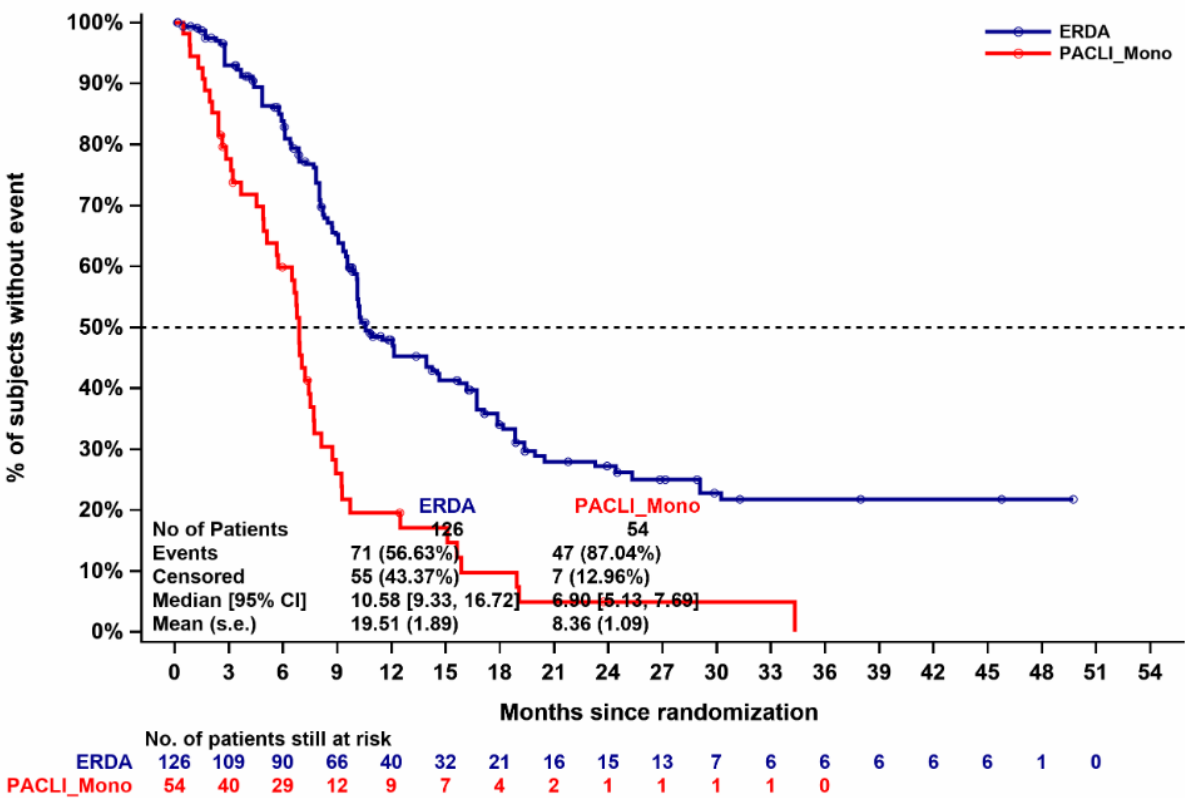
	Erdafitinib (N=126)	**Paclitaxel mono (N=54)**	**Total (N=180)**
Prior lines of treatment			
1	42 (33.3%)	30 (55.6%)	72 (40%)
2	84 (66.7%)	24 (44.4%)	108 (60%)
Age			
<65	69 (54.8%)	24 (44.4%)	93 (51.7%)
>=65	57 (45.2%)	30 (55.6%)	87 (48.3%)
Sex			
Male	89 (70.6%)	40 (74.1%)	129 (71.7%)
Female	37 (29.4%)	14 (25.9%)	51 (28.3%)
Tumor location			
Lower	85 (67.5%)	34 (63%)	119 (66.1%)
Upper	41 (32.5%)	20 (37%)	61 (33.9%)
ECOG			
0	57 (45.2%)	18 (33.3%)	75 (41.7%)
1-2	69 (54.8%)	36 (66.7%)	105 (58.3%)
Stage at diagnosis			
1-2	32 (25.4%)	15 (27.8%)	47 (26.1%)
3-4	94 (74.6%)	39 (72.2%)	133 (73.9%)
Cisplatin ineligible			
No	104 (82.5%)	40 (74.1%)	144 (80%)
Yes	22 (17.5%)	14 (25.9%)	36 (20%)

Table 41. Paclitaxel monotherapy summary results of the ITC (ATC)

	OS HR (95% CI)	p-value
Base case	0.38 (0.25-0.59)	<0.0001

Missing excluded	0.26 (0.14-0.47)	<0.0001

Figure 63. Kaplan-Meier curve for ATC-adjusted OS comparison for erdafitinib versus paclitaxel monotherapy

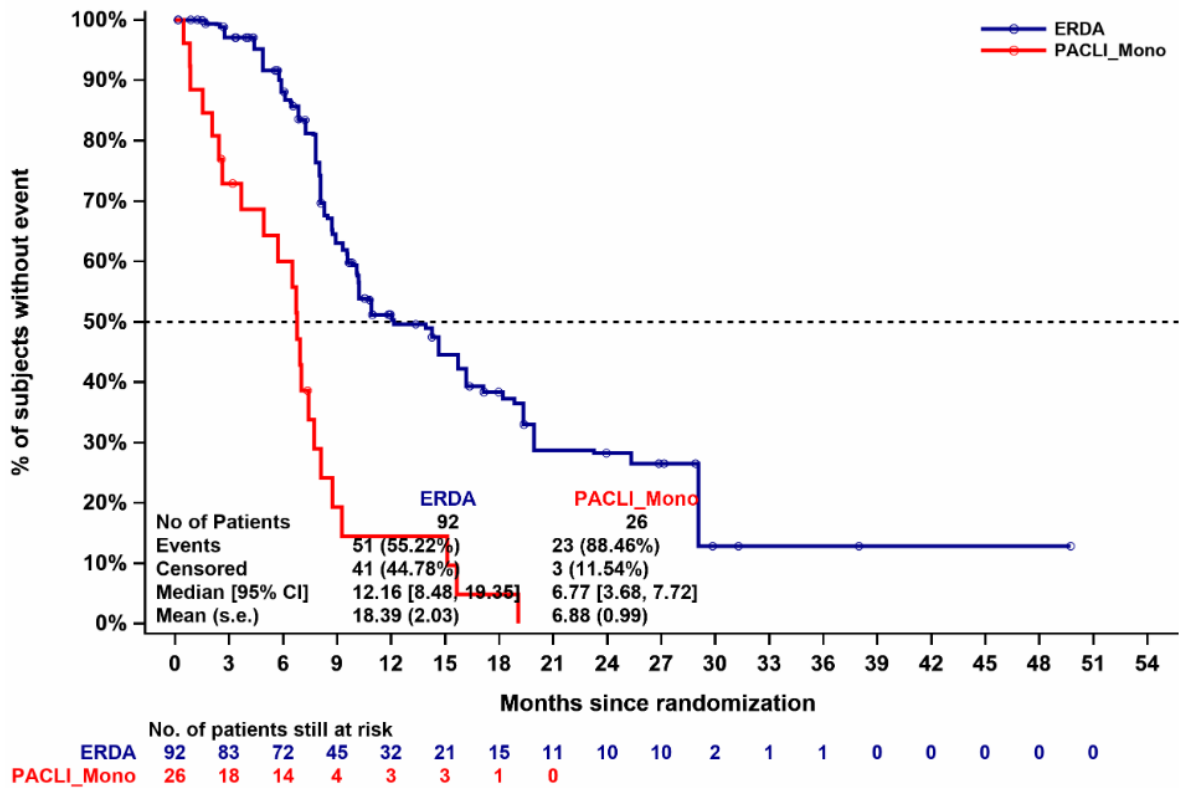


Treatment	Time	Number at risk	Events*	Cum. N of events	Censored patients*	Cum. N of censoring
Erdafitinib	0	126	0	0	0	0
	3	109	8	8	9	9
	6	90	10	18	8	17
	9	66	19	38	4	22
	12	40	17	54	10	31
	15	32	5	60	3	34
	18	21	5	65	6	40
	21	16	4	69	1	41
	24	15	0	69	1	42
	27	13	1	70	1	43
	30	7	1	71	5	48
	33	6	0	71	1	48
	36	6	0	71	0	48
	39	6	0	71	0	49

	42	6	0	71	0	49
	45	6	0	71	0	49
	48	1	0	71	4	53
	51	0	0	71	1	55
Paclitaxel monotherapy	0	54	0	0	0	0
	3	40	12	12	2	2
	6	29	9	21	2	4
	9	12	16	37	1	5
	12	9	3	40	0	5
	15	7	1	41	1	6
	18	4	3	44	0	6
	21	2	2	46	0	6
	24	1	0	46	1	7
	27	1	0	46	0	7
	30	1	0	46	0	7
	33	1	0	46	0	7
	36	0	1	47	0	7

*Number of event and censored patients in the erdafitinib arm are obtained from the re-weighted population and the numbers are rounded to make the table more readable

Figure 64. Kaplan-Meier curve for ATC-adjusted OS comparison for erdafitinib versus paclitaxel monotherapy (excluding missing)



Treatment	Time	Number at risk	Events*	Cum. N of events	Censored patients*	Cum. N of censoring

Erdafitinib	0	92	0	0	0	0
	3	83	3	3	6	6
	6	72	7	10	4	10
	9	45	18	28	8	18
	12	32	8	37	5	23
	15	21	4	40	8	31
	18	15	3	43	3	34
	21	11	4	47	0	35
	24	10	0	47	0	35
	27	10	1	48	0	35
	30	2	3	51	4	39
	33	1	0	51	1	41
	36	1	0	51	0	41
	39	0	0	51	0	41
	42	0	0	51	0	41
	45	0	0	51	0	41
	48	0	0	51	0	41
	51	0	0	51	0	41
Paclitaxel monotherapy	0	26	0	0	0	0
	3	18	7	7	1	1
	6	14	3	10	1	2
	9	4	9	19	1	3
	12	3	1	20	0	3
	15	3	0	20	0	3
	18	1	2	22	0	3
	21	0	1	23	0	3

*Number of event and censored patients in the Erdafitinib arm are obtained from the re-weighted population and the numbers are rounded to make the table more readable

Overall survival – Paclitaxel + carboplatin

Table 42. Paclitaxel + carboplatin baseline characteristics

	Erdafitinib (N=126)	**Paclitaxel + carboplatin (N=18)**	**Total (N=144)**
Prior lines of treatment			
1	42 (33.3%)	6 (33.3%)	48 (33.3%)
2	84 (66.7%)	12 (66.7%)	96 (66.7%)
Age			
<65	69 (54.8%)	10 (55.6%)	79 (54.9%)
>=65	57 (45.2%)	8 (44.4%)	65 (45.1%)
Sex			
Male	89 (70.6%)	14 (77.8%)	103 (71.5%)
Female	37 (29.4%)	4 (22.2%)	41 (28.5%)

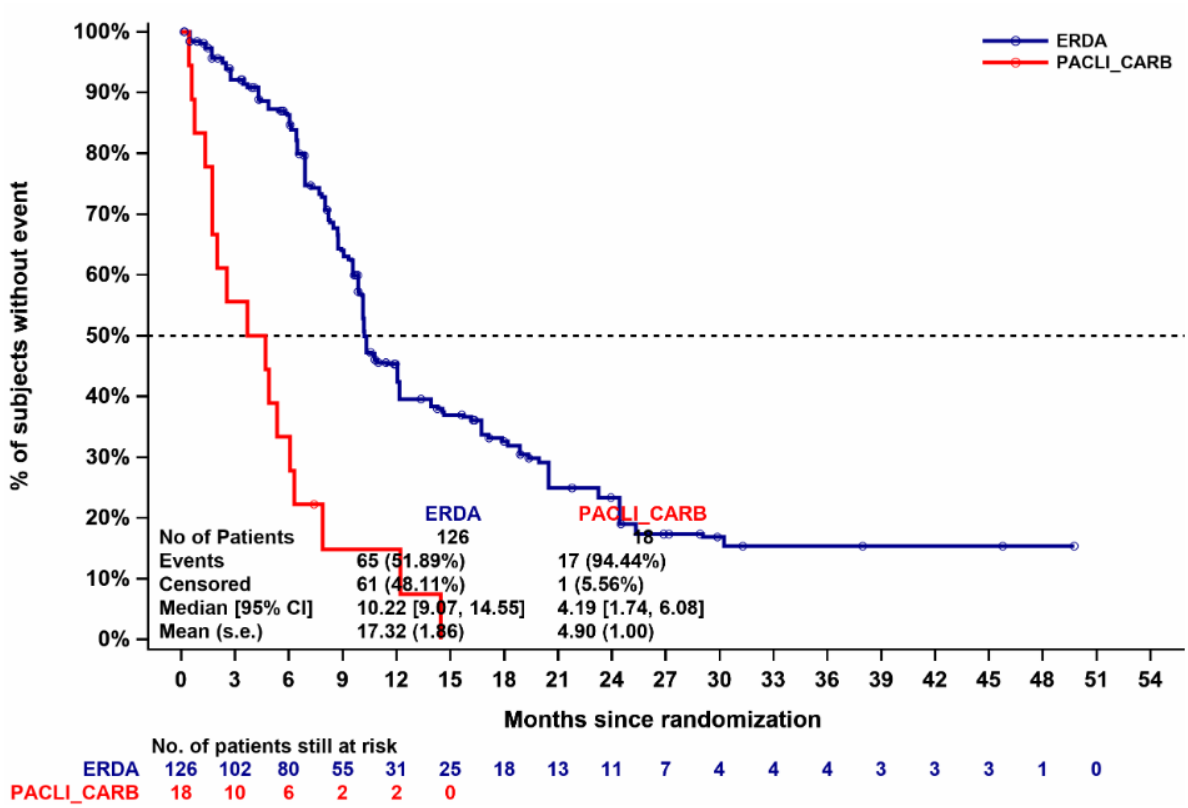
Tumor location			
Lower	85 (67.5%)	11 (61.1%)	96 (66.7%)
Upper	41 (32.5%)	7 (38.9%)	48 (33.3%)
ECOG			
0	57 (45.2%)	3 (16.7%)	60 (41.7%)
1-2	69 (54.8%)	15 (83.3%)	84 (58.3%)
Stage at diagnosis			
1-2	32 (25.4%)	3 (16.7%)	35 (24.3%)
3-4	94 (74.6%)	15 (83.3%)	109 (75.7%)
Cisplatin ineligible			
No	104 (82.5%)	15 (83.3%)	119 (82.6%)
Yes	22 (17.5%)	3 (16.7%)	25 (17.4%)

Table 43. Paclitaxel + carboplatin summary of the ITC (ATC)

	OS HR (95% CI)	p-value
Base case	0.22 (0.11-0.44)	<0.0001
Missing excluded*	NA	NA

*Only 5 patients remained in the paclitaxel + carboplatin after excluding those with missing ECOG PS. Therefore, it was not possible to perform any adjusted analysis.

Figure 65. Kaplan-Meier curve for ATC-adjusted OS comparison for erdafitinib versus paclitaxel + carboplatin



Treatment	Time	Number at risk	Events*	Cum. N of events	Censored patients*	Cum. N of censoring
Erdafitinib	0	126	0	0	0	0
	3	102	9	9	14	14
	6	80	6	15	17	31
	9	55	20	34	5	37
	12	31	15	49	10	46
	15	25	6	55	0	47
	18	18	3	57	4	51
	21	13	4	61	1	52
	24	11	1	62	0	53
	27	7	3	65	2	54
	30	4	0	65	3	57
	33	4	0	65	0	57
	36	4	0	65	0	57
	39	3	0	65	0	57
	42	3	0	65	0	57
	45	3	0	65	0	57
	48	1	0	65	3	60
	51	0	0	65	1	61

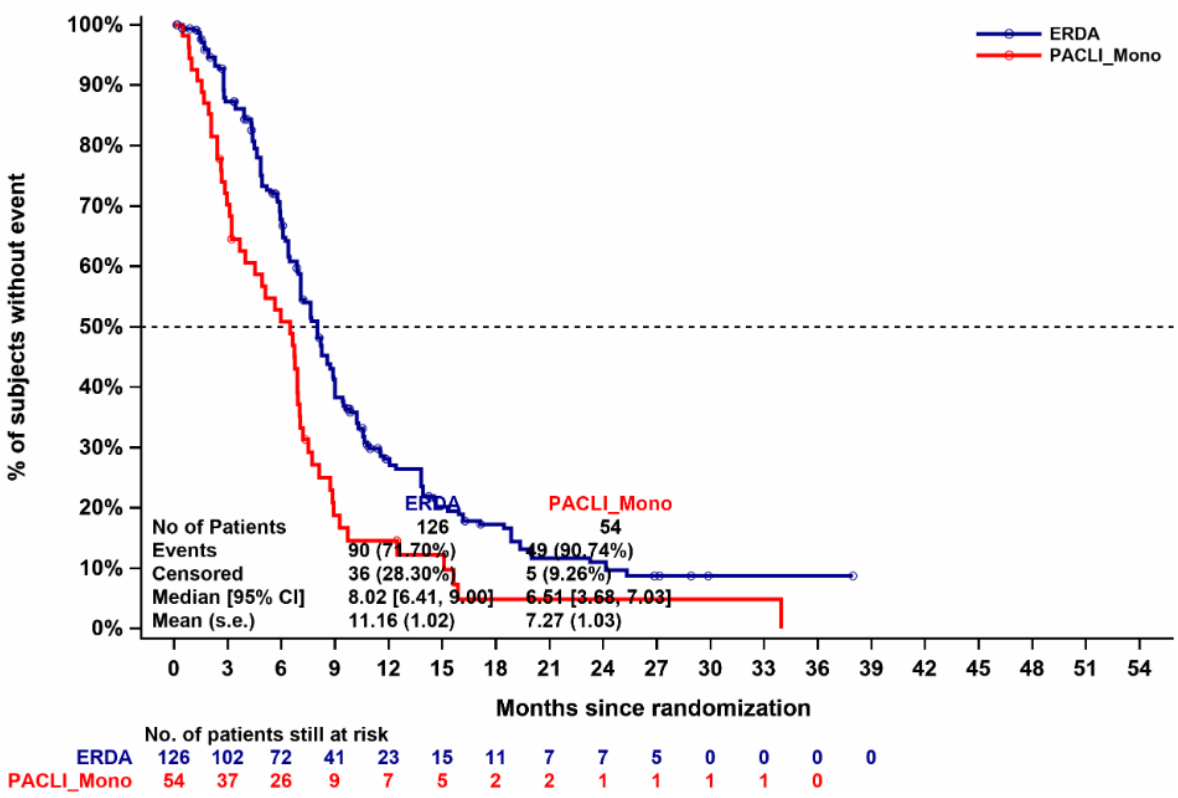
Paclitaxel + carboplatin	0	18	0	0	0	0
	3	10	8	8	0	0
	6	6	4	12	0	0
	9	2	3	15	1	1
	12	2	0	15	0	1
	15	0	2	17	0	1

Time to next treatment – Paclitaxel monotherapy

Table 44. Paclitaxel monotherapy summary results of the ITC (ATC)

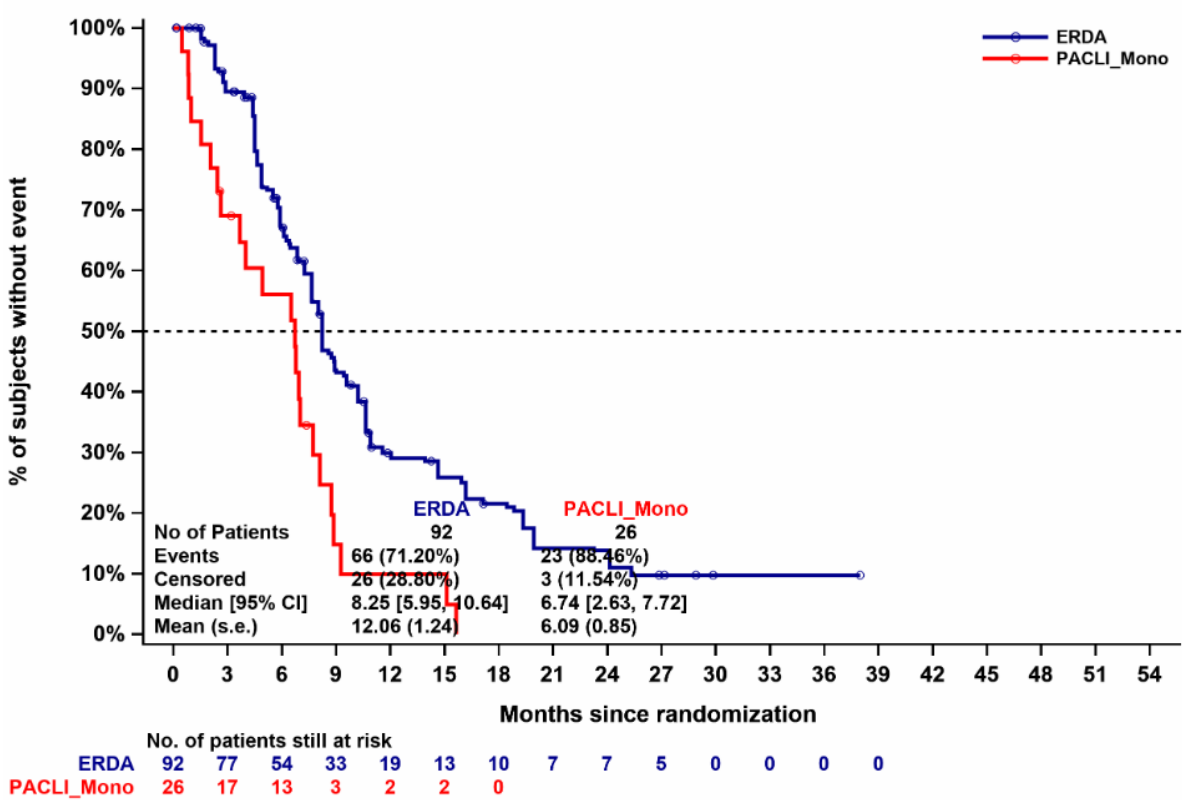
	TTNT HR (95% CI)	p-value
Base case	0.59 (0.39-0.87)	0.0084
Missing excluded	0.44 (0.26-0.73)	0.0016

Figure 66. Kaplan-Meier curve for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel monotherapy



Treatment	Time	Number at risk	Events*	Cum. N of events	Censored patients*	Cum. N of censoring
Erdafitinib	0	126	0	0	0	0
	3	102	15	15	9	9
	6	72	21	37	8	17
	9	41	27	64	3	21
	12	23	12	76	6	27
	15	15	6	83	1	28
	18	11	2	85	2	30
	21	7	4	88	0	30
	24	7	0	89	0	30
	27	5	1	90	0	30
	30	0	0	90	5	35
	33	0	0	90	0	35
	36	0	0	90	0	35
	39	0	0	90	0	36
Paclitaxel monotherapy	0	54	0	0	0	0
	3	37	16	16	1	1
	6	26	10	26	1	2
	9	9	16	42	1	3
	12	7	2	44	0	3
	15	5	1	45	1	4
	18	2	3	48	0	4
	21	2	0	48	0	4
	24	1	0	48	1	5
	27	1	0	48	0	5
	30	1	0	48	0	5
	33	1	0	48	0	5
	36	0	1	49	0	5

Figure 67. Kaplan-Meier curve for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel monotherapy (excluding missing)



Treatment	Time	Number at risk	Events*	Cum. N of events	Censored patients*	Cum. N of censoring
Erdafitinib	0	92	0	0	0	0
	3	77	9	9	6	6
	6	54	19	28	4	10
	9	33	18	46	3	13
	12	19	10	55	5	18
	15	13	2	58	3	21
	18	10	2	60	1	22
	21	7	4	63	0	22
	24	7	0	64	0	22
	27	5	2	66	0	22
	30	0	0	66	4	26
	33	0	0	66	0	26
	36	0	0	66	0	26
	39	0	0	66	0	26
Paclitaxel monotherapy	0	26	0	0	0	0
	3	17	8	8	1	1
	6	13	3	11	1	2
	9	3	9	20	1	3
	12	2	1	21	0	3
	15	2	0	21	0	3

	18	0	2	23	0	3

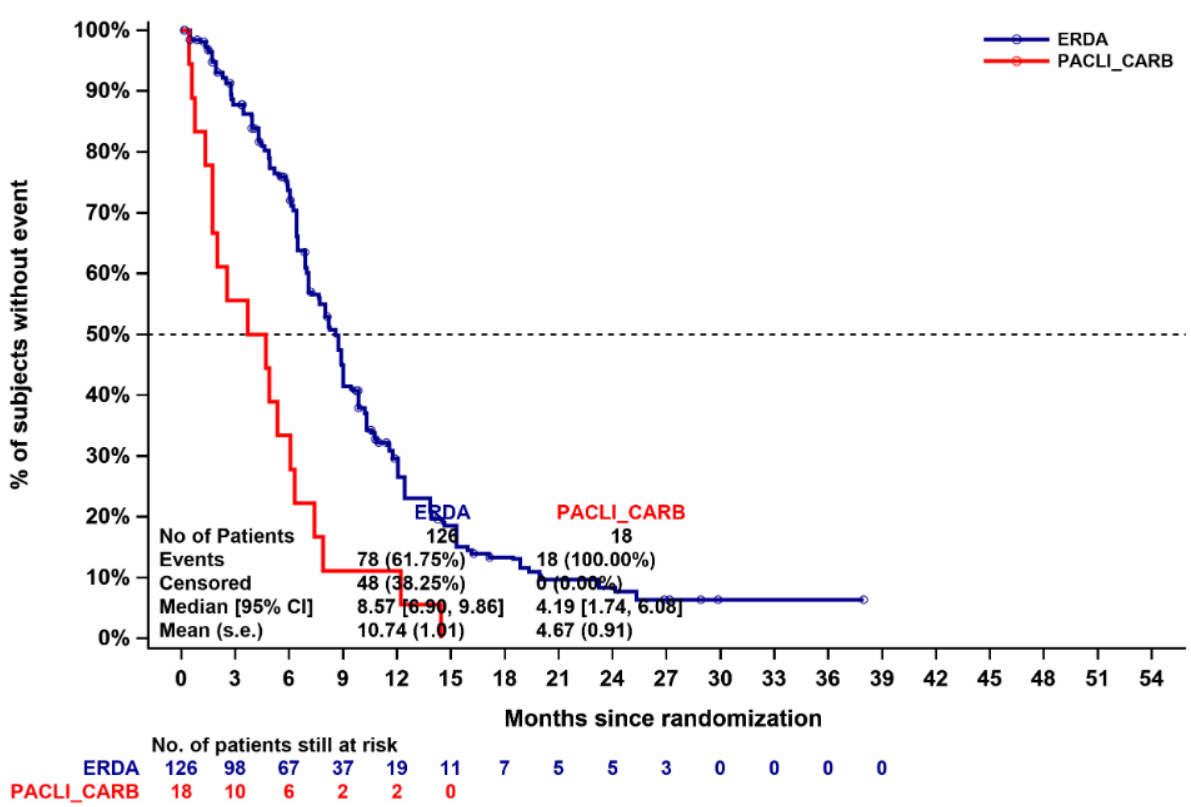
Time to next treatment – Paclitaxel + carboplatin

Table 45. Paclitaxel + carboplatin summary results of the ITC (ATC)

	OS HR (95% CI)	p-value
Base case	0.34 (0.18-0.64)	0.0008
Missing excluded*	NA	NA

*Only 5 patients remained in the Paclitaxel combination after excluding those with missing ECOG PS. Therefore, it was not possible to perform any adjusted analysis.

Figure 68. Kaplan-Meier curve for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel + carboplatin



Treatment	Time	Number at risk	Events*	Cum. N of events	Censored patients*	Cum. N of censoring
Erdafitinib	0	126	0	0	0	0
	3	98	14	14	14	14
	6	67	14	28	17	31

	9	37	25	53	5	36
	12	19	11	64	7	44
	15	11	7	71	0	44
	18	7	3	74	1	45
	21	5	2	76	0	45
	24	5	1	77	0	45
	27	3	1	78	1	45
	30	0	0	78	3	48
	33	0	0	78	0	48
	36	0	0	78	0	48
	39	0	0	78	0	48
Paclitaxel + carboplatin	0	18	0	0	0	0
	3	10	8	8	0	0
	6	6	4	12	0	0
	9	2	4	16	0	0
	12	2	0	16	0	0
	15	0	2	18	0	0

Quality of life

B15. Priority question. EQ-5D data from the THOR trial was used to estimate health state utility values in the economic model.

a. Please provide an overview of the data included, the amount of missing data (per arm and time point), the pattern of missingness, and how missing data were handled.

b. If data imputation was not performed, please provide analyses using imputed data.

c. EQ-5D-5L data were mapped to obtain EQ-5D-3L data. Please provide the details of the mapping procedure.

a. Table 46 provides an overview of EQ-5D-5L questionnaire completion and proportion of missing questionnaires (based on the number of patients expected to provide questionnaires at any time point) up to cycle 21 (approximately day 421), which was the last time point included in the utility analysis. The proportion of missing data is similar in both trial arms and there is no clear pattern over time, even though the absolute number of completed

questionnaires decreases more rapidly in the chemotherapy arm. Missing data were not explicitly imputed.

Table 46. EQ-5D questionnaire completion over time in THOR

Timepoint	Erdafitinib			Chemotherapy		
	Number expected	Number received	Missing (%)	Number expected	Number received	Missing (%)
Cycle 01 Day 1	136	126	7.4%	130	106	18.5%
Cycle 01 Day 14	131	110	16.0%	93	70	24.7%
Cycle 02 Day 1	128	117	8.6%	82	75	8.5%
Cycle 03 Day 1	124	104	16.1%	65	52	20.0%
Cycle 04 Day 1	117	98	16.2%	52	44	15.4%
Cycle 05 Day 1	106	86	18.9%	43	33	23.3%
Cycle 06 Day 1	96	77	19.8%	38	32	15.8%
Cycle 07 Day 1	88	74	15.9%	32	28	12.5%
Cycle 08 Day 1	76	59	22.4%	25	21	16.0%
Cycle 09 Day 1	65	55	15.4%	21	16	23.8%
Cycle 10 Day 1	54	41	24.1%	17	11	35.3%
Cycle 11 Day 1	46	41	10.9%	12	10	16.7%
Cycle 12 Day 1	44	38	13.6%	11	7	36.4%
Cycle 13 Day 1	40	33	17.5%	10	6	40.0%
Cycle 14 Day 1	36	28	22.2%	7	5	28.6%
Cycle 15 Day 1	31	29	6.5%	7	4	42.9%
Cycle 16 Day 1	29	26	10.3%	6	4	33.3%
Cycle 17 Day 1	26	22	15.4%	5	4	20.0%
Cycle 18 Day 1	23	20	13.0%	4	3	25.0%
Cycle 19 Day 1	21	18	14.3%	4	3	25.0%

Cycle 20 Day 1	19	18	5.3%	3	1	66.7%
Cycle 21 Day 1	18	16	11.1%	3	2	33.3%

b. Mixed models for repeated measures impute missing observations implicitly[31, 32]; therefore, no additional imputation was performed.

c. The EQ-5D-5L data was mapped to the EQ-5D-3L using the UK value set before conducting further statistical analyses. The mapping follows the Hernandez-Alava et al. algorithm, following NICE guidance.[33, 34]

B16. Priority question. The linear mixed models used pooled data from both treatment arms, while the comparator arm of the THOR trial included chemotherapy regimens that are not standard of care in the UK (i.e. docetaxel and vinflunine).

a. Please provide the rationale for including both treatment arms to estimate health state utility values, while the comparator arm is not in line with UK clinical practice.

b. Please conduct separate analyses using the linear mixed models for repeated measures for the erdafitinib and chemotherapy arms of the THOR trial and elaborate on the findings.

a. A mixed-effects regression analysis exploring the impact of various predictors on EQ-5D score in THOR has been conducted and it strongly supports the assumption that treatment received (erdafitinib, docetaxel or vinflunine) does not have an effect on utility independently of progression status and baseline performance status (see Table 47).

Table 47: Regression analysis of EQ-5D score in THOR

		Mean	SE	95% CI	p-value
Intercept		0.776	0.020	(0.736, 0.816)	-
Progression status	Progression-free (ref)	-	-	-	-
	Post-progression	−0.108	0.010	(−0.127, -0.089)	< 0.001

Treatment	Erdafitinib (ref)	-	-	-	-
	Docetaxel	0.020	0.029	(−0.038, 0.078)	0.503
	Vinflunine	−0.007	0.034	(−0.074, 0.061)	0.850
Baseline ECOG	0 (ref)	-	-	-	-
	1	−0.121	0.026	(−0.171, −0.070)	< 0.001
	2	−0.399	0.047	(−0.492, −0.306)	< 0.001

b. Pre-progression utilities estimated independently in the erdafitinib, and chemotherapy arms of THOR are presented in Table 48. The estimate for chemotherapy is based on cycles up to 9, as the number of observations is too low to reliably estimate utility at later time points.

Table 48: Pre-progression utility, independent estimates for erdafitinib and chemotherapy

	Erdafitinib	Chemotherapy
EQ-5D score (mean, SE)	0.7505 (0.00211)	0.7039 (0.00204)

B17. Priority question. In the CS it is stated that "*The PF health state utility was based on the area under the curve (AUC) of mean utility estimates for each treatment cycle among patients remaining PF in that cycle. PD state utility was estimated from questionnaires of patients who were known to have progressed (i.e., excluding questionnaires after censoring) using a single MMRM that accounted for correlations between EQ-5D measurements from the same patient*." Please provide detailed methods for the estimation of utility values in the PF and PD health states and elaborate on the different approaches used for obtaining PF (i.e. based on a AUC approach) and PD (i.e. based on a single measurement) utility values.

PD health state utility was estimated from individuals who progressed in THOR (patients censored for PFS were not included), using a standard mixed model for repeated measures (MMRM) that accounted for correlations between EQ-5D measurements from the same patients.

PF utilities were also obtained using MMRMs, but they were estimated for each treatment cycle before progression. At each cycle, a separate MMRM was fitted using information only from patients who stayed progression-free until that time point,

including all their available EQ-5D results up to and including that time point, and using visit as a categorical predictor, to get time-specific utility estimates. From each of these MMRMs, the mean estimate of the last time point was used as the utility estimate for that time point. Each of the MMRMs had a compound symmetry correlation structure, which assumes that variances are homogenous. This means that variability of utility measurements is constant at each cycle. Compound symmetry structure was selected based on the lowest AIC from an MMRM that included all EQ-5D values during PFS. The area under the curve of these time-specific utilities was used as the progression-free utility estimate.

Time-specific utility estimates among progression-free patients are shown in Table 49.

Table 49: Time-specific progression-free utility estimates in THOR

Time	Mean estimate	Standard error
Cycle 01 Day 1	0.6988	0.01765
Cycle 01 Day 14	0.7312	0.01744
Cycle 02 Day 1	0.7038	0.01752
Cycle 03 Day 1	0.7154	0.01887
Cycle 04 Day 1	0.7111	0.01836
Cycle 05 Day 1	0.7130	0.02001
Cycle 06 Day 1	0.7205	0.02102
Cycle 07 Day 1	0.6954	0.02287
Cycle 08 Day 1	0.6817	0.02633
Cycle 09 Day 1	0.7028	0.02873
Cycle 10 Day 1	0.7207	0.02771
Cycle 11 Day 1	0.7365	0.02956
Cycle 12 Day 1	0.7100	0.03184
Cycle 13 Day 1	0.7414	0.03457
Cycle 14 Day 1	0.7028	0.03926
Cycle 15 Day 1	0.6938	0.04131
Cycle 16 Day 1	0.6744	0.04416
Cycle 17 Day 1	0.7021	0.05215
Cycle 18 Day 1	0.7016	0.07155
Cycle 19 Day 1	0.7151	0.07141
Cycle 20 Day 1	0.6902	0.07226

B18. Priority question. In the base case approach, utilities were estimated with linear mixed models for repeated measures, while an alternative approach used a multivariable regression model.

a. Please elaborate on the reasons why the first approach was deemed more appropriate compared to the multivariable regression model.

b. Please elaborate on the face validity of the utility values derived from the linear mixed model approach and the multivariable regression model approach and how they compare to the utility values from other TAs in CS Table 41.

a. The first approach was deemed more appropriate for several reasons. Multivariable models that include baseline characteristics may not be valid for cohort models unless the distribution of those characteristics is tracked over time. It can be expected that over time, as patients progress or die, the distribution of baseline characteristics in the remaining cohort in a health state or among patients entering a new health state will change from the initial values. Therefore, by using initial baseline values in a multivariable model, the results may be biased. It is thus preferable to estimate utilities for use in cohort models without adjusting for such characteristics to reflect the dynamics in real patient cohorts.

   In addition, fitting a joint mixed model for repeated measures for progression-free and progressed health states would mean that a patient's HRQoL prior to progression would influence their estimated utility after progression. This is undesirable especially in the case of patients spending much more time in pre-progression than in post-progression.

   Finally, the first approach was deemed more appropriate as it produced utility values that are very close to those in TA522.

b. As we stated in the CS, page 122, the utility values derived from THOR were similar to those in TA522. However, they were lower than those in TA788. This difference in values could be attributed to variances in the patients' fitness level. In TA788, patients were still undergoing first-line treatment and subsequently

received maintenance therapy. On the other hand, in our trial, patients received erdafitinib as either a second or third-line treatment.

Costs and resource use

B20. Priority question. A dose modifier for erdafitinib was included in the economic model (i.e. 17.07% of missed doses in the THOR trial).

a. Please explain how relative dose intensity was incorporated for the comparators, or, if relative dose intensity was not incorporated, please justify why this was not done.

b. Please provide an updated economic model and scenario analysis including a relative dose intensity for the comparators.

c. Please provide an updated economic model and scenario analysis using the same assumptions for chemotherapy as for erdafitinib regarding the relative dose intensity (i.e. a scenario analysis including 17.07% of missed doses of chemotherapy).

a. Relative dose intensity (RDI) was applied to all comparators within the economic model. The RDI for paclitaxel ± carboplatin was assumed to be equal to the RDI of chemotherapy witnessed in the THOR trial.

b. Not applicable as per Question B.20.a.

c. Whilst there in uncertainty in the rationale for this scenario, adjusting the RDI of the comparator, paclitaxel ± carboplatin, down to the same proportion of missed doses of erdafitinib, adjusts the input value from 98.8% down to 82.9%. The impact of this change is an increase in the ICER of £83.85 per QALY gain. The ICER rises from £26,489.96 to £26,573.80 per QALY gain. RDI is therefore relatively immaterial for decision making.

B21. Priority question. Treatment administration costs have a significant impact on the total costs in the chemotherapy arms.

a. **Please justify why "*first attendance*" costs (SB12Z) were used for all cycles of chemotherapy, while also a subsequent cycle costs are available in the NHS costs (i.e., SB13Z).**

b. **Please provide an updated model using subsequent treatment cycle costs for chemotherapy.**

a. The code SB13Z is for delivery of complex parenteral chemotherapy at first attendance; we assume the question actually refers to SB15Z. That code is used for "subsequent elements of a chemotherapy cycle" rather than for subsequent cycles of chemotherapy. In other words, it applies to any administrations within a cycle that take place after day 1. However, day 1 infusion costs fall under SB12Z or SB13Z code in every treatment cycle.

   As paclitaxel, carboplatin and docetaxel are administered only on day 1 of each cycle, SB15Z cost does not apply to them. The only treatment in the model that this cost is used for is carboplatin plus gemcitabine (as subsequent treatment).

b. In light of the response to a, no update was required.

B22. Priority question. Table 51 in the CS provides details on the health care resources used in the economic model.

a. **Many resource use categories are based on expert opinion; please provide resource use based on literature or other TAs wherever possible.**

b. **Please justify the differences in resource use between erdafitinib and chemotherapy, both pre- and post-progression. For example, why no blood tests are required for erdafitinib, while 3 blood tests every 28 days are required for chemotherapy. Especially, when serum phosphate levels have to be checked in patients receiving erdafitinib after 14-21 days after initiating treatment.**

c. In CS Table 52 the total HCRU costs per cycle per health state are detailed; please explain the differences between the costs for erdafitinib and chemotherapy.

d. Please elaborate on how ophthalmological testing was included in the model and, the potential effect of delays in ophthalmological testing on the cost-effectiveness estimates.

e. Please provide an updated economic model and scenario analysis where resource use for erdafitinib is equal to that of chemotherapy.

a. In our submission, the assessment of medical resource utilisation for urothelial cancers was based on data extracted from previous submissions to NICE, specifically TA272, TA525, TA530, and TA788. Oncologists were then asked to validate these in an advisory board. The frequency of medical resource utilisation documented in the previous appraisals, particularly for mUC, heavily relied on inputs from TA272, which were predominantly based on expert opinions. To obtain pertinent data, we compiled a summary of resource utilisation information from these previous appraisals and sought validation from oncologists in an advisory board.[5] Through their evaluation, certain aspects, such as dietician services and home visits for health purposes, were deemed outdated and no longer necessary. As a result, our aim was to re-evaluate and validate these patterns of utilisation to ensure their current relevance and accuracy. As shown in Table 50, the values used in this submission are largely in line with previous estimates although some cost components incorporated in previous appraisals were deemed irrelevant.

Table 50: HCRU. Italicised text in blue shows components that were deemed not appropriate during the advisory board

Cost component		Paclitaxel ± carboplatin	Source	Erdafitinib	Source
Pre-progression					
Investigations and tests	Blood test	3 every 28 days	Expert opinion	No tests	Expert opinion
		3 times per every 4-week cycle (TA530)			
	CT scan	At least 1 per 3 months	Expert opinion	No scans	Expert opinion
		Every 9 weeks (TA530)	*Advisory board*		
Treatments and procedures	Blood transfusions	1-2 per month for 20-30% patients	Expert opinion	None	Expert opinion
Primary care	GP visits	At least 4-6 per year	Expert opinion	At least 4-6 per year	Expert opinion
	GP home consultation	*1 per month (TA272)*	*Expert opinion*		
		1 per month (TA525)			
		0.26 per month (TA788)	*Expert opinion*		
	Consultant-led oncologist	*0.88 per month (TA788)*	*Expert opinion*		
	Urologist	*0.07 per month (TA788)*	*Expert opinion*		
	Community nurse visits	4 per month	TA272 and expert opinion	4 per month	TA272 and expert opinion
		4 per week (TA272)			
		4 per month (TA525)			
	District nurse	*0.27 per month*	*Expert opinion*		
	Clinical nurse specialist	*0.62 per month (TA788)*	*Expert opinion*		
	Health home visitor	*1 per month (TA272)*	*Expert opinion*		
		1 per month (TA525)			
	Dietician	*1 per month (TA272)*	*Expert opinion*		
		1 per month (TA525)			
		0.06 per month (TA788)	*Expert opinion*		
Secondary care	A&E visits	2 per year	Johnson & Johnson RWE	2 per year	Johnson & Johnson RWE
	Outpatient visits	3 per month	Expert opinion	1.5 per month	Expert opinion

Cost component		Paclitaxel ± carboplatin	Source	Erdafitinib	Source
	Inpatient visits	4 per year	Johnson & Johnson RWE	4 per year	Assumed to be similar to chemotherapy
Post-progression					
Investigations and tests	Blood test	1 per 6 weeks	Expert opinion	No tests	Expert opinion
	CT scan	No scans as on best supportive care	Expert opinion	No scans	Expert opinion
Treatments and procedures	Blood transfusions	None	Expert opinion	None	Expert opinion
	Palliative radiotherapy	Once for 9.3% of patients	TA530 (originally from CheckMate 275)	Once for 9.3% of patients	TA530 (originally from CheckMate 275)
	Interventional radiology	Once for 3.3% of patients (*also TA272*)	TA530 (originally from CheckMate 275)	Once for 3.3% of patients	TA530 (originally from CheckMate 275)
Primary care	GP visits	2 per month	Expert opinion	2 per month	Expert opinion
	GP home consultation	*1 per month (TA272)*	*Expert opinion*		
		1 per month (TA525)			
		0.72 per month (TA788)	*Expert opinion*		
	Consultant-led oncologist	*0.93 per month (TA788)*	*Expert opinion*		
	Urologist	*0.04 per month (TA788)*	*Expert opinion*		
	Community nurse visits	4 per month	TA272 and Expert opinion	4 per month	TA272 and Expert opinion
		4 per month (TA272)	*Expert opinion*		
		4 per month (TA525)			
	District nurse	*0.96 per month (TA788)*	*Expert opinion*		
	Clinical nurse specialist	*1 per month (TA788)*	*Expert opinion*		
	Health home visitor	*1 per month (TA272)*	*Expert opinion*		
		1 per month (TA525)			
	Dietician	*1 per month (TA272)*	*Expert opinion*		
		1 per month (TA525)			
		0.16 per month (TA788)	*Expert opinion*		

Cost component		Paclitaxel ± carboplatin	Source	Erdafitinib	Source
Secondary care	A&E visits	2 per year	Johnson & Johnson RWE	2 per year	Assumed to be similar to chemotherapy
	Outpatient visits	1 per month	Expert opinion	1 per month	Expert opinion
	Inpatient visits	4 per year	Johnson & Johnson RWE	4 per year	Assumed to be similar to chemotherapy
Key: CT, computed tomography; GP, general practitioner; HCRU, healthcare resource use; RWE, real-world evidence.					

With the hospitalisations, clinicians mentioned that it would be useful to distinguish between SACT complications and complications of their cancer. We assumed 50% will be complications of cancer with the cost of SACT complications covered by AE costs.

b. A single blood test is required on day 14 of cycle 1 to determine serum phosphate concentration. We have added a one-off cost for a blood test for patients who receive erdafitinib in the model.

c. The difference between erdafitinib and chemotherapy costs are given in Table 51 (now updated with the correct frequency of inpatient admissions). The discrepancy observed prior to disease progression can be attributed to a lower number of outpatient visits among patients receiving erdafitinib in comparison to those receiving paclitaxel ± carboplatin. Clinicians suggested that prior to disease progression, patients on chemotherapy would visit the outpatient department 3 times per month while those on erdafitinib would come once for collection of the drugs, with a proportion of patients (~30%) requiring an extra appointment for toxicity check, averaging about 1.5 outpatient visits per month on those receiving erdafitinib. The costs per treatment cycle for erdafitinib were assumed equivalent to those for chemotherapy after disease progression. It is important to note that this assumption is conservative since patients receiving erdafitinib have been shown to experience prolonged survival compared to those on chemotherapy, indicating potential improvements in overall health. Consequently, this could potentially lead to reduced requirements for ongoing disease management following disease progression.

Table 51: Differences in HCRU costs for erdafitinib and chemotherapy per cycle per health state

Resource	Erdafitinib				Paclitaxel ± carboplatin			
	% use	Amount	Frequency (every X months)	Cost per cycle	% use	Amount	Frequency (every X months)	Cost per cycle
Pre-progression								
GP visit	100.0%	6.0	[redacted]	[redacted]	100.0%	6.0	[redacted]	[redacted]
District nurse	100.0%	4.0			100.0%	4.0		
A&E visit	100.0%	2.0			100.0%	2.0		
Outpatient visit	100.0%	3.0			100.0%	3.0		
Inpatient visit	100.0%	2.0			100.0%	2.0		
Blood transfusion	0.0%	0.0			25.0%	1.5		
Blood test	0.0%	0.0			100.0%	3.0		
CT scan	0.0%	0.0			100.0%	1.0		
Radiotherapy	0.0%	0.0			0.0%	0.0		
Interventional radiology	0.0%	0.0			0.0%	0.0		
Post-progression			[redacted]	[redacted]			[redacted]	[redacted]
GP visit	100.0%	2.0			100.0%	2.0		

District nurse	100.0%	4.0	[redacted]	[redacted]	100.0%	4.0	[redacted]	[redacted]
A&E visit	100.0%	2.0			100.0%	2.0		
Outpatient visit	100.0%	1.0			100.0%	1.0		
Inpatient visit	100.0%	2.0			100.0%	2.0		
Blood transfusion	0.0%	0.0			0.0%	0.0		
Blood test	0.0%	0.0			100.0%	1.0		
CT scan	0.0%	0.0			0.0%	0.0		
Radiotherapy	0.0%	0.0			0.0%	0.0		
Interventional radiology	0.0%	0.0			0.0%	0.0		

d. Erdafitinib is associated with potential ophthalmology complications. Trials identified that erdafitinib causes a slightly elevated risk of eye conditions such as central serous retinopathy and retinal pigment epithelial detachment, which can cause a visual field defect. To ensure that this is detected as soon as possible, and that subsequent dose adjustments could be made, testing is recommended. Patients are assumed to require monthly ophthalmological examinations during the first 4 months of treatment and every 3 months afterwards. The model assumes a consultation cost of £178.35 (a single ophthalmology consultation was costed as £166.64 in line with the 2021–22 NHS reference costs, and subsequently inflated to £178.35 (2022/2023)).

e. Scenario where resource use of erdafitinib is equal to that of chemotherapy. We use the inputs presented in Table 52 to produce outcomes in Table 53 and Table 54.

Table 52. Similar HCRU costs for erdafitinib and chemotherapy per cycle per health state

Resource	**Erdafitinib**				**Paclitaxel ± carboplatin**			
	% use	**Amount**	**Frequency (every X months)**	**Cost per cycle**	**% use**	**Amount**	**Frequency (every X months)**	**Cost per cycle**
Pre-progression								
GP visit	100.0%	6.0	[redacted]	[redacted]	100.0%	6.0	[redacted]	[redacted]
District nurse	100.0%	4.0			100.0%	4.0		
A&E visit	100.0%	2.0			100.0%	2.0		
Outpatient visit	100.0%	3.0			100.0%	3.0		
Inpatient visit	100.0%	2.0			100.0%	2.0		
Blood transfusion	25.0%	1.5			25.0%	1.5		
Blood test	100.0%	3.0			100.0%	3.0		
CT scan	100.0%	1.0			100.0%	1.0		
Post-progression								

GP visit	100.0%	2.0	[redacted]	[redacted]	[redacted]	[redacted]	100.0%	2.0	[redacted]	[redacted]	[redacted]	[redacted]
District nurse	100.0%	4.0	[redacted]	[redacted]	[redacted]	[redacted]	100.0%	4.0	[redacted]	[redacted]	[redacted]	[redacted]
A&E visit	100.0%	2.0	[redacted]	[redacted]	[redacted]	[redacted]	100.0%	2.0	[redacted]	[redacted]	[redacted]	[redacted]
Outpatient visit	100.0%	1.0	[redacted]	[redacted]	[redacted]	[redacted]	100.0%	1.0	[redacted]	[redacted]	[redacted]	[redacted]
Inpatient visit	100.0%	2.0	[redacted]	[redacted]	[redacted]	[redacted]	100.0%	2.0	[redacted]	[redacted]	[redacted]	[redacted]
Blood transfusion	0.0%	0.0	[redacted]	[redacted]	[redacted]	[redacted]	0.0%	0.0	[redacted]	[redacted]	[redacted]	[redacted]
Blood test	100.0%	1.0	[redacted]	[redacted]	[redacted]	[redacted]	100.0%	1.0	[redacted]	[redacted]	[redacted]	[redacted]
CT scan	0.0%	0.0	[redacted]	[redacted]	[redacted]	[redacted]	0.0%	0.0	[redacted]	[redacted]	[redacted]	[redacted]

Table 53. Cost-effectiveness results when resource use of erdafitinib is equal to that of chemotherapy

	Total outcomes by treatment			**Incremental outcomes**			
	LYs	**QALYs**	**Costs**	**LYs**	**QALYs**	**Costs**	**ICER**
Erdafitinib	1.66	[redacted]	[redacted]				
Paclitaxel ± carboplatin	0.73	0.86	[redacted]	0.93	[redacted]	[redacted]	£29,258

Table 54. Costs breakdown

	Drug acquisition	**Drug administration**	**Subsequent treatment acquisition**	**Subsequent treatment administration**	**Adverse events**	**Other healthcare resource use**	**Death (end-of-life)**
Erdafitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Paclitaxel ± carboplatin	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Results

B28. Priority question. In sections B3.9 and B3.10 of the CS, the company only provided results versus paclitaxel ± carboplatin.

a. **Please also provide the pairwise base-case results, as well as probabilistic sensitivity analyses, deterministic sensitivity analyses and scenario analyses for erdafitinib versus all other relevant comparators.**

b. **Please provide a fully incremental analysis including all relevant comparators and enable fully incremental analysis in the economic model with all comparators listed in the NICE scope as comparators modelled separately.**

a. As detailed in prior question responses, paclitaxel ± carboplatin is the only relevant comparator for this patient population with adequate evidence to conduct sufficient analyses for decision making.

b. As above, given the base case comparator of paclitaxel ± carboplatin is the only relevant comparator, no further incremental analysis is required.

Appendix A: Correction to inpatient hospitalisations for comparators

In addition to addressing the provided responses to the Clarification Questions, J&J IM has picked an error in the cost-effectiveness model. Specifically, in the "HCRU Costs" Excel sheet, within the section pertaining to health care resource use in the progressed state for comparators. It has been identified that Cells I172, I185, and I198 (now Cells I181, I194, and I207 in the updated model) erroneously indicated an inpatient frequency of 1 instead of the correct value of 12, as per the inputs stated in Table 51 of the CS.

Additionally, we have incorporated the cost associated with a singular blood test that is necessary on day 14 to determine the serum phosphate concentration in patients receiving erdafitinib treatment. These modifications have been made within the Excel Sheet named "HCRU Costs," under the section Erdafitinib tests. The relevant alterations have been made within rows 59 to 64.

The other modification was made in light of Clarification Question B24 concerning the approach used to incorporate the cost of erdafitinib in the model, which did not align with the CS. In the previous submitted model, the cost of erdafitinib was applied on a per "treatment cycle" basis, defined as a duration of 21 days according to the clinical trial. However, for uniformity, it should be applied once every 28 days. Consequently, J&J IM has made adjustments in this updated model version by altering the Treatment cycle (Cell K64) from 3 weeks to 4 weeks and the number of treatment administrations per cycle (Cell M64) from 21 days to 28 days within the "Drug Costs" section.

PFS for the treatment regimen of paclitaxel ± carboplatin is now represented by a more credible and relevant curve obtained from literature (Vaishampayan et al. 2005[26]). This update replaces the previously assumed curve, which was derived based on the PFS to time-to-next-treatment (TTNT) ratio for erdafitinib.

A summary of the changes to the base case are given in Table 55.

Table 55. Summary of changes from the CS original base case and the justification

Original base	Revised base case	Justification
Frequency of inpatient hospitalisations was incorrectly given as 2 visits every month	Corrected to 2 every year to match the input table in the CS	This was an error in the model that was fixed.
No blood tests to determine phosphate levels were included for patients receiving erdafitinib	A one-off blood test cost has been included in the model.	A single blood test is required on day 14 to determine serum phosphate concentration. Clarification Question B22 (b) and B25
Erdafitinib drug cost was applied once every "treatment cycle", which was defined as 21 days based on the trial	Erdafitinib drug cost is now applied once every "treatment cycle", which is defined as 28 days	Clarification Question B24
The ratio of the PFS to TTNT for erdafitinib was applied to the paclitaxel ± carboplatin TTNT extrapolation to derive a PFS extrapolation for paclitaxel ± carboplatin.	The PFS curve from Vaishampayan et al 2005[26] for paclitaxel ± carboplatin	Data from literature derived from patients with prior platinum treatment is plausible. Generalized gamma fit gave the best AIC/BIC, but it predicted a very long-tail. Log-logistic and log-normal fit well and are more reasonable, so a log-logistic was preferred to match the choice for erdafitinib.

Results from the original Company submission and updated model version are shown in Table 56 and Table 57, respectively.

Table 56. Company submission original base case (deterministic, PAS price, 1.7x severity modifier applied)

Treatment	Total LYs	Total QALYs	Total costs	Incremental LYs	Incremental QALYs	Incremental costs	ICER (£/QALY)
Erdafitinib	1.66	[redacted]	[redacted]	-	-	-	
Paclitaxel ± carboplatin	0.73	0.80	[redacted]	0.93	[redacted]	[redacted]	£26,210
Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.							

Table 57. Company revised base case (deterministic, PAS price, 1.7x severity modifier applied)

Treatment	Total LYs	Total QALYs	Total costs	Incremental LYs	Incremental QALYs	Incremental costs	ICER (£/QALY)
Erdafitinib	1.66	[redacted]	[redacted]	-	-	-	
Paclitaxel ± carboplatin	0.73	0.86	[redacted]	0.93	[redacted]	[redacted]	£26,490
Key: ICER, incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.							

J&J IM understand that a fully revised version of the economic model results contained within Document B may be needed, which include the corrections. J&J IM are willing to provide this updated Document B at the request of NICE or the EAG.

Appendix B: Corrected TTNT results from original submission

During the updates to data analysis the following minor error was noted when calculating the TTNT for erdafitinib:

Time to next treatment was defined from initiation of erdafitinib to overall survival, suggesting that those who switched treatment had their TTNT over estimated. This was corrected to make sure it measured the time from initiation of treatment to change of treatment. The updated ITC analysis for TTNT are provided.

Table 58. Summary of results of the ITC (ATC)

	TTNT HR (95% CI)	p-value
Base case	0.53 (0.37-0.76)	0.0005
Missing excluded	0.35 (0.21-0.58)	<0.0001

Figure 69. Kaplan–Meier curve for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel (base case)

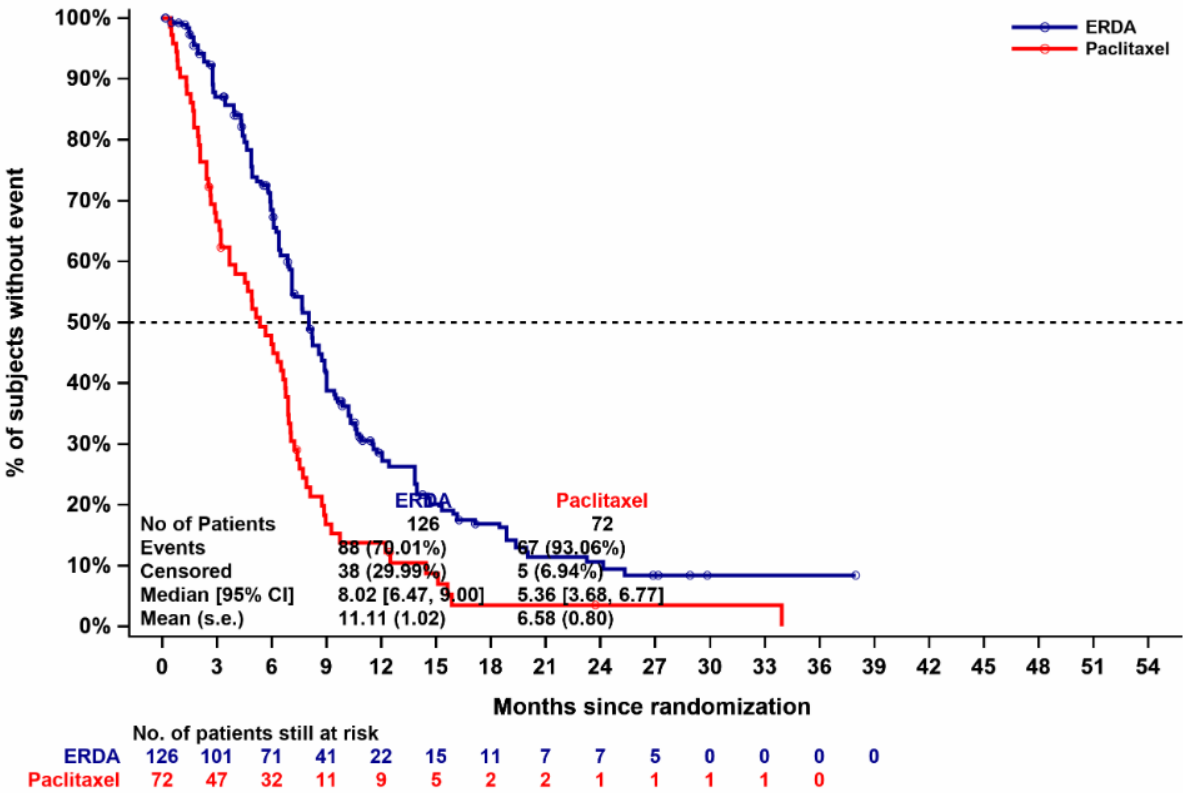
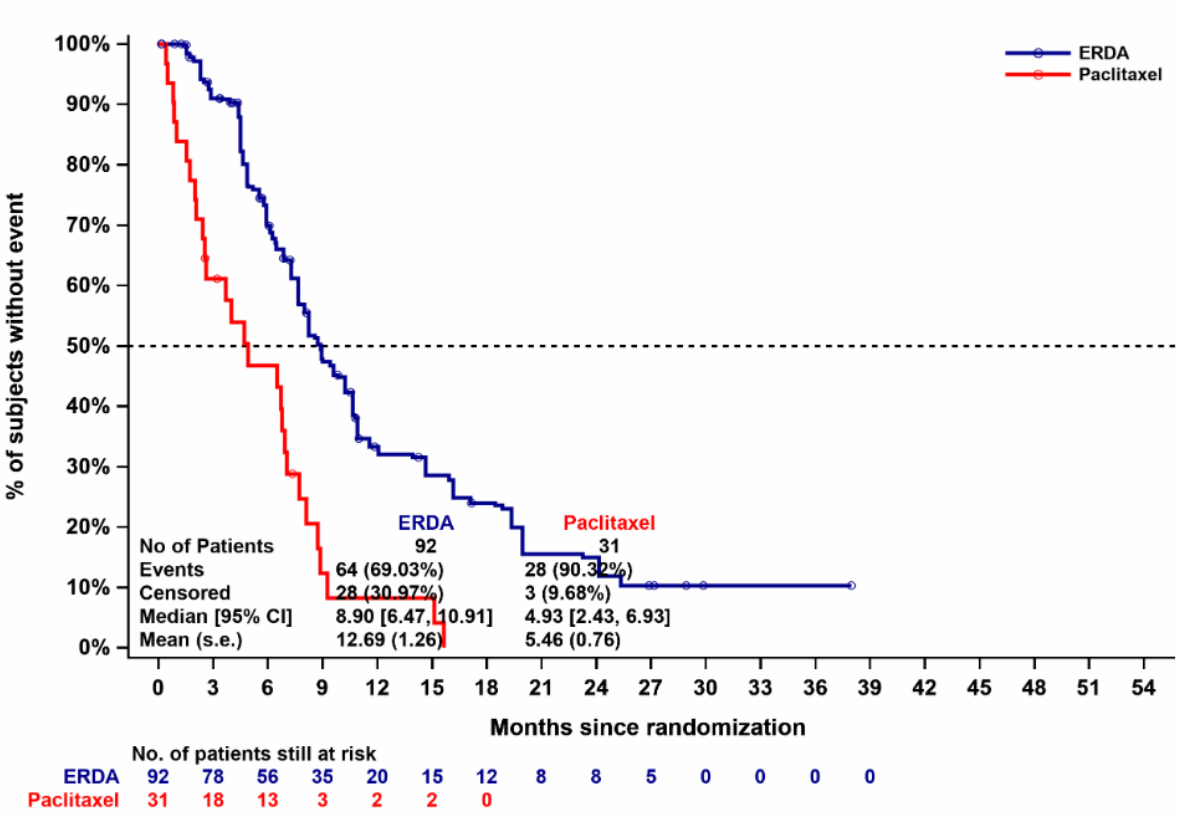


Figure 70. Kaplan–Meier curve for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel (excluded cases)



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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

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

Clarification questions

[August 2024]

File name	Version	Contains confidential information	Date
ID1333 erdafitinib clarification questions to PM for company [CON]_non_priority_FULLY_REDACTED.docx	V1	Yes	8 August 2024

Notes for company

Highlighting in the template

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Section A: Clarification on effectiveness data

Population and generalisability

A6. The company's proposed positioning of erdafitinib is as second- and third-line therapy in the clinical care pathway of urothelial cancer.

a. According to the clinical experts, [redacted]. Please justify whether this statement is still relevant. Please provide an estimation of the percentage of patients in UK clinical practice that will receive EV+P as 1L.

b. Please discuss the differences in comparators for second line and third line treatment in the UK and elaborate on the difference in treatment effectiveness, QoL, and resource use in each group. Please provide supporting evidence from available literature or clinical experts' opinion.

c. Please summarise the distribution of patients by line of therapy recommended by the clinical experts consulted.

a. Regarding the estimation of market shares for enfortumab vedotin (EV) and/or pembrolizumab, it should be noted that J&J is not the manufacturer for these products. As a result, we are unable to provide an estimation of expected patients to be treated in this regard. It is not possible for J&J to speculate on future market share as EV plus pembrolizumab is unlicensed, the indication has not been assessed by NICE and it is therefore not yet available for use within the NHS and beyond the scope of this appraisal.

   J&J also considers that the statement requires clarification. EV is an antibody-drug conjugate that facilitates selective delivery of a chemotherapy payload to tumours, it therefore could be considered or seen as a form of chemotherapy treatment.[1] Therefore, should combination therapy with EV and pembrolizumab be recommended by NICE, the frontline treatment would consist of a PD-(L)1

inhibitor and a form of chemotherapy. Erdafitinib could therefore be prescribed as a second-line treatment in line with erdafitinib's anticipated marketing authorisation positioning [redacted]. Furthermore, and regardless of EV + pembrolizumab, the use of front-line PD-(L)1 inhibitors is increasing due to recent developments in clinical practice. Currently, a significant majority of patients (approximately 70%) who show stable disease or a response to first-line platinum-based chemotherapy are subsequently administered avelumab (a PD-L1 inhibitor) as a maintenance therapy. Therefore, the use of avelumab as an addition to first line treatment will increase the total use of immunotherapy (IO) in front line. Patients with a [redacted], would be eligible for receiving erdafitinib as a second-line treatment.

The statement suggesting that only a small minority, potentially up to 10%, of patients would receive front-line IO monotherapy is nearly accurate, but the actual percentage might be even smaller than 10%. The recommendation of IO monotherapy use in front line treatment was only temporarily advised in an interim guidance from NHS England during the COVID-19 pandemic and is not current clinical practice (please see Doc B1.3.5.2.).[2]

b. There are no differences in comparators in second and third-line treatments for metastatic urothelial carcinoma patients in the UK. Considering the critical analysis of the UK RW mUC study, clinician recommendation and the available data, the main comparator for erdafitinib is paclitaxel, as a monotherapy or less commonly in combination with carboplatin. The rationale for this has been captured in Doc A.2 and Doc B.1.3.5.2. In addition, investigating potential differences in treatment effectiveness of treatments in second- and third-line, the RW UK mUC study also showed that the efficacy of second line and third line was similar based on the median OS of 7.0 months (95% CI: 6.4, 7.7) and 6.9 months (95% CI: 6.1 – 7.7), respectively. However, it should be noted that the attrition rate was high and median OS only focusses on patients that actually received an active treatment. Clinical experts commented "2L taxanes are largely ineffective in 90% of patients", "the clinical benefit of taxanes in 2L treatments is vanishingly small" and would be offered "with a view to help symptom relief".[3] In the third-line setting, clinical experts noted "there's no real

evidence-based treatment"[3] and "for patients who have managed to get onto third-line paclitaxel, predicted survival is around 4 months".[2]

There is no clearly defined standard of care in second and third line in the treatment pathway and the treatment options are defined by earlier lines of therapies. There is limited evidence available to indicate any significant differences in QoL and resource utilisation between the second and third line.

c. From the expert advice, and as detailed in the budget impact analysis (BIA, Table 4), there is a high attrition rate between lines of therapy for metastatic urothelial carcinoma. According to expert advice, 40-50% of patients receive an active first-line treatment of which 30% receive an active second-line treatment.[2] However, in our RW UK mUC study, the attrition rate was higher and even fewer patients received a front line (36.5% [3942/10787]), second line (24.3% [959/3942]) or third line treatment (4.0% [158/3942]) (Appendix O).

A8. As highlighted within the clinical expert report:

"The difference in median OS improvement (12.1 months for erdafitinib versus 7.8 months for chemotherapy) observed between the erdafitinib and chemotherapy arm was greater than the difference in the PFS improvement seen between these two arms (5.6 months versus 2.7 months, respectively). when looking at the hazard ratios, normally there is a much bigger gap for PFS than OS. This might raise some questions that need to be addressed, suggesting there's a need to articulate a response as to why the OS data look better than the PFS, otherwise there is the risk they will be perceived to be 'too good to be true'. He also noted that survival gain looks longer than the duration of response, which is a bit strange and also needs to be explained."
Please provide critical rationale underlying the unexpected patterns present within the THOR trial and discuss their implications for interpreting the overall efficacy of erdafitinib.

Before answering the question, it should be noted that the statement has several questions or suggestions included. It states:

- *The median improvement in OS is longer than the PFS,*

- *Looking at the HR, a bigger gap is expected for PFS than OS*
- *Articulate why the OS data looks better than PFS*
- *Explain why survival gain looks longer than the duration of response*

To set the scene, we agree that the improvement, measured by a HR, is better for PFS than OS. However, these are relative measures and caution should be exercised in comparing these.

One of the possible explanations can be found in the PFS events observed from THOR. In the erdafitinib arm, the PFS events due to progression accounted for 92 patients (91.1%) versus 64 patients (71.1%) in the chemotherapy arm. The PFS events due to death were in 9 patients (8.9%) and 26 patients (28.9%) in the erdafitinib and chemotherapy arms respectively. As death is usually expected after PFS, the high proportion of deaths (in the absence of progression) in the chemotherapy arm being counted as a PFS event contributed to a short median PFS in the chemotherapy arm. The majority of these deaths also occurred early (within 2-2.5 months of follow-up) contributing to the larger difference in median OS.

In addition, a similar proportion of patients received a subsequent therapy in the two study arms, so this could be excluded as contributing factor. The observed greater difference in OS vs PFS for the two arms may be related to a variety of factors in addition to the additional superior efficacy of erdafitinib as reflected in a significantly higher response rate and PFS. For example, survival following progression may be related to the depth of initial response (deeper responses with erdafitinib treatment vs chemotherapy), and ability to tolerate (fewer residual toxicities after receiving erdafitinib vs chemotherapy) and respond to subsequent therapy due to differences in overall condition and residual toxicities following discontinuation of study treatment, potentially allowing more patients who received erdafitinib to receive greater benefit from subsequent therapy. The observed prolongation in OS in addition to that in PFS provides additional confidence that treatment with erdafitinib in this patient population does not adversely impact prognosis following treatment discontinuation.

Further, erdafitinib could provide a continued benefit even after disease progression leading to prolonged OS despite PFS showing earlier progression. This is because

erdafitinib may control disease even when radiographic progression is noted. Investigators did continue with erdafitinib at least until confirmation of disease progression radiographically, however, patients receiving erdafitinib were permitted to continue treatment beyond progression. This extended treatment could have helped manage disease symptoms and complications contributing to a longer OS despite PFS showing earlier progression.

The Duration of Response (DoR) in the study was 4.9 months (95% CI, 3.8 to 7.5), which is longer than the difference in OS benefit (4.3 months). Therefore, J&J would like to clarify the clinician statement above, as the data appears to show that the OS benefit is not longer than the DoR. We hope that the provided explanations help to address concerns regarding the discrepancy in the impact between OS and PFS and duration of response.

Adverse events (AEs)

A8. Please review the following questions for clarification of Adverse events (AEs)

a. The company states that "*Erdafitinib with dose modifications had a manageable tolerability profile compared with that of chemotherapy*." Please clarify if this implies that without dose modifications, erdafitinib has an unmanageable tolerability profile. Please provide a transparent comparison of the safety profiles with and without dose modifications. Please also provide further details on the dose modification e.g., whether this was based on pre-agreed criteria. Please provide clarity on the duration of AEs and management as highlighted within the clinical advisors' safety concerns.

b. For the paclitaxel ± carboplatin arm AEs were derived from the PLUTO trial, which included patients receiving paclitaxel monotherapy. In the company submission (CS) it is stated that "*In reality, it is possible that this assumption reflects a conservative view of AEs associated with platinum-containing doublet chemotherapy*." Please elaborate on why this is likely to be a conservative assumption and reflect on the dosing of paclitaxel monotherapy compared to the dosing of paclitaxel when combined with carboplatin.

a. Any systemic anticancer treatment has guidance on drug modifications, and this is not different with erdafitinib. Erdafitinib has not been evaluated in a phase 3 randomised clinical trial outside of the THOR study which required dose modifications based on protocol guidance to manage the impact of expected adverse events associated with erdafitinib. Therefore, in the absence of data without dose modifications we are unable to provide the requested comparison. J&J would like to clarify as per protocol, clear guidance for dose modification specifically for eye, skin/nail, dry mouth/mucositis and phosphate related adverse events was provided. This was not required for all adverse events. In addition, depending on the adverse event of interest and the respective grading, no dose modification was required as described in sections 6.1.1 and 6.1.2 of the protocol. For example, for patients with grade 1 and 2 dry mouth and dry skin and grade 1 mucositis, onycholysis/onychodystrophy, paronychia protocol guidelines stated continue study drug at current dose. In addition, for patients with elevated serum phosphate concentrations up to 6.9 mg/dL, protocol guidelines state continuation with erdafitinib treatment. In line with the trial protocol, dose modifications were ultimately based on clinical judgement by the treating physician.

   The statement in question is also applicable to chemotherapy. Sections 6.2.1.1 and 6.2.2.1 provide guidance on dose management for patients treated with vinflunine and docetaxel respectively based on the adverse event of interest, grade classification and occurrence. As erdafitinib is administered daily and chemotherapy is administered intermittently (every 3 weeks), there were fewer opportunities for dose modification due to toxicities in the chemotherapy group. Therefore, daily administration with erdafitinib permits an opportunity to limit the duration of any potential adverse events.

b. Paclitaxel monotherapy is administered weekly for 3 weeks on days 1, 8 and 15 at a dose of 80mg/m2 followed by 1 week off. When paclitaxel is administered in combination with carboplatin every 3 weeks, paclitaxel is dosed at 175 mg/m² over a period of 3 hours, alongside carboplatin, which is dosed to a targeted area under the curve (AUC) of 6 mg/ml as a 30-minute IV infusion over 30 minutes every 3 weeks in 500 ml glucose 5%. Single agent paclitaxel

is less likely to cause toxicity compared with the double agents recommended by NICE (including paclitaxel + carboplatin).[4] Thrombocytopenia, neutropenia, anaemia and leukopenia are common adverse events observed in patients treated with carboplatin.[5, 6] Considering that potential adverse events specifically attributable to carboplatin exposure in addition to a higher dose of paclitaxel have not been accounted for, the assumption is expected to hold true. Importantly, the PLUTO trial population had only been exposed to platinum-based chemotherapy, without any prior exposure to PD-(L)1 inhibitors. The patient population in scope of this appraisal will be less fit as prior exposure to PD-(L)-1 inhibitors is required. With 75% of patients receiving paclitaxel monotherapy and with no available literature on the combination in the relevant patient population, it is reasonable to assume that any additional adverse events arising from the 25% of patients on combination treatment would have minimal impact on the overall outcomes.

Indirect treatment comparisons

A9. The ITC appears to focus solely on efficacy outcomes. Please provide a comparative safety analysis between erdafitinib and paclitaxel ± carboplatin, or justify its omission. Additionally, the UK real-world study lacked information on patients' FGFR mutation status. Please consider how this limitation may impact the validity of indirect comparison and potentially bias the relative estimates for erdafitinib.

We were unable to perform a comparative safety analysis between erdafitinib and paclitaxel ± carboplatin due to the lack of safety outcomes from the UK real-world evidence (RWE) study. Additionally, detailed information regarding FGFR alterations was unavailable as the registry cohort consisted of an untested population. Currently, there are no treatment options specifically targeting FGFR3 alterations. Consequently, we evaluated the comparative efficacy of chemotherapy in an untested population versus a FGFR3-positive population both following PD-(L)1 treatment. To assess the validity of the indirect comparison, we conducted a matching-adjusted indirect comparison (MAIC) using the EV-301 study against THOR (Appendix Q.1). Our analysis of the chemotherapy arms in both THOR (with known FGFR3 status) and EV-301 (with unknown FGFR3 status) studies revealed no significant differences in OS, PFS and ORR between the two chemotherapy groups, with a slight trend in favour of

the chemotherapy efficacy in the untested population. Thus, the efficacy observed in the UK real-world untested mUC population can be considered comparable, if not conservative, when compared to an equivalent FGFR3-altered population. Consequently, any bias related to FGFR mutation status in the ITC would be against erdafitinib.

Section B: Clarification on cost-effectiveness data

Intervention and comparator

B4. Erdafitinib can administered to patients until progression, withdrawal or toxicity.

a. Please clarify whether a similar stopping rule applies to paclitaxel ± carboplatin and provide details on how it was implemented in the economic model.

b. Please clarify whether a similar stopping rule applies to docetaxel and atezolizumab.

c. Please provide published literature supporting the stopping rule for the intervention and comparators included in the economic model.

a. Treating patients until progression, withdrawal or toxicity does not fall under the definition of a stopping rule – it is simply a treatment protocol which is common in treat-to-progression therapies. A stopping rule does not apply to paclitaxel ± carboplatin and therefore it was not incorporated into the economic model. Due to the relatively short time to next treatment, the economic model predicts that at 2-years there are expected to be zero patients on treatment, receiving paclitaxel ± carboplatin.

   Further, and more importantly, paclitaxel monotherapy is administered in 28-day cycles, for a maximum of six cycles.[5, 7, 8] When used in combination with carboplatin, i.e. paclitaxel + carboplatin, treatment is given in 21-day cycles, up to a maximum of six cycles.[9] Given both treatment options last for a maximum of approximately six months, no stopping rule is required for paclitaxel ± carboplatin.

b. Docetaxel, like paclitaxel ± carboplatin, is a time-limited treatment. Cycles are every 21 days and patients have up to six cycles.[10] A stopping rule is not required for docetaxel. In NICE TA525[11] for atezolizumab following platinum-containing chemotherapy, the Final Appraisal Document outlined the implementation of a stopping rule of two years of uninterrupted treatment if progression has not occurred.

c. There is no rationale to support a stopping rule for erdafitinib as it is not detailed in the draft SmPC. There is no rationale to incorporate a stopping rule for paclitaxel ± carboplatin given the treatment is time-limited for up to approximately six months.

Model structure

B5. The National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) TSD 19 recommended the use of state transition models (STMs) alongside partitioned survival models (PSMs) to verify the plausibility of PSM extrapolations and explore key clinical uncertainties in the extrapolation period:

a. Please justify the use of a PSM given the issues highlighted in NICE DSU TSD 19, particularly regarding the extrapolation of progression-free survival (PFS) and overall survival (OS) while assuming structural independence between these endpoints.
b. Please use state transition modelling to assist in verifying the plausibility of the PSM extrapolations and to address uncertainties in the extrapolation period (NICE DSU TSD 19, recommendation 11).

a. A PSM is the most appropriate modelling structure. It is the simplest possible structure required to meet the needs of the decision problem and capture benefits of the intervention and comparators. It is consistent with previous appraisals. In the most relevant technology appraisals: TA525[11], TA530[12], TA692[13], TA739[14], and TA788[15]; three-state partitioned survival modelling was used (Document B, Table 26). This is the most appropriate structure given the clinical endpoints of progression-free survival and overall survival.

b. Whilst conducting a state transition model to verify the plausibility of extrapolations and address uncertainty in the extrapolation period would be of use, this requires significant resource and time which Johnson & Johnson does not have available. One of the disadvantages of using the PSM structure is that it cannot readily handle adjustment for a different subsequent therapy case mix, however this is not relevant to this decision problem therefore there is limited benefit of building a state transition model. In conclusion, the PSM is the simplest possible structure required to meet the needs of the decision problem and capture benefits of the intervention versus comparators.

B6. According to the CS, a half-cycle correction is not applied in the economic model due to the short model cycle length (i.e., seven days). However, the half-cycle correction seems to be applied in the company's economic model (See cell H20, from 'Control' sheet). Please clarify this discrepancy. If the company prefers to omit the half-cycle correction, please update the economic model and results accordingly.

The half cycle correction is not required given the short model cycle length, but it was utilised as an option within the modelling. The correction has a very limited impact on the ICER. The base-case outlined not using the correction, however this was switched on in the modelling. Therefore, the base-case does incorporate half-cycle correction. The base-case ICER of £26,487 changes to £26,523 when half-cycle correction is switched off. Therefore, noting the error, half-cycle correction is not a major factor on decision making as it reduces the ICER by £36.

Treatment effectiveness

B11. No treatment effectiveness waning was assumed in the company's base-case analysis.

a. Please provide implied hazard ratio plots for PFS and OS versus time with numbers of patients at risk over time to justify this assumption.

b. If indicated by the implied hazard ratio plots, please provide an updated economic model and scenario analyses exploring treatment effectiveness waning onset at different time points.

a. The implied OS HR of erdafitinib vs paclitaxel ± carboplatin over the model time horizon is presented in Figure 1. As PFS was not available for paclitaxel ± carboplatin, the implied TTNT HR is shown instead in Figure 2. The PFS of paclitaxel from PLUTO, which was used in a scenario, was modelled by applying a HR to erdafitinib, so the modelled HR was assumed constant over time.

Figure 1. Implied OS HR over time, erdafitinib vs paclitaxel ± carboplatin

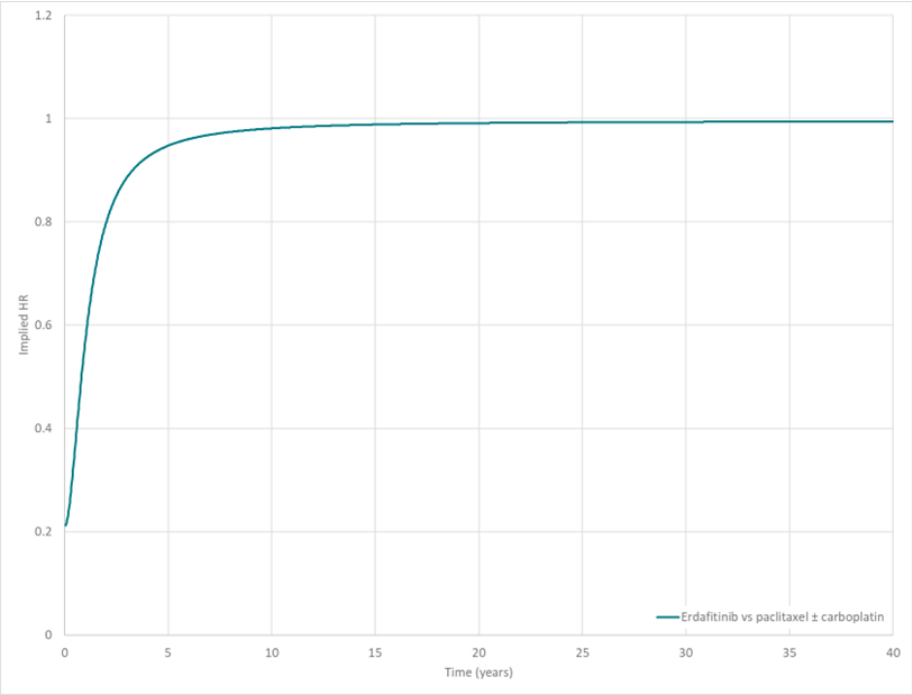
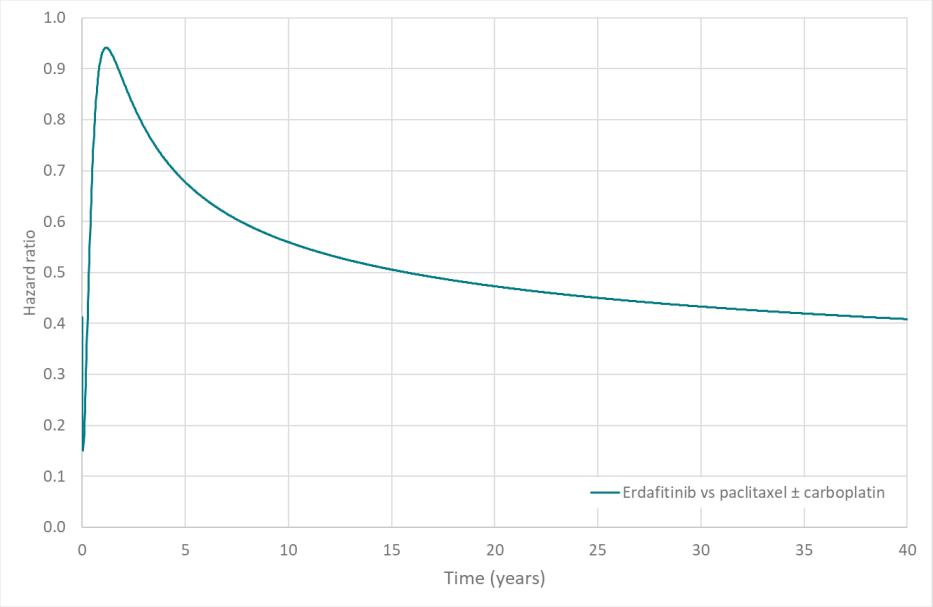


Figure 2. Implied TTNT HR over time, erdafitinib vs paclitaxel ± carboplatin



b. As the time-to-event curves of erdafitinib and paclitaxel ± carboplatin were modelled independently, a constant treatment effect was not assumed. Instead, the implied treatment effect could vary over time according to trends observed in the data that the independent statistical models capture. Therefore, the available data could not justify placing additional constraints on the treatment effect.

   Constant effect is assumed when HRs are used to derive OS and PFS for PLUTO-based paclitaxel scenario analysis, of which the latter can also inform the PFS of paclitaxel ± carboplatin. However, the point estimate of PFS HR is close to 1, which means that treatment effect waning for this outcome would only have minimal impact on results.

Adverse events

B12. In the CS, it was stated that "*Treatment-specific grade 3+ AEs with incidence of greater than 5% of patients in the erdafitinib arm of THOR and/or paclitaxel arm from PLUTO were included*." Please provide a scenario analysis including all grade 3+ AEs, not only those with an incidence above 5%.

The proportion of patients with grade 3+ AEs are presented in Table 1 and the model inputs are presented in Table 2.

Table 1. All grade 3+ AEs

	Erdafitinib (n = 135)		**Paclitaxel (n = 64)**	
	Any grade	**Grade 3–4**	**Any grade**	**Grade 3–4**
No. of patients, n (%)				
Diarrhoea	84 (62.2)	4 (3.0)	27 (42.2)	2 (3.1)
Stomatitis	65 (48.1)	11 (8.1)	-	-
Nausea	20 (14.8)	-	41 (64.1)	-
Vomiting	13 (9.6)	2 (1.5)	-	-
Hyperphosphataemia	108 (80.0)	7 (5.2)	38 (59.4)	6 (9.4)
Decreased appetite	36 (26.7)	4 (3.0)	-	-
Hyponatraemia	16 (11.9)	10 (7.4)	-	-
Asthenia	20 (14.8)	2 (1.5)	-	-
Fatigue	20 (14.8)	-	64 (100.0)	5 (7.8)
Alopecia	34 (25.2)	-	41 (64.1)	-
Palmar-plantar erythrodysesthesia syndrome	41 (30.4)	13 (9.6)	-	-
Onycholysis	31 (23.0)	8 (5.9)	-	-

	Erdafitinib (n = 135)		Paclitaxel (n = 64)	
	Any grade	**Grade 3–4**	**Any grade**	**Grade 3–4**
Nail disorder/dystrophy	19 (14.1)	3 (2.2)	-	-
Urinary tract infection	15 (11.1)	6 (4.4)	-	-
Paronychia	16 (11.9)	-	-	-
Anaemia	35 (25.9)	10 (7.4)	-	-
Neutropenia	-	-	36 (56.3)	6 (9.4)
Alanine aminotransferase increased	37 (27.4)	4 (3.0)	34 (53.1)	2 (3.1)
Weight decreased	30 (22.2)	3 (2.2)	-	-
Aspartate aminotransferase increased	29 (21.5)	3 (2.2)	-	-
Blood alkaline phosphatase increased	14 (10.4)	3 (2.2)	-	-
Mucositis	-	-	20 (31.3)	2 (3.1)
Neuropathy	-	-	38 (59.4)	2 (3.1)
Haematuria	16 (11.9)	3 (2.2)	-	-
Key: TEAE, treatment-emergent adverse event. **Source:** THOR clinical study report.[16]				

Table 2. AE-related disutilities, durations and costs

Adverse event	**Disutility**		**Duration (days)**		**Costs**	
	Value	Reference	Value	Reference		
Diarrhoea	-0.047	TA831	4.32	TA831	£714.93	TA11186[a]
Stomatitis	-0.040	TA498	16.6	THOR	£958.38	Non-elective inpatient - short stay
Nausea	-0.048	TA788	19.0	TA581	£176.99	Assumed equal to vomiting
Vomiting	-0.048	TA788	19.0	TA581	£176.99	TA788
Hyperphosphataemia	-0.073	Nafees et al.[17]	9.4	THOR	£2.96	DAPS05
Decreased appetite	-0.038	Hudgens et al 2016[18]	115.53	TA983	£1058.38	TA11186[b]
Hyponatraemia	-0.073	Nafees et al.[17]	12.9	THOR	£2.96	DAPS05 - DAPS - Haematology
Asthenia	-0.073	TA788	108.0	TA788	£1010.38	TA11186[c]
Fatigue	-0.073	Nafees et al.[17]	129.5	THOR	£1010.38	TA788
Alopecia (hair loss)	-0.045	Nafees et al.[17]	21.0	Bullement et al.[19]	£0	Bullement et al.[19]
Palmar-plantar erythrodysesthesia syndrome	-0.040	Assumed equal to Stomatitis	31.2	THOR	£599.88	NHS reference costs

Onycholysis	-0.032	Nafees et al.[17]	80.1	THOR	£499.58	NHS reference costs
Nail disorder/dystrophy	-0.045	Assumed equal to alopecia	21.0	Assumed	£0	Assumed
Urinary tract infection	-0.009	TA788	14	TA788	£1,454.75	TA788 (2018/19)
Paronychia	-0.08	Yue et al.[20]	26.1	Assumed equal to anaemia	£194.17	Assumed. KOL stated insignificant costs
Anaemia	-0.090	Beusterien et al. (2010)	26.1	THOR	£808.02	SA01G-K
Neutropenia	-0.090	Nafees et al.[17]	16.4		£833.70	WJ11Z
Alanine aminotransferase increased	0	TA722	8.3	TA722	£194.17	Assumed similar to Amylase increased
Weight decreased	-0.038	Assumed equal to reduced appetite	30.0	Assumed	£698.50	TA11186[d]
Aspartate aminotransferase increased	0	TA722	6.8	TA722	£194.17	TA788
Blood alkaline phosphatase increased	0	Assumed equal to Aspartate increased	6.8	Assumed equal to Aspartate increased	£194.17	Assumed similar to Amylase increased
Mucositis	-0.068	Hagiwara et al.[21]	21.0	Assumed	£194.17	Assumed. KOL stated

						insignificant costs
Neuropathy	-0.084	Hagiwara et al.[21]	21.0	Assumed	£194.17	Assumed. KOL stated insignificant costs
Haematuria	-0.009	TA788	14.0	TA788	£1,454.75	TA788 (2018/19)

[a]Weighted average FD10A-M Non-malignant gastrointestinal tract disorders without interventions, non-elective short stay (2022 price)
[b]Weighted average LB06N-S. Kidney, urinary tract or prostate neoplasms, without interventions. Non-elective short stay + dietician cost per session (2022)
[c]Weighted average LB06N-S. Kidney, urinary tract or prostate neoplasms, without interventions. Non-elective short stay + nurse (GP practice) cost per hour (2022)
[d]Weighted average FD04A-E. Non-elective short stay (2022).

Table 3 shows a scenario that includes all grade 3+ AEs. Due to the low incidence of grade 3+ AEs, the overall impact on QALYs is small in both arms (-0.0026 is applied to the erdafitinib arm, compared with -0.0029 applied to the paclitaxel ± carboplatin arm), a change from -0.0017 and -0.0026 for erdafitinib and paclitaxel ± paclitaxel, respectively, when only AEs with an incidence of 5% are considered.

The resulting one-off costs for AE management which were applied in the model were £460.56 for erdafitinib and £210.55 for paclitaxel ± carboplatin (£241.55 and £168.44, respectively when only AEs with at least 5% incidence were considered).

Table 3. Cost-effectiveness results based on all Grade 3+ AEs

	Total outcomes by treatment			**Incremental outcomes**			
	LYs	**QALYs**	**Costs**	**LYs**	**QALYs**	**Costs**	**ICER**
Erdafitinib	1.66	[redacted]	[redacted]				
Paclitaxel ± carboplatin	0.73	0.86	[redacted]	0.93	[redacted]	[redacted]	£26,695

B13. In the company's base case approach, health state utilities were estimated with linear mixed models for repeated measures, while an alternative approach used a multivariable regression model including AEs (model 3).

a. Please elaborate on the reasons for choosing AE disutilities based on literature instead of the trial based AE disutilities from the multivariable regression model.

b. Please compare the total QALY loss due to AEs derived from both methods per modelled treatment option.

a. AE disutilities based on literature were used in the base case because they more accurately capture the different impact on utility of different AE types. It was not possible to differentiate between types of AEs in the analysis of trial data, and consequently only a single effect estimate for all AEs is available from that analysis. Applying it in the economic model would lead to less accurate representation of different safety profiles of the modelled interventions.

b. Total QALY loss with each intervention using the two methods is shown in Table 4.

Table 4. QALY loss due to AEs based on alternative disutility sources

Intervention	QALY loss due to AEs based on literature	QALY loss due to AEs using trial-based disutility
Erdafitinib	0.0018	0.0024
Paclitaxel ± carboplatin	0.0027	0.0024
Chemotherapy (THOR)	0.0025	0.0021

B14. AE disutilities and costs were listed in CS Tables 44 and 53, respectively.

a. Please justify why different disutilities were chosen for hyponatraemia and hyperphosphataemia (both assumed equivalent to fatigue based on Lloyd et al. 2006) and the fatigue disutility based on Nafees et al. 2009.

b. Please justify why neutropenia and decreased neutrophil count have different cost, while the cost for decreased neutrophil count is based on the costs of neutropenia.

c. Please justify the relatively high unit cost of fatigue.

a. For consistency, the utilities for hyponatraemia and hyperphosphataemia are now based on fatigue taken from Nafees et al. 2009. This change reduces the ICER by only £3. To note that in a previous appraisal (TA722), these two AEs were assigned a disutility of zero as they were deemed to have a limited impact on health-related quality of life. Clinicians use phosphate levels as a biomarker to check patient response and there is no burden on patient as part of routine blood test and bone profile assessments. Hyponatraemia treatments recommended are dietary changes and fluid restrictions.

b. Decreased neutrophil count was left in Table 53 in error, as it is not included in the submitted model.

c. The cost of fatigue was taken from a previous appraisal (TA11186)[22] and is lower than the value used in TA788[15] of £3,519. In TA11186, the cost of fatigue was calculated based on the weighted average of costs from HRG codes LB06N to LB06S (i.e., kidney, urinary tract or prostate neoplasms, without interventions. Non-elective short stay + nurse (GP practice) cost per hour).

Quality of life

B19. ECOG performance status was included in the multivariable regression model, and the weighted average of the ECOG 1-2 coefficients were applied to the model intercept to calculate the PF health state utility. In the company model, weights were as follows: ECOG 0: 0.429, ECOG 1: 0.477 and ECOG 2: 0.094. These proportions are different from the proportions stated in Table 29 of Appendix P. Please explain how these proportions were derived and the difference between the proportions in Table 29.

Within the economic model, the ECOG scores were weighted as per the full THOR ITT population, n = 266. The ITC, and Table 29, however, incorporates the enrolled patients in the erdafitinib arm of the THOR trial, adjusted to the UK RW mUC patient population, n = 126. The THOR ITT population values were used in the base-case, and this is therefore why the modelled ECOG scores differ from the ITC ECOG scores.

Costs and resource use

B23. In the CS, it is stated that erdafitinib is prescribed and distributed in packs of tablets of 28 days, and that if a new drug pack is required, the full new drug packet is costed upfront. Please elaborate on how this is exactly done in the economic model, with reference to specific cells.

Erdafitinib cost was applied once every ‘treatment cycle’, defined as 21 days based on the trial. We have changed the inputs so that it is applied once every 28 days. We have updated the treatment cycle from 3 to 4 (Cell K64) and number of administrations from 21 to 28 days (Cell M64) in the “Drug Costs” sheet.

B24. In their base case analysis, the company assumes that there will be no wastage in clinical practice. "*the model assumes that there will be no wastage in clinical practice (i.e., there is no tablet splitting or vial sharing*)"

a. The wording in the CS seems contradictory, as no wastage would mean that packs are split and vials are shared between patients. Please clarify what is meant here and what is assumed in the CS base case.

b. Please provide an updated economic model and scenario analysis where wastage is included.

a. We acknowledge that the wording in the CS is confusing. In the base case analysis, it is assumed that the cost of erdafitinib is incurred every 28 days, regardless of whether all the tablets are utilised within this cycle. This approach accounts for the cost of any wasted medication in the model. Additionally, it is customary in appraisals to assume that no vial sharing occurs during chemotherapy administration, despite the fact that vial sharing may indeed be practiced in clinical settings.

b. The model already includes the cost of any wastage with erdafitinib by assuming costs every 28 days. For chemotherapy, a scenario can be run whereby wastage for paclitaxel ± carboplatin is included (see "Controls" Sheet, Cell H60). In this scenario, there is a decrease in the ICER of £141 per QALY gain. The ICER falls from the base case of £26,487 to £26,346. The impact of wastage is therefore relatively small on the decision.

B25. In the CS it is stated that erdafitinib is associated with hyperphosphataemia. While there were no serious TEAEs associated with hyperphosphataemia in the THOR trial, the erdafitinib dose was reduced in 4.4% and treatment was interrupted in 7.4% of patients.

a. Please clarify how testing for hyperphosphataemia was reflected in the model.

b. Please clarify how the dose reductions and interruptions related to hyperphosphataemia were reflected in the model.

a. Testing for phosphate levels was not included in the model. We have now included a one-off cost to reflect that a single blood test is required on day 14 to determine serum phosphate concentration.

b. Dose reductions and interruptions related to hyperphosphataemia are reflected in the 17.07% input value calculated from the THOR trial. We don't distinguish dose interruptions by adverse event.

Severity

B26. Different severity modifier weights were applied in the economic model, depending on the selected comparator arm (paclitaxel ± carboplatin: 1.7x, paclitaxel monotherapy [PLUTO]: 1.2x and chemotherapy [THOR]: 1.2x). However, the severity weight may vary depending on uncertainty in the results (i.e. total modelled QALY gains in the comparator arms). Please calculate the severity weight for each PSA iteration and report on the percentage of simulations with a 1.0x, 1.2x and 1.7x severity weight for all comparators.

The appropriate method for calculating the severity modifier is through the patient population characteristics of the UK RW mUC study and the associated QALYs. Assessing the modifier using the PSA methodology is not appropriate for this submission. This method incorporates several input parameters that are not relevant for calculating the QALYs remaining for patients being treated with standard treatment in the UK. For example, the underlying variation of all parameters which are related to costs are not relevant in understanding QALYs remaining, and therefore including them in the severity modifier calculation is inappropriate. Further, the use of the trial comparators and paclitaxel monotherapy from PLUTO to determine the QALYs remaining for the general population is inappropriate, as these are patients in a clinical trial setting who are typically, preselected, potentially fitter and possibly younger than the patient population witnessed in true clinical practice.

Whilst this is not standard practice, the calculation of the severity weight for each PSA iteration was conducted for erdafitinib versus paclitaxel ± carboplatin. In 50.6% of PSA simulations, the 1.7x severity modifier was met, with a proportional shortfall above 95.0%. In 49.4% of simulations, the 1.2x severity modifier was met. The 1.0x modifier was not witnessed for any of the simulations. Therefore, whilst the appropriate method

for calculating the severity modifier is through the patient population characteristics of the UK RW mUC study and not through a PSA, the PSA iteration method shows that in more than 50% of the 1500 simulations, the 1.7x modifier remains the most appropriate. Note that some of the sampled parameters may have resulted in survival curves that are not clinically plausible as demonstrated by the results of the OWSA (Document B, Table 66). The main purpose of the PSA is to demonstrate that parameter variability does not result in a significant deviation from the deterministic case.

B27. The severity weight was estimated based on the THOR trial population (i.e., a population with the average age of 66.5 years and a 26% females). In question B1, an updated model and scenario analysis were requested using population baseline characteristics in line with the UK population. Please also update the QALY shortfall calculation and provide severity weights in line with the UK population.

As described in B1, the proposed ages are based on a very small sample (n = 12) and therefore could not be regarded as representative of the UK population. The average age of 66.5 years and a female population of 26% are derived from the erdafitinib arm, re-weighted to reflect the UK real-world mUC population who received paclitaxel ± carboplatin treatment. This selection ensures that the average age and gender distribution align with that of the UK population. It should be noted that the unweighted erdafitinib arm had a mean age of 64.8 years. The THOR trial and the UK real-world mUC study cohort both provide evidence suggesting that the patient population in question is younger than 69 years (THOR intent-to-treat analysis: mean age of 66.3 years, UK real-world mUC study: mean age of 68.8 years for all patients who received prior PD-(L)1 therapy).

Results

B29. Please provide a breakdown of the LY and QALY gains in the observed versus extrapolated period for erdafitinib and all comparators.

J&J considers 3 years as the observed period and calculate the LY and QALY gains within 3 years and beyond 3 years, stratifying by health state (progression-free and

progressed). Results are presented in Table 5. We also provide a breakdown of LYs and QALYs by health state in the economic model (Sheet “Results Breakdown”).

Table 5. Breakdown of LY and QALY gains in observed (up to 3 years) versus extrapolated period (beyond 3 years)

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

B30. There seems to be a mismatch between the CE plane presented in CS Figure 25 and the statement that 73.9% of simulations are cost-effective at the £30,000/QALY willingness-to-pay threshold. Please explain this difference and provide an updated CE plane if needed.

There is no mismatch, the cost-effectiveness plane has the standard axes inverted, such that incremental QALYs are on the y-axis, and the incremental costs on the x-axis. Figure 3 shows the cost-effectiveness plane using the standard axes, with no change in the results.

Figure 3: Cost-effectiveness plane

B31. According to Table 44 of Appendix R, the input parameters to inform the proportions of patients receiving various subsequent treatments appear to be excluded from the OWSA.

a. Please justify why these parameters were left out of the OWSA

b. Please provide an updated economic model including these parameters in the OWSA and report the results.

a. Proportions of patients receiving various subsequent treatments were omitted from the OWSA as they were deemed not to be influential on the decision. Due to high attrition rates, few patients receive 3L or 4L therapy. In the UK RWE study, only 19 patients were on 4L treatment.

b. We have updated the model to include the proportion of patients on subsequent treatment. Only the proportions of patients who received atezolizumab after either erdafitinib or paclitaxel ± carboplatin were in the top 10 influential parameters; however, their impact did not affect the decision as erdafitinib remained cost-effective at a willingness to pay threshold of £30,000/QALY, see Table 6.

Table 6. Top 10 parameters influential in the one-way sensitivity analysis (OWSA)

Parameter name (lower bound, upper bound)	**Lower bound ICER**	**Upper bound ICER**	**ICER delta**
OS log-logistic scale parameter: Erdafitinib (2.364 - 2.750)	£36,302	£20,953	£15,349
OS log-logistic shape parameter: Erdafitinib (0.387 - 0.774)	£21,212	£33,926	£12,714
TTD log-logistic scale parameter: Erdafitinib (1.606 - 1.890)	£22,581	£30,985	£8,405
TTD log-logistic shape parameter: Erdafitinib (0.642 - 0.969)	£30,543	£23,712	£6,830
OS log-logistic scale parameter: Paclitaxel ± carboplatin (NCRAS) (1.450 - 1.903)	£24,125	£30,879	£6,754
OS log-logistic shape parameter: Paclitaxel ± carboplatin (NCRAS) (0.381 - 0.789)	£30,926	£25,112	£5,814
Utility: progressed (0.587 - 0.680)	£28,669	£24,659	£4,010
Subsequent treatment: proportion receiving atezolizumab after paclitaxel ± carboplatin (NCRAS) (4.16% - 15.01%)	£27,887	£24,631	£3,255
Subsequent treatment: proportion receiving atezolizumab after erdafitinib (3.99% - 14.46%)	£25,141	£28,274	£3,133
Cost per administration: IV - simple (£249.68 - £369.86)	£27,832	£25,006	£2,826

Validation

B32: The model was internally validated both by the external health economist who constructed the economic model, and an economist not involved in developing the cost-effectiveness model.

a) For the technical implementation of calculations and coding for correctness, reviewing and testing inputs and checking for implementation and/or logical inconsistencies, the CS suggests that a checklist of modelling errors and corrections was utilised. Please provide a detailed description of the validity assessment performed as well as the results.

b) Please complete the TECH-VER checklist (Büyükkaramikli et al. 2019, https://pubmed.ncbi.nlm.nih.gov/31705406/) and provide the results.

The **QC report** and the **TECH-VER checklist** have been uploaded as separate Annexes to the Clarification Questions.

B33. The company provided a cross validation with the atezolizumab appraisal (TA525). In addition to TA525, please provide cross validations for all relevant NICE TAs focussed on similar, potentially relevant, diseases, and elaborate on the differences regarding:

a) Model structure and assumptions

b) Input parameters related to:

   i. Clinical effectiveness

   ii. Health state utility values

   iii. Resource use and costs

c) Estimated (disaggregated) outcomes per comparator/intervention

   i. Life years

   ii. QALYs

   iii. Costs

a. In line with previous appraisals, we employed an identical model structure for the current submission (Table 7). It is important to note, however, that while the previous appraisals focused on second-line treatments, there are significant distinctions in the patient population for our submission. These variations primarily pertain to the FGFR3-altered status and the prerequisite that patients must have undergone prior treatments, at least one of which included an anti-PD-(L)1 inhibitor. In addition, all the previous appraisals in second line did not incorporate treatment waning in their economic models.

Table 7. Model structure and assumptions

Study	**TA525[11]**	**TA530[12]**	**TA692[13] (TA519)**	**TA739[14]**	**TA788[15]**	**ID1333**
Intervention and Line of Therapy	Atezolizumab 2L	Nivolumab 2L	Pembrolizumab 2L	Atezolizumab with carboplatin + gemcitabine 1L	Avelumab 1L maintenance	Erdafitinib FGFR+ 2L+ after exposure to at least an anti-PD-L1 treatment.
Model Structure	Three-state partitioned survival model	Three-state partitioned survival model	Three-state partitioned survival model	Three-state partitioned survival model	Three-state partitioned survival model	Three-state partitioned survival model
Time horizon	20 years	Lifetime	35 years (lifetime)	20 years	25 years (lifetime)	40 years
Treatment waning	No	No	No	Scenario analyses	No	No

b) Input parameters related to:

i. Clinical effectiveness

Table 8. Clinical effectiveness inputs

Study	**TA525[11]**	**TA530[12]**	**TA692[13] (TA519)**	**TA739[14]**	**TA788[15]**	**ID1333**

	Atezolizumab 2L	Nivolumab 2L	Pembrolizumab 2L	Atezolizumab with carboplatin + gemcitabine 1L	Avelumab 1L maintenance	Erdafitinib FGFR+ 2L+ after exposure to at least an anti-PD-L1 treatment.
Clinical outcomes used in the model	OS PFS	OS PFS TTD	OS Pembrolizumab: 10.1 (95% CI: 7.6, 12.9) Taxanes: 6.2 (95% CI: 5.2, 7.4) PFS Pembrolizumab: 2.1 (95% CI: 2.0, 2.2) Taxanes: 3.3 (2.3, 3.5) ToT Pembrolizumab: 6.84 (7.62) Paclitaxel: 2.96 (3.17) Docetaxel: 2.12 (2.02)		OS PFS TTD	

Models fitted	Atezolizumab OS: parametric mix-cure rate models Taxanes OS: Standard parametric models	All outcomes: standard parametric curves	OS: adjusted for treatment switching		Standard parametric curves Spline-based parametric survival model extrapolations	

ii. Health state utility values

Some appraisals (TA525 and TA530) had utilities by treatment, health state and on whether patients were on or off treatment (Table 9).

Table 9. Comparison of the health state utilities between the current submission and prior NICE HTA submissions

Study	**TA525**	**TA530**	**TA692 (TA519)**	**TA739**	**TA788**	**ID1333**
Intervention and Line of Therapy	Atezolizumab 2L	Nivolumab 2L	Pembrolizumab 2L	Atezolizumab with carboplatin + gemcitabine 1L	Avelumab 1L maintenance	Erdafitinib FGFR+ 2L+
Progression-free utilities	Atezolizumab: 0.684, Taxanes: 0.660	On treatment: 0.723 Off treatment: 0.650	0.731	0.642	0.772	[redacted]

Progressed disease utilities	Atezolizumab: 0.547, Taxanes: 0.547	On treatment: 0.666 Off treatment: 0.573	0.641	0.567	0.698	[redacted]

biii. Resource use and costs (unit costs, frequency per month) are presented in Table 10.

Table 10: HCRU and associated costs

Study	**TA525**	**TA530**	**TA692 (TA519)**	**TA739**	**TA788**	**ID1333**
Intervention and Line of Therapy	Atezolizumab 2L (frequency per month)	Nivolumab 2L (frequency per month)	Pembrolizumab 2L	Atezolizumab with carboplatin + gemcitabine 1L	Avelumab 1L maintenance	Erdafitinib FGFR+ 2L+
Consultant led oncologist follow-up visit	£163 PF: 1.00 PP: 0.00	£163 2 per cycle	£167.08 PF: 1.00 PP: 0.00		£194.17 PF: 0.88 PP: 0.93	
Non-consultant led oncologist follow-up visit	£100 PF: 0.00 PP: 1.00		£86.44 PF: 0.00 PP: 1.00		£147.38 PF: NR PP: NR	
Urologist					£104.92 PF: 0.07 PP: 0.04	
Hospice care	£1,119 PP: 70% of patients					
Health home visitor	£40 PF: 1.00 PP: 1.00		£77.01 PF: 1.00 PP: 1.00		£28 PF: NR PP: NR	

Community nurse specialist visit	£38 PF: 4.00 PP: 4.00	£69.20 PF: 2.00 PP: 2.00	£76.00 PF: 4.00 PP: 4.00		£84 PF: 0.62 PP: 1.00	£53.00 PF: 4.00 PP: 4.00
Clinical Nurse specialist					£84 PF: 0.62 PP: 1.00	
Dietician	£81 PF: 1.00 PP: 1.00		£33.00 PF: 1.00 PP: 1.00		£35 PF: 0.06 PP: 0.16	
GP home consultation		£77.22 PF: 2.00 PP: 2.00	£91.26 PF: 1.00 PP: 1.00		£156 PF: 0.26 PP: 0.72	£55.00 PF: 0.33 – 0.50 PP: 2.00
District nurse					£84 PF: 0.27 PP: 0.96	
GP Consultation	£36 PF: 1.00 PP: 1.00					
Pain medication	£3.69 PF: 0.00 PP: 30 daily					
Palliative chemotherapy	£277 PP: For 30% of the patients who will receive 2 cycles					
Palliative radiation therapy	£283 PP: For 42.7% of the population who will receive 1.9 courses	£128.22 PP: For 9.3% of patients				

Subsequent surgery		£3,201.68 PP: For 3.3% of patients				
Blood tests		£1 3-5 tests				£2.39 / £2.96 PF: 0.00 / 0.00 PP: 0.00 / 0.00
Blood transfusions		£170.14 For 10% of patients				
A&E Visit						£157.00 PF: 0.50 PP: 0.50
Outpatient visit						£197.00 PF: 1.50 PP: 1.00
Inpatient visit						£523.00 PF: 0.33 PP: 0.33
CT scan		£115 Every 8-9 weeks				£165.76 PF: 0.00 PP: 0.00
Radiotherapy						£790.00 PF: 0.00 PP: once for 9.3% of patients
Interventional radiotherapy						£194.00 PF: 0.00

						PP: once for 9.3% of patients
Terminal care		£6,153				

c. Disaggregated outcomes per intervention

No disaggregated outcomes were presented in the previous appraisals. We show the summary results in Table 11.

Table 11. Comparison of the disaggregated outcomes per intervention

Study	**TA525**	**TA530**	**TA692 (TA519)**	**TA739**	**TA788**	**ID1333**
Intervention and Line of Therapy	Atezolizumab 2L	Nivolumab 2L	Pembrolizumab 2L	Atezolizumab with carboplatin + gemcitabine 1L	Avelumab 1L maintenance	Erdafitinib FGFR+ 2L+
Life years	3.74	2.78	NR	NR	NR	1.66
QALYs	2.69	NR	1.95	NR	NR	[redacted]
Total costs	£77,211	NR	£60,634	NR	NR	[redacted]

B34. Although an advisory board was held to externally validate the economic model, further external validation of modelled effectiveness would be desirable. Please assess the validity of the model outcomes by comparing them with:

a) Evidence used to develop the model (e.g. the pivotal trial).

b) Evidence not used to develop the model (e.g. registry data).

a. Survival probabilities derived from the models were assessed by comparing them to the observed probabilities for OS, PFS, and TTD. This analysis facilitated the identification and selection of the most suitable fitting model. The comparative results can be found in Clarification Question B8.

b. Given the limited availability of data regarding clinical outcomes in patients with mUC who have undergone prior immunotherapy, it was not feasible to validate the predictions of our model using an appropriate patient cohort. However, to assess the outcomes of our current submission, we conducted a comparative analysis with similar appraisals, namely TA525[11] and TA692[13], which provided valuable insights for comparison.

Section C: Textual clarification and additional points

Implementation and NHS considerations:

C1. In respect to clinical advisor concerns noting regular ophthalmological testing is required for patients on erdafitinib. Please discuss how potential delays in receiving eye test results might impact timely administration of erdafitinib and its adoption in clinical practice compared to more readily available treatments.

J&J recognise clinical advisor concerns which could arise with the introduction of any new therapy however, we take this opportunity to clarify that regular ophthalmological testing is not defined as 2-3 weekly. In line with the THOR trial protocol and (draft) Summary of Product Characteristics for erdafitinib, a baseline ophthalmological examination should be performed prior to initiating erdafitinib and monthly during the first four months of treatment and every 3 months afterwards, and urgently at any time for visual symptoms. As detailed in the Budget Impact Analysis, the estimated population in England eligible to initiate erdafitinib is [redacted] patients in year 1 rising to [redacted]

patients in year 5. Therefore, J&J do not anticipate ophthalmological testing to impact timely administration and adoption of erdafitinib in clinical practice.

C2. In respect to the clinical advisor reports, please outline strategies for ensuring:

a. Adequate ophthalmological resources to support erdafitinib rollout, addressing the clinical advisors' shared concerns raised about NHS capacity and the need for regular (2–3 weekly) ophthalmological testing, consider how might this also impact economic estimates.

> *"The NHS are unlikely to have the capacity for the required testing"*
>
> "*It would be extremely difficult to find the adequate ophthalmological resources required to support the rollout of erdafitinib within the NHS."*
>
> *"This sentiment was echoed by the advisors, who all reiterated that they do not have the necessary competence to conduct ophthalmological testing themselves and would therefore rely on ophthalmologists to furnish them with the test results they'd need to manage potentially asymptomatic eye disorders".*

b. Details on any planned educational programs to help oncologists manage patients on erdafitinib, as recommended by your clinical advisors and any associated costs.

> *"There could be quite a steep learning curve for treating oncologists to encounter, as they will not have regular exposure to erdafitinib, and may therefore struggle with learning how to deal with associated treatment toxicities. SC emphasised that an educational programme would be needed to help oncologists get up to speed with how to manage patients on erdafitinib".*

a. With regards to ophthalmological examinations, the (draft) SmPC submitted to the MHRA provides guidance under section 4.4 Special warnings and precautions for use on ocular disorders. In contrary to the 2-3 weekly ophthalmological testing frequency in the advisor's statement above, the SmPC states "Perform monthly ophthalmological examinations including an

Amsler grid test during the first 4 months of treatment and every 3 months afterwards, and urgently at any time for visual symptoms (see section 4.2). In the THOR clinical trial, post-baseline ophthalmologic examinations were performed only when deemed clinically necessary based on the findings of the Amsler grid tests and clinical assessment, or at regular intervals as deemed necessary by the screening ophthalmologist. Therefore, the SmPC states if any abnormality is observed, follow the management guidelines in Table 3." Prior to initiating erdafitinib, a baseline ophthalmological exam should be performed. The cost of ophthalmology consultations has been included in section B.3.5.4.3. of document B as follows: A single ophthalmology consultation was costed as £166.64 in line with the 2021–22 NHS reference costs, and subsequently inflated to £178.35 (2022/2023).[113] In the economic model, patients on treatment with erdafitinib require monthly ophthalmological examinations during the first 4 months of treatment and every 3 months afterwards.

b. J&J are planning a national medical education program in partnership with oncologists with clinical experience in managing patients through the THOR trial or pre-approval access programme. The program is aimed at oncologists and agenda topics will include clinical management focusing on erdafitinib dosing, dose reduction and management of adverse reactions in line with guidance outlined in section 4.2 of the erdafitinib SmPC. The cost of which will be absorbed by J&J.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

NICE National Institute for Health and Care Excellence

About you

1.Your name	**JEANNIE RIGBY**
2. Name of organisation	ACTION BLADDER CANCER UK
3. Job title or position	CHIEF EXECUTIVE
4a. Brief description of the organisation (including who funds it). How many members does it have?	Action Bladder Cancer UK is a national registered charity dedicated to providing information and support to those with bladder cancer and their families and carers; raising awareness; improving outcomes; providing health professional learning and funding research. ABC UK is governed by a trustee board (10 members) and has full time Chief Executive and core staff, and many patient volunteers, and a network of patient support groups. ABC UK are funded mainly by public donations, legacies and fundraising, together with a smaller amount of corporate arms length grants.
4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.]	Not applicable in the past 12 months

If so, please state the name of the company, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	NONE
5. How did you gather information about the experiences of patients and carers to include in your submission?	A core remit of ABC UK is to provide support and information for those with bladder cancer and their carers. We work closely with many patients (or family members) every year by providing direct support by phone helpline and email – many of these contacts with patients will concern treatment choices (or lack of), the effects of treatment and the impact of bladder cancer on daily life and coping with this disease along what can be a long, and sometimes complicated, treatment pathway. We set up and sustain patient support groups across the UK. We run a programme of patient support events. We also collect information about patient experience through our extensive education programme for specialist urology/cancer nurses. We conduct patient surveys to gather information on the direct impact of bladder cancer, impacts of treatments and on-going surveillance and monitoring and potential recurrence of bladder cancer. We provide patient views and input to many clinical trials and research projects. We also encourage many research projects to include PROMS aspect to their research, sometimes funding this work or providing patient participants for this research. As part of our core Governance, patients make up 50% of our Trustee board (together with clinicians forming the other 50%). We have many patient volunteers who help us to deliver our work and programmes. We work closely with patients on the production, and regular updating, of all of our ABC UK information materials and web content. Patients also input into all submissions to both NICE and SMC regarding use of medicines for the treatment of bladder cancer, and have reviewed and inputted into this submission.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	A common psychological impact is patients struggling to come to terms with the very poor outcomes presented on their diagnosis. It is also very distressing to realise that treatment options are extremely scarce. Many of the calls we get from these patients (or a family member) ask whether there are any other treatment options available for them. In addition to coming to terms with the very poor outlook they must also endure the adverse side effects of currently available treatments, leaving patients both emotionally and physically exhausted. This can have a toll on more general health, including mental health. Family members and carers struggle between providing optimistic support and hoping that the ordeal they are forced to witness gets no worse, or lasts too long, giving rise in many cases to feelings of guilt at their own mixed emotions. They can also feel anger or helpless at the lack of availability of alternative treatments and the poor quality of life the patient is having to endure. Our patient groups, our patient survey responses and patient support helpline enquiries all reflect these views and similar experiences for patients with this condition. ABC UK are often asked by these patients (or a carer/family member) what else can be done – if there are other treatment options, or treatments which may have less adverse treatment effects than already undergone. Of significant concern to these patients is the lack of any progress in new treatment options over very many years, especially compared with most other forms of cancer. 62 yr old male deceased: 'It was a shock to be told my cancer had gone through the [bladder] wall … I had chemotherapy and that made me really ill so they had to stop it. Then I was told they couldn't do much more. That's it.'

Current treatment of the condition in the NHS **7. What do patients or carers think of current treatments and care available on the NHS?**	The aim of treatment for most patients in this group is to control the cancer, relieve symptoms and maintain quality of life. However, treatment options for bladder cancer are very limited, patients and families can be shocked by the limited treatment options are available. The current treatment options for this patient group can also adversely affect quality of life. It can be difficult to decide which treatment to try or whether to have treatment at all, issues which also have to be considered are how the treatment might affect your quality of life. This includes the possible side effects as well as the process of any treatment. A patient might undergo one, or more, of the treatments below for metastatic bladder cancer: • chemotherapy • immunotherapy or targeted cancer drugs (there are very few immunotherapy treatments widely available in the UK) • radiotherapy to the site where the cancer has spread • surgery to remove cancer tumour in the bladder • surgery to unblock the ureters or urethra • a clinical trial. Chemotherapy is a common treatment offered for metastatic bladder cancer – however side effects include: sickness; loss of appetite; losing weight; extreme tiredness; increased risk of getting an infection; bleeding and bruising easily; diarrhoea or constipation; hair loss. Some patients may also not be eligible for further chemotherapy due to co-morbidities, the percentage of treatment-related adverse events or longer-term tolerability with chemotherapy.
8. Is there an unmet need for patients with this condition?	Yes. There is an unmet need for treatment for this patient group following chemotherapy or where chemotherapy has proved unsuitable. There is little other treatment choice available.

9. What do patients or carers think are the advantages of the technology?	**Clinical trial results have shown that Erdafitnib can give a significantly improved survival rate, with a lower rate of adverse treatment events for this patient group.** Clinical trials evidence lead us to believe that Erdafitnib would improve a patient's quality of life and experience of care: • By improving the patient experience of care by providing alternatives and treatment options which may be more suitable to their own personal health needs and diagnosis. • By providing a treatment in circumstances where the few other treatment options available have been tried, or had to cease (due to side effects, extreme fatigue, toxicity etc). • Many previous clinical studies have shown that health related quality of life can be seriously impaired in patients with metastatic bladder cancer which is treated with chemotherapy as demonstrated in the relatively low percentage of patients who are deemed suitable to receive this chemotherapy, or who are able to tolerate a complete treatment regime because of serious, negative side effects. • This is reinforced by ABC UK's own experience of patients telling us (through our helpline, support groups and surveys) about the negative impact chemotherapy side effects can have on their quality of life through treatment-related toxicities, extreme fatigue, nausea etc. **Erdafitnib vs Chemotherapy** Patients feel that Erdafitnib has particular advantages given trial results demonstrate longer overall survival with Erdafitnib than chemotherapy (current most common treatment) among patients with metastatic urothelial carcinoma. A randomised clinical trial as compared Erdafitnib with chemotherapy in patients with metastatic urothelial carcinoma with susceptible *FGFR3/2* alterations who had progression after one or two previous treatments. The primary end point was overall survival. A total of 266 patients underwent randomization to Erdafitinib or to chemotherapy. With a median follow-up of 15.9 months, the median overall survival was significantly longer with erdafitinib than with chemotherapy (12.1 months vs. 7.8 months).

	The median progression-free survival was also longer with erdafitinib than with chemotherapy (5.6 months vs. 2.7 months). Treatment-related adverse events that led to death were less common with Erdafitinib than with chemotherapy (in 0.7% vs. 5.4% of patients). The conclusion that Erdafitinib therapy resulted in **significantly longer overall survival than chemotherapy** among patients with metastatic urothelial carcinoma was felt to be of paramount importance by patients and carers. The other key point noted by patients was **progression-free survival and its affect on quality of life** for both patients and carers. The patient benefits of Quality of Life, benefits to physical and mental well-being, less adverse effects, as well as improved survival should be given adequate weight for a patient group with very limited available treatment options. Erdafitnib is currently taken in tablet form, this is perceived to have advantages over courses of chemotherapy given intravesically. Patients also told us it was of key importance to them and other patients that such new therapies (ie: targeted), are given a full and extensive opportunity to be used in wider clinical practice to not only benefit patients who currently have metastatic bladder cancer, but also to provide results and evidence for further development of this therapy for use at other stages of bladder cancer. This is particularly in the context of the paucity of effective treatment options for bladder cancer. This would have the potential not only to improve outcomes for a wider coterie of patients, but also for longer-term cost savings within the NHS. This treatment offers real hope for a group of very poorly served patients of a longer survival and time with their families, with less adverse effects and improved quality of life.

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Reactions from patients and carers consulted regarding Erdafitnib, and related clinical trial results and descriptions of how the therapy is administered, have been mainly positive. Any disadvantages perceived by patients were due to potential limited, or lack of, access to those patients who would benefit most from Erdafitnib.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients require to be tested for eligibility for treatment with Erdafitnib. Those not eligible would not be treated with Erdafitnib. Those who would benefit most are those who test to be eligible, who may be offered significant improvement in survival and progression free survival, with less adverse treatment effects than conventional chemotherapy.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Equality of access.

Other issues

13. Are there any other issues that you would like the committee to consider?	Erdafitnib represents a new area of treatment for bladder cancer – approval for use in the UK would not only add to the very limited treatment options, but also provide an opportunity for wider clinical use which would provide highly valuable evidence for further development and guidance, as well as potential for use in other stages/types of bladder cancer. Bladder cancer has been neglected in terms of access to new treatments, which directly reflects on the widespread poorer outcomes for those with bladder cancer, and the negative impact on them and their families. The patient benefits of QoL, benefits to physical and mental well-being, less adverse effects, as well as improved survival should be given adequate weight for this disease area.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	• There are very limited treatment options for this patient group, it is vital that new, effective, therapies for bladder cancer are made available for patients. • Metastatic bladder cancer has a severe impact on quality of life, and of those of carers/families. • Clinical trial results have shown that Erdafitnib can give a significant improved survival rate, with a lower rate of adverse treatment events for this patient group. • Trial results have shown that patients can experience an improvement in their quality of life which, together with improved survival, is of significant benefit to themselves and their carers/families. • It is imperative that new, groundbreaking, therapies are made available for wider clinical use to provide cumulative evidence of effectiveness and to allow further development into usage in other areas/stages of the disease.

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Single Technology Appraisal

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

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

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- Your response should not be longer than 10 pages.

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About you

1.Your name	[redacted]
2. Name of organisation	Fight Bladder Cancer
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Fight Bladder Cancer is a patient-led charity dedicated to supporting individuals affected by bladder cancer, raising awareness of the disease, and advocating for improved research and treatment options. The charity provides information, support, and resources for patients, carers, and healthcare professionals, as well as facilitating peer-to-peer support through online forums and local groups. Fight Bladder Cancer is funded through a combination of donations, fundraising events, and grants from trusts and the pharmaceutical industry. The organisation has a community of thousands, including patients, carers, healthcare professionals, and supporters.

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	Patient Information Booklets & National Cancer Patient Experience Survey (02/11/2023) Amount: £10,000.00 Company: Roche UK Global RFP Request for Proposals (RFP) Engaging the Bladder Cancer Patient Community in Research and Publications (22/11/2023) Amount: £15,552.36 Company: Pfizer Charity Leaders Forum (31/01/2024) Amount: £1,200.00 Company: Pfizer Look. And You Will C Us. Translations (30/04/2024) Amount: £10,000.00 Company: Gilead Awareness - Conferences & Events (30/04/2024) Amount: £9,000.00 Company: Janssen J&J Johnson & Johnson Innovative Medicine Policy - Exemplar (30/04/2024) Amount: £30,000.00 Company: Janssen J&J Johnson & Johnson Innovative Medicine Patient and Carer Information Booklets (09/05/2024) Amount: £9,094.80 Company: Janssen J&J Johnson & Johnson Innovative Medicine

4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gathered information about the experiences of patients and carers through several methods. Surveys were distributed to patients and carers affected by metastatic or unresectable bladder cancer, capturing their experiences with the condition, current treatments, and quality of life. Feedback was also collected from online bladder cancer support communities. Lastly, we collaborated with other bladder cancer patient organisations to gather insights from their members, especially regarding unmet needs and the impact of current treatments.

Living with the condition

6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Living with metastatic or unresectable bladder cancer is a harrowing and emotionally draining experience for both patients and carers. Patients endure relentless treatments like chemotherapy, radiotherapy, and clinical trials, all of which come with significant side effects such as fatigue, infections, and changes in bodily functions. These treatments often leave patients in constant pain and discomfort, while the progression of the disease leads to a steep decline in quality of life. Many patients express deep frustration at the inefficacy of treatments or delays in care, heightening their fear and anxiety as they face limited options for effective treatment. "My cancer has spread to my lungs and bones, and the treatments are just delaying the inevitable." "I've had 3 cycles of chemo and the side effects are unbearable, leaving me in constant pain and unable to move around as I used to." For carers, the emotional burden is immense as they watch their loved ones suffer. They take on the responsibility of managing daily care, coordinating medical appointments, and coping with their loved ones' deteriorating health. The emotional weight of caring for someone in such severe decline, combined with the physical demands of the role, can leave carers feeling overwhelmed, helpless, and emotionally drained. Many struggle with poor communication from healthcare providers, which adds to their stress and uncertainty about treatment outcomes. "I'm exhausted, physically and emotionally. Between hospital visits and managing his care at home, I hardly have time to take a breath." "I feel like I'm drowning in responsibility. Every day brings something new, and I'm constantly afraid of what's next." Both patients and carers often describe the experience as isolating, exhausting, and fraught with fear and frustration. The emotional toll is compounded by feelings of injustice as they confront the limitations of medical intervention. While some find comfort in support groups or online communities, the journey through metastatic or unresectable bladder cancer is marked by profound pain and emotional turmoil, for both those living with the disease and those caring for them.

	"I feel like we're battling this alone, and the healthcare system is just dragging its feet." "The lack of clear communication from doctors only adds to our stress and uncertainty. It feels like we're constantly left in the dark."

Current treatment of the condition in the NHS

7. What do patients or carers think of current treatments and care available on the NHS?	Patients and carers express mixed feelings about the treatments and care available on the NHS for bladder cancer. Some praise the quality of care, feeling fortunate to receive free treatment and access to advanced therapies. "I feel incredibly lucky to have access to treatment through the NHS. The care I've received has been top-notch, and I can't imagine going through this without it." "The nurses and doctors have been amazing. They've been there every step of the way, making sure I understand my treatment and what's next." However, many voice significant frustrations, particularly with delays in diagnosis, treatment timelines, and communication with healthcare providers. "I am angry at my doctor not telling me how long I have left to live… He told me I had incurable cancer and that it has spread to the lungs." "The communications, or lack of, through Urology are beyond awful and are creating a lot of stress and anxiety for my husband." "I thought that was too long to wait but got told that the secretary was on holiday till the first week of July… I've never waited this long in 11 years of having this." Access to alternative treatments and clinical trials is another issue. While some patients benefit from therapies like immunotherapy or chemotherapy, others feel their options are limited and not tailored to their needs. "We had to push for advanced genomic testing after the standard treatments stopped working. Why isn't this offered earlier?"

8. Is there an unmet need for patients with this condition?	The situation for metastatic or unresectable bladder cancer patients is dire, with glaring gaps in care that leave many struggling in uncertainty and fear. Communication with healthcare providers is woefully inadequate, often leaving patients in the dark about their treatment plans. The lack of clear, consistent updates exacerbates the emotional toll, as patients face the terrifying prospect of battling an aggressive cancer without knowing what lies ahead or when help will arrive. Delays in treatment are a critical failure, with life-saving procedures postponed or cancelled at alarming rates. Patients with are left waiting in anguish, knowing that every lost day could allow their cancer to advance. The system's inability to respond urgently to these high-risk cases leaves many feeling abandoned and powerless as they watch their condition deteriorate. Even more alarming is the limited access to alternative treatments. Patients have few options. The promise of clinical trials or personalised treatments like advanced genomic testing remains out of reach for many, leaving them to endure treatments that are ineffective or not tailored to their needs. The lack of innovation and personalised care in the face of such a deadly disease is nothing short of devastating.

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The THOR study compared erdafitinib to both chemotherapy and pembrolizumab in people with advanced bladder cancer. Erdafitinib significantly improved survival compared to chemotherapy, with patients living an average of 12.1 months versus 7.8 months. Erdafitinib also delayed cancer progression and increased tumour shrinkage more effectively than chemotherapy. More patients experienced tumour shrinkage with erdafitinib than with pembrolizumab (40% vs. 22%). Both treatments had manageable side effects, but erdafitinib resulted in fewer treatment-related deaths compared to chemotherapy or pembrolizumab. "Just had my cystoscopy today, and all clear! One year on this amazing clinical trial." “Check-up time to see if this trial drug is working, update, it's only bloody worked, no tumour, it's gone!"

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	In the THOR trial, people with advanced bladder cancer treated with erdafitinib or chemotherapy experienced similar rates of serious side effects (around 46%). Common side effects of erdafitinib included hand-foot syndrome (10%), mouth inflammation (8%), nail disorders (6%), and high phosphate levels (5.2%), while chemotherapy commonly caused low white blood cell counts (13%) and anaemia (6%). Erdafitinib also led to a specific eye condition, central serous retinopathy, in 17% of people, though mostly mild. Deaths related to treatment were lower with erdafitinib (0.7%) compared to chemotherapy (5.4%). Over time, cancer cells may also become resistant to erdafitinib, reducing its effectiveness in the long run. Patients taking this drug need regular check-ups, especially to monitor their phosphate levels and eye health, which can be time-consuming and may add extra stress. "After 9 months on a clinical trial, I'm on my third water infection [urinary tract infection], not liking the look of this one though, definitely blood in my wee and lower abdomen pain." "2nd week of no treatment as went to see ophthalmologist yesterday and there is thickening of cornea in both eyes."

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Benefit more: Certain groups of patients with advanced urothelial cancer may benefit more from erdafitinib than others. Specifically, patients who have already undergone chemotherapy and immune checkpoint inhibitor treatments (such as anti–PD-1 or anti–PD-L1 agents like pembrolizumab) could experience better outcomes with erdafitinib. This drug offers a targeted mechanism that focuses on FGFR alterations, which tend to respond poorly to immunotherapies. Patients with upper tract urothelial cancer may also gain more from erdafitinib. FGFR alterations are more common in this subtype, with about 36% of cases showing these genetic changes. Additionally, people whose tumours exhibit low levels of PD-L1 expression might respond better to erdafitinib. FGFR-altered tumours often have low PD-L1 expression and fewer immune cell infiltrations, making them less responsive to immunotherapy. Erdafitinib, by contrast, directly targets tumour growth driven by FGFR mutations, bypassing the limitations of immune-based treatments. Finally, patients who are unsuitable for further chemotherapy due to prior toxicities or underlying health conditions may find erdafitinib a valuable alternative. Its distinct safety profile and targeted action offer a different treatment option that could be less taxing than traditional chemotherapy. Benefit less: Because erdafitinib can cause central serous retinopathy and other ocular side effects, people with pre-existing significant eye conditions may find these risks outweigh the benefits. If a person is doing well on immunotherapy, such as pembrolizumab, switching to erdafitinib may offer no added benefit.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	The new NICE severity modifier may not fully address the needs of people with metastatic or unresectable FGFR-altered urothelial cancer. This group of patients, often older and with limited treatment options, faces significant challenges in accessing innovative therapies like erdafitinib. The severity modifier, introduced to assign additional value to treatments for severe conditions, aims to replace the previous end-of-life modifier. However, it may still fall short in capturing the true value of treatments for those in later stages of cancer. In the case of erdafitinib, although it offers a clear benefit by extending survival and improving quality of life, the weighting applied under the severity modifier might not be sufficient to reflect its full impact on this specific population. This is especially true for older patients, whose remaining life expectancy is shorter, potentially leading to a lower QALY gain and, consequently, a lower overall score in NICE's cost-effectiveness assessment. As a result, some treatments that would have qualified for the highest end-of-life weighting may no longer receive the highest severity weighting, risking limited access for patients who urgently need these therapies. Adjustments in how the severity modifier is applied could help ensure broader access to innovative treatments like erdafitinib, reducing health inequalities and improving outcomes for a vulnerable population. Another key issue in the English healthcare system is access to genetic testing. Patients need to undergo FGFR testing to determine their eligibility for erdafitinib. However, inequalities in access to advanced genetic testing may exist across different regions of the NHS, particularly in areas with fewer specialised diagnostic services. This could lead to some patients being excluded from potentially life-saving treatments due to a lack of local testing infrastructure. Ethnic diversity in clinical trials is another factor to consider. Urothelial cancer trials, including those for erdafitinib, often underrepresent certain racial and ethnic groups. For example, Black and minority ethnic patients tend to be underrepresented, which limits the data available on how erdafitinib performs across different populations. This lack of diversity could affect how widely the treatment is applied in practice. Geographic disparities within England also need to be addressed. Advanced cancer treatments like erdafitinib may be more readily available in large urban centres with specialist oncology services, whereas patients in rural or less-resourced areas may have limited access. This could exacerbate existing inequalities in cancer treatment across the country.

Other issues

13. Are there any other issues that you would like the committee to consider?	Introducing erdafitinib widely may require investments in diagnostic facilities, genetic testing capacity, and clinician education. Ensuring that healthcare systems are prepared to accommodate these needs is essential for equitable access to the therapy.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission.	- People with metastatic or unresectable FGFR-altered urothelial cancer face severe challenges with limited treatment options, making innovative therapies like erdafitinib essential. - Erdafitinib, as shown in the THOR trial, significantly improves survival and delays cancer progression compared to chemotherapy and pembrolizumab, with manageable side effects. - Access to erdafitinib may be hindered by inequalities in genetic testing availability, particularly in regions with less diagnostic infrastructure, limiting patient access to this life-saving treatment. - The NICE severity modifier may not adequately reflect the value of erdafitinib for older patients, leading to potential inequalities in access to treatment. - Geographic and ethnic disparities in clinical trials and treatment availability may further limit access to erdafitinib for vulnerable populations in rural areas or among minority groups.

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Single Technology Appraisal

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

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you

NICE National Institute for Health and Care Excellence

1. Your name	[redacted]
2. Name of organisation	British Uro-oncology Group
3. Job title or position	[redacted]
4. Are you (please select Yes or No):	An employee or representative of a healthcare professional organisation that represents clinicians? Yes A specialist in the treatment of people with this condition? Yes A specialist in the clinical evidence base for this condition or technology? Yes Other (please specify):
5a. Brief description of the organisation (including who funds it).	The British Uro-oncology Group (BUG) was formed in 2004 to meet the needs of clinical and medical oncologists specialising in the field of urology. As the only dedicated professional association for uro-oncologists, its overriding aim is to provide a networking and support forum for discussion and exchange of research and policy ideas. Funding is from the members.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] **If so, please state the name of manufacturer, amount, and purpose of funding.**	Not to my knowledge.
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

The aim of treatment for this condition

6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To stop progression and to extend overall survival in patients who have incurable advanced urothelial carcinoma that harbours an FGFR gene alteration.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	I think that extended survival and a period without cancer progression (and so hopefully maintenance of symptom control) are probably more important measures of efficacy. However, the percentage of patients with an objective radiological response was higher with erdafitinib than with chemotherapy in the THOR trial (45.6% vs. 11.5%; relative benefit, 3.94; 95% CI, 2.37 to 6.57; P<0.001)
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes. There are no other life extending treatment options for this group of patients that the NHS currently reimburses. Their prognosis is poor (median overall survival of 7.8 months in the chemotherapy control arm of the THOR trial).

What is the expected place of the technology in current practice?

9. How is the condition currently treated in the NHS?	First line treatment for metastatic urothelial carcinoma is with platinum-based (cisplatin or carboplatin) combination chemotherapy and/or immunotherapy. In those fit to receive it, this is optimally delivered as chemotherapy followed by maintenance treatment with avelumab immunotherapy. Beyond that, further chemotherapy is of limited efficacy and is not known to extend survival (median survival 7.8 months) and the alternative is palliative care. Alternatives to these options that do extend survival (enfortumab vedotin) are not currently reimbursed by the NHS.

9a. Are any clinical guidelines used in the treatment of the condition, and if so, which?	The EAU and ESMO guidelines were both updated in the last 12 months and recommend the use of erdafitinib in the manner under consideration in this technology appraisal. European Association of Urology: https://uroweb.org/guidelines European Association of Medical Oncology: Ann Oncol 2024 35485-490; DOI: (10.1016/j.annonc.2024.03.001) (NICE guidance on bladder cancer does not mention erdafitinib because it is 9 years old)
9b. Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is currently well defined and there is strong consensus for the approach outlined above including the use (if available) of erdafitinib in the manner being considered in this TA.
9c. What impact would the technology have on the current pathway of care?	All patients with metastatic urothelial carcinoma would have somatic testing for FGFR gene alterations done on their archival biopsy or surgical sample (this test is already on the national test directory and so available for use). At the point of cancer progression after the use of chemotherapy and immunotherapy, those with an FGFR gene alteration would be treated with erdafitinib.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Erdafitinib has been available through an access scheme from Janssen prior to licensing and this TA. We have therefore had a short period of access that has reflected the manner being considered in this TA.
10a. How does healthcare resource use differ between the technology and current care?	As described above, patients receive platinum-based chemotherapy and immunotherapy first. When cancer progression occurs subsequently, we have no currently available life extending treatment options. The option currently available at this point is therefore further chemotherapy (which is not very effective) or palliative care. If erdafitinib were available, we would use this instead in patients who had a cancer with an FGFR gene alteration because this extends median survival.

10b. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Oncology clinics led by oncologists who specialise in urothelial carcinoma and within a bladder cancer multi-disciplinary team.
10c. What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	FGFR gene testing on archival biopsy or surgical tumour samples is already on the national test directory and so ready for use. Many UK centres have already been using erdafitinib in the THOR trial and through the Janssen access program. The oncology clinics are already in place for the other treatments that these patients receive (chemotherapy, immunotherapy). There is no particular investment needed beyond this.
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Erdafitinib is proven to extend overall survival with a manageable toxicity profile in the THOR trial. Otherwise, there are no life extending treatment options that the NHS currently reimburses.
11a. Do you expect the technology to increase length of life more than current care?	Yes. The THOR trial showed this.
11b. Do you expect the technology to increase health-related quality of life more than current care?	To my knowledge, these data have not yet been presented for the THOR trial.
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No (beyond the requirement for a somatic FGFR alteration within the patient's cancer). Subgroups based on clinical characteristics all appeared to benefit from erdafitinib rather than chemotherapy in the THOR trial.

The use of the technology

13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	FGFR gene testing will be required on archival tumour samples but this is already available on the national test directory and mirrors processes in place in other cancers. Beyond that, this is no different to many other cancer drugs in terms of the practicalities of delivery. And there will be some benefits of an oral drug over the alternative of intravenous chemotherapy in terms of chemotherapy unit resources (pharmacist capacity, chemo nurse capacity, chemo chair time) which most centres find a challenge. The only difference that will impact usage will be the need to refer a small minority of patients to ophthalmology for central serous retinopathy which can occur in some patients. We have not found this to be a challenge when we have used this drug in our centre.
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Patients will continue erdafitinib until they have cancer progression based on interval imaging or stop due to toxicity. This is no different than for other treatment options (chemotherapy, immunotherapy).
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No.

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	This is the first biomarker selected treatment option for urothelial carcinoma based on a somatic gene alteration. A life extending precision medicine option for this disease, rather than chemotherapy, is a welcome advance.
16a. Is the technology a 'step-change' in the management of the condition?	Yes in the sense that this is the first biomarker selected treatment option for this disease. Targeting the biology of this subset of cancers rather than poisoning with chemotherapy seems like a step forward.
16b. Does the use of the technology address any particular unmet need of the patient population?	It extends their median survival which is otherwise under 1 year. We do not have an alternative way to do this that is currently reimbursed through the NHS.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	This drug has a toxicity profile that is broadly similar in frequency and severity overall compared to chemotherapy. However, the pattern is a little different to chemotherapy. In particular, a small minority of patients develop central serous retinopathy, which can require input from ophthalmology. The other side effects are common for tyrosine kinase inhibitor drugs, for which we have wide experience in oncology in other settings.

Sources of evidence

18. Do the clinical trials on the technology reflect	Yes. We took part in the THOR trial in the UK.

current UK clinical practice?	
18a. If not, how could the results be extrapolated to the UK setting?	They are directly relevant.
18b. What, in your view, are the most important outcomes, and were they measured in the trials?	Overall survival (the primary endpoint in THOR) is the key endpoint, which was extended. The other secondary endpoints were suitably comprehensive and favour the use of erdafitinib.
18c. If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable.
18d. Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not in my experience of using it.
19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No.
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA525 or TA739?	No.

21. How do data on real-world experience compare with the trial data?	They are similar with no concerns.

Equality

22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not that I can think of.
22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.	• This drug extends median survival in circumstances where this is otherwise under 1 year • This is the first biomarker selected treatment option for urothelial carcinoma • The toxicity profile is predictable and manageable • These patients have no other useful treatment options that the NHS currently reimburses •

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

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

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

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Declared competing interests of the authors: None.

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

Rider on responsibility for report:

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors:

Jonathan Emerson acted as joint project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence, critiqued the company's definition of the decision problem and contributed to the writing of the report. Willem Witlox acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Mirre Scholte, Andrea Fernández Coves, and Teebah Abu-Zahra acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Caro Noake critiqued the search methods in the submission and contributed to the writing of the report. Jiongyu Chen acted as a hybrid systematic reviewer/health economist, critiqued the clinical effectiveness methods/evidence and economic evaluation and contributed to the writing of the report. Kevin McDermott acted as systematic reviewer, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Nigel Armstrong acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Manuela Joore acted as health economist on this assessment, critiqued the company's economic evaluation, contributed to the writing of the report and provided general guidance. Robert Wolff acted as joint project lead, supervised meetings and the running of the project, and contributed to the writing of the report.

Abbreviations

1L	First-line
2L	Second-line
3L	Third-line
4L	Fourth-line
ADCs	Antibody-drug conjugates
AdViSHE	Assessment of the Validation Status of Health-Economic
AE	Adverse event
AESI	Adverse events of special interest
AIC	Akaike information criterion
ASCO	American Society of Clinical Oncology
ATC	Average treatment effect for the control
ATE	Average treatment effect
ATO	Average treatment effect for overlap
ATT	Average treatment effect for the treated
AUC	Area under the curve
BIC	Bayesian information criterion
BOR	Best overall response
BSA	Body surface area
BSC	Best supportive care
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CEA	Cost effectiveness analysis
CEM	Cost effectiveness model
CENTRAL	Cochrane Central Register of Controlled Trials
CI	Confidence interval
CNS	Central nervous system
CON	Confidential
COVID-19	Coronavirus disease 2019
CPS	Combined positive score
CR	Complete response
CRD	Centre for Reviews and Dissemination
CS	Company submission
CYP3A4	Cytochrome P450 3A4
DAPS	Directly Accessed Pathology Services
DCR	Disease control rate
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
EAG	Evidence Assessment Group
EAU	European Association of Urology
ECO	European Cancer Organization
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
eMIT	Electronic market information tool
EORTC QLQ C30	European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire
EQ-5D-3L	European Quality of Life-5 Dimension, 3-Level
EQ-5D-5L	European Quality of Life-5 Dimension, 5-Level
ESMO	European Society for Medical Oncology
ESS	Effective sample size
EU-CTR	European Union-Clinical Trials Register
FACT-Bl	Functional Assessment of Cancer Therapy – Bladder

FDA	Food and Drug Administration
FE	Fixing errors
FGFR	Fibroblast growth factor receptor
FGFR3	Fibroblast growth factor receptor 3
FV	Fixing violations
GFR	Glomerular filtration rate
HCRU	Healthcare resource use
HR	Hazard ratio
HRG	Healthcare Resource Group
HRQL	Health-related quality of life
HRQoL	Health-related quality of life
HSUVs	Health state utility values
ICER	Incremental cost-effectiveness ratio
ICTRP	International Clinical Trials Registry Platform
Incr.	Incremental
IPD	Individual patient data
IPW	Inverse probability weighting
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
KM	Kaplan-Meier
KSR	Kleijnen Systematic Reviews Ltd
LY	Life year
MAIC	Matching-adjusted indirect comparison
Max	Maximum
Min	Minimum
MJ	Matters of judgement
MMRM	Mixed models for repeated measures
mUC	Metastatic urothelial carcinoma
MVAC	Methotrexate, vinblastine, doxorubicin, and cisplatin
N	Number of patients
N/A	Not applicable
NCRAS	National Cancer Registration and Analysis Service
NE	Not evaluable
NES	Non-elective short stay
NEL	Non-elective long stay
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NL	The Netherlands
NMA	Network meta-analysis
NMB	Net monetary benefit
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PAS	Patient Access Scheme
PD	Progressive disease/progressed disease
PD-1	Programmed death receptor-1
PD-(L)1	Programmed death-(ligand)1
PF	Progression free
PFS	Progression-free survival
PGI-S	Patient Global Impression of Severity scale
PH	Proportional hazards
PRESS	Peer Review of Electronic Search Strategies

PR	Partial response
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PRO	Patient-reported outcome
PSA	Probabilistic sensitivity analysis
PSM	Partitioned survival model
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
QoL	Quality of life
RCT	Randomised controlled trial
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria In Solid Tumours
RW	Real-world
RWE	Real-world evidence
SACT	Systemic anti-cancer treatment
SAE	Serious adverse event
SD	Standard deviation
SD	Stable disease
SE	Standard error
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SoC	Standard of care
STA	Single technology appraisal
TA	Technology appraisal
TEAE	Treatment-emergent adverse event
THOR	Trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations
TRAEs	Treatment-related adverse event
TSD	Technical Support Document
TTD	Time to treatment discontinuation
TTNT	Time to next treatment
UC	Urothelial carcinoma
UK	United Kingdom
UMC+	University Medical Center+
US	United States
VAS	Visual analogue scale
WHO	World Health Organization

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1. Executive summary

This report presents an independent review and critical appraisal of the clinical and cost effectiveness evidence submitted by Janssen for erdafitinib (Balversa®) in the treatment of metastatic or unresectable fibroblast growth factor receptor (FGFR)-altered urothelial cancer. Commissioned by the National Institute for Health and Care Excellence (NICE) as part of the Single Technology Appraisal (STA) process, this evaluation aims to inform the NICE appraisal committee's decision-making regarding the potential recommendation of erdafitinib for use within the National Health Service (NHS).

The summary highlights key issues identified by the Evidence Assessment Group (EAG) that are potentially crucial for decision-making concerning the treatment of metastatic or unresectable FGFR-altered urothelial cancer with erdafitinib. Whenever possible, the EAG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs) are also included.

Background information on the condition, technology, and evidence, as well as information on key and non-key issues, are detailed in the main EAG report. See Sections 2 (decision problem), 3 (clinical effectiveness), and 4 (cost effectiveness) for more details.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table 1.1: Summary of key issues

ID1333	Summary of issue	Report Sections
1	Population definition: The CS focuses on a narrower population than specified in the NICE final scope, potentially limiting generalisability to the NHS population.	2.1 and 3.2
2	Comparator selection: The company's focus on paclitaxel ± carboplatin omits other relevant comparators specified in the NICE final scope, potentially leading to an incomplete understanding of erdafitinib's relative efficacy and cost effectiveness within the full treatment landscape.	2.3 and 3.2 to 3.4
3	Generalisability of trial population: The THOR trial population may not fully represent the UK patient population, with underrepresentation of certain ethnic groups and patients with poorer PS. This could raise concerns about the applicability of the trial results to the NHS population.	2.1 and 3.2
4	Long-term effectiveness: The short median follow-up (15.9 months) in the THOR trial raises uncertainty about the long-term effectiveness of erdafitinib, which could lead to overly optimistic cost effectiveness results.	3.2
5	RWE and ICT: The use of limited RWE sources for comparators, lack of FGFR status information and missing data introduce uncertainty into the comparative effectiveness estimates crucial for CEAs.	3.3 and 3.4
6	A worst-case scenario approach was used for dealing with missing data in population adjustment, rather than using alternative data imputation methods	4.2.3
7	Paclitaxel ± carboplatin was implemented as a basket of paclitaxel monotherapy and paclitaxel + carboplatin, which may bias the overall effectiveness of the comparator and may not be aligned with UK clinical practice.	4.2.4

ID1333	Summary of issue	Report Sections
8	Paclitaxel monotherapy and paclitaxel + carboplatin are recommended to be given for a maximum of 6 treatment cycles for mUC in the UK. However, this stopping rule was not applied in the company's economic model.	4.2.4
9	Lack of PFS and TTD data for paclitaxel ± carboplatin in the UK RW mUC study.	4.2.6
10	Issues related to the assessment of the best-fitting parametric survival curves.	4.2.6
11	PF and PD HSUVs were estimated separately without including additional covariates, which may result in potentially biased health state utility values.	4.2.8
12	Modelling different HCRU for erdafitinib and paclitaxel ± carboplatin based on expert opinion.	4.2.9
13	Uncertainty in the modelled patient characteristics and treatment effectiveness of the comparators, which impact the estimated severity weight.	4.2.10
14	The majority of the LY and QALY gains for erdafitinib, which was given until disease progression, were acquired in the PD health state.	5.1

CEA = cost-effectiveness analysis; CS = company submission; FGFR = fibroblast growth factor receptor, HCRU = healthcare resource use; HSUVs = health state utility values; ITC = indirect treatment comparison; LY = life year; mUC = metastatic urothelial carcinoma; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PD = progressed disease; PF = progression free; PFS = progression-free survival; PS = performance status; QALY = quality-adjusted life year; RWE = real-world evidence; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; TTD = time to treatment discontinuation; UK = United Kingdom

1.2 Overview of key model outcomes

NICE Technology Appraisals (TAs) compare how much a new technology improves overall survival (OS) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, erdafitinib is modelled in the company's revised economic model to affect QALYs by:

- Increased OS. Incremental QALYs in the progressed disease (PD) health state were [redacted] compared to paclitaxel ± carboplatin (98% of total incremental QALYs, including 1.7x severity weight).

Overall, erdafitinib is modelled in the company's revised economic model to affect costs by:

- Increased treatment costs (additional cost of [redacted] compared to paclitaxel ± carboplatin, 67% of the total incremental costs).
- Reduced administration costs (reduction of [redacted] compared to paclitaxel ± carboplatin, 18.97% of the total incremental costs).
- Increased resource-use costs (additional cost of [redacted] compared to paclitaxel ± carboplatin, 13.05% of the total incremental costs).

DSA showed that the parameters that had the greatest effect on the ICER compared to paclitaxel ± carboplatin, were:

- The OS extrapolation of erdafitinib.

- The time to treatment discontinuation (TTD) extrapolation of erdafitinib.

Scenario analyses showed that the three most influential scenarios were:

- Assuming the THOR (trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations) intention-to-treat (ITT) arm as a comparator.
- The OS extrapolation of erdafitinib using the Gamma curve.
- The OS extrapolation of erdafitinib using the Gompertz curve.

1.3 The decision problem: summary of the EAG's key issues

Two key issues related to the decision problem were identified, namely regarding the population (see Table 1.2) and the comparators (see Table 1.3).

Table 1.2: Key issue 1: Population considered by company narrower than population in NICE final scope

Report Sections	2.1 and 3.2
Description of issue and why the EAG has identified it as important	The population in the decision problem is narrower than the population defined in the NICE final scope. It is limited to the marketing authorisation by the FDA, i.e. [redacted]
What alternative approach has the EAG suggested?	No alternative approach suggested.
What is the expected effect on the cost effectiveness estimates?	N/A if NICE can only make a decision for this limited population: otherwise, the effect is unknown.
What additional evidence or analyses might help to resolve this key issue?	N/A if NICE only make a decision for this limited population. Otherwise, the evidence in the submission including the key trial will need to be supplemented to be generalisable to the broader population.
EAG = Evidence Assessment Group; FDA = Food and Drug Administration; FGFR3 = fibroblast growth factor receptor 3; N/A = not applicable; NICE = National Institute for Health and Care Excellence; PD-1 = programmed death receptor-1; PD-(L)1 = programmed death-(ligand)1	

Table 1.3: Key issue 2: Comparator selection in CS

Report Sections	2.3 and 3.2 to 3.4
Description of issue and why the EAG has identified it as important	The CS focuses primarily on paclitaxel ± carboplatin, omitting relevant comparators specified in the NICE final scope, particularly docetaxel, atezolizumab, and BSC. This is important because the exclusion of key comparators may lead to an incomplete understanding of erdafitinib's relative efficacy and cost effectiveness in the context of all available treatment options.
What alternative approach has the EAG suggested?	The EAG suggests including all relevant comparators specified in the NICE final scope or providing transparent, evidence-based justification for any exclusions. If data are not available for direct

Report Sections	2.3 and 3.2 to 3.4
	comparisons, the company should consider ITCs or NMAs where appropriate.
What is the expected effect on the cost effectiveness estimates?	Omitting relevant comparators could potentially lead to an overestimation of erdafitinib's cost effectiveness if more effective or less costly alternatives are not considered. The magnitude of this effect is uncertain and would depend on the relative efficacy and costs of the omitted comparators.
What additional evidence or analyses might help to resolve this key issue?	Inclusion of analyses comparing erdafitinib to all relevant comparators specified in the NICE final scope would help resolve this issue. If direct comparisons are not possible, indirect comparisons or NMAs should be conducted. If certain comparators are excluded, a robust, evidence-based justification should be provided.
BSC = best supportive care; CS = company submission; EAG = Evidence Assessment Group; ITCs = indirect treatment comparisons; NICE = National Institute for Health and Care Excellence; NMAs = network meta-analyses	

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

The EAG identified three key issues, namely regarding 1) the generalisability of the THOR trial population (see Table 1.4), 2) the uncertainty in the long-term effectiveness of erdafitinib (see Table 1.5), and 3) limitation of real-world evidence (RWE) and indirect treatment comparison (ITC), see Table 1.6.

Table 1.4: Key issue 3: Generalisability of THOR trial population

Report Sections	2.1 and 3.2
Description of issue and why the EAG has identified it as important	The THOR trial population may not fully represent the UK NHS population eligible for erdafitinib. Specifically, there appears to be an underrepresentation of patients who are of Black or African American race, an overrepresentation of Asian patients, and a predominance of patients with an ECOG PS of 0-1, indicating a healthier population than might be seen in UK clinical practice, where patients might have poorer PS (e.g., ECOG PS 2+). Additionally, subgroup analyses from the trial may signal effect modification indicating that treatment outcomes may not be uniform across all patient subgroups. Given that the subgroup analyses were not powered to detect significant differences, there is a risk of Type II errors, where real differences in treatment effect are not detected due to small sample sizes. These potential differences are critical for external validity, particularly if variables such as race differ significantly between the trial population and the target population in England and Wales.
What alternative approach has the EAG suggested?	Other than conducting a new trial with a population that aligns with the decision problem, no alternative trial approach is suggested.
What is the expected effect on the cost effectiveness estimates?	These concerns raise doubts about the applicability of the trial results to RW UK patients, potentially affecting both clinical and cost effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	No additional trial evidence is immediately suggested.

Report Sections	2.1 and 3.2
EAG = Evidence Assessment Group; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FGFR = fibroblast growth factor receptor; NHS = National Health Service; RW = real-world; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; UK = United Kingdom	

Table 1.5: Key issue 4: Uncertainty in long-term effectiveness of erdafitinib

Report Section	3.2
Description of issue and why the EAG has identified it as important	The short follow-up time (median follow-up in THOR trial: 15.9 months) and limited long-term data raises uncertainty about the durability of erdafitinib's treatment effect. This is important because assumptions about long-term effectiveness significantly impact cost effectiveness estimates, especially in a condition like metastatic urothelial cancer where long-term survival is a key outcome.
What alternative approach has the EAG suggested?	The EAG suggests critically examining the extrapolation methods and assumptions used for long-term effectiveness. This should include exploring multiple plausible extrapolation scenarios and conducting sensitivity analyses to assess the impact of different long-term effectiveness assumptions on cost effectiveness estimates.
What is the expected effect on the cost effectiveness estimates?	Overestimation of long-term effectiveness could lead to an overestimation of erdafitinib's cost effectiveness. The magnitude of this effect could be substantial, given the importance of long-term outcomes in the economic model.
What additional evidence or analyses might help to resolve this key issue?	Longer-term follow-up data from the THOR trial or other studies of erdafitinib would be ideal to resolve this issue. In the absence of such data, robust sensitivity analyses exploring a range of plausible long-term effectiveness scenarios should be conducted. Expert clinical opinion on the plausibility of different long-term effectiveness scenarios could also be sought to inform these analyses.
EAG = Evidence Assessment Group; FGFR = fibroblast growth factor receptor; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations	

Table 1.6: Key issue 5: Limitations in RWE and ITC

Report Sections	3.3 and 3.4
Description of issue and why the EAG has identified it as important	The RWE sources used to identify comparators for the ITC were not comprehensive, leading to uncertainty in the benefits of erdafitinib compared with relevant comparators. The use of RW data for comparators introduces significant uncertainty into the comparative effectiveness estimates, particularly due to the lack of FGFR status information in the RW data. This is important because it affects the reliability of the comparative effectiveness estimates, which are crucial for the CEA. While the use of RW data can provide valuable insights, the lack of FGFR status information and potential differences in patient populations introduce substantial uncertainty. The validity of these comparisons should be carefully scrutinised.
What alternative approach has the EAG suggested?	The EAG suggests using more comprehensive RW sources where possible and conducting sensitivity analyses to account for the uncertainties introduced by the use of RW data. The EAG also recommends exploring methods to address the lack of FGFR status

Report Sections	3.3 and 3.4
	information in the RW data, such as using statistical techniques to adjust for potential differences in patient populations.
What is the expected effect on the cost effectiveness estimates?	The uncertainties in the comparative effectiveness estimates could have a significant impact on the cost effectiveness results. The direction and magnitude of this effect are unclear and would depend on how the RW data compare to the trial data for erdafitinib. It could potentially lead to either an over- or under-estimation of erdafitinib's cost effectiveness.
What additional evidence or analyses might help to resolve this key issue?	More comprehensive RW data, ideally including FGFR status information, would help resolve this issue. In the absence of such data, extensive sensitivity analyses addressing the uncertainties in the comparative effectiveness estimates should be conducted. This could include scenario analyses using different assumptions about the comparability of the RW and trial populations, and the potential impact of FGFR status on treatment outcomes.
CEA = cost effectiveness analysis; EAG = Evidence Assessment Group; FGFR = fibroblast growth factor receptor; ITC = indirect treatment comparison; RW = real-world; RWE = real-world evidence	

1.5 The cost effectiveness evidence: summary of the EAG's key issues

A full summary of the cost effectiveness evidence review conclusions can be found in Section 6.4 of this report. The company's cost effectiveness results are presented in Section 5, the EAG's summary and detailed critique in Section 4, and the EAG's amendments to the company's model and results are presented in Section 6. The key issues in the cost effectiveness evidence are discussed in the issue Tables below.

Table 1.7: Key issue 6: Worst-case scenario approach used for dealing with missing data in population adjustment

Report Section	4.2.3
Description of issue and why the EAG has identified it as important	The company used a worst-case approach for patients with missing disease stage or ECOG PS. The EAG questions the company's approach and assumption that data were not missing at random.
What alternative approach has the EAG suggested?	The EAG would like to see an updated economic model and scenario analysis using an alternative data imputation method (e.g., multiple imputation) for dealing with missing data in the ATC. Additionally, the EAG would like to see a best-case scenario analysis.
What is the expected effect on the cost effectiveness estimates?	Unclear
What additional evidence or analyses might help to resolve this key issue?	The EAG would like to see an updated economic model and scenario analysis using an alternative data imputation method (e.g., multiple imputation) for dealing with missing data in the ATC. Additionally, the EAG would like to see a best-case scenario analysis.
ATC = average treatment effect for the control, EAG = Evidence Assessment Group, ECOG PS = Eastern Cooperative Oncology Group Performance Status	

Table 1.8: Key issue 7: Use of a basket of comparators

Report Section	4.2.4
Description of issue and why the EAG has identified it as important	The main comparator considered in the CS was paclitaxel ± carboplatin, implemented as a basket of paclitaxel monotherapy and paclitaxel + carboplatin, weighted 3:1, respectively. This may bias the overall effectiveness of the comparator, and may not be aligned with UK clinical practice.
What alternative approach has the EAG suggested?	The EAG prefers to also present its base-case results and scenario analyses for erdafitinib versus the individual comparators (i.e. paclitaxel monotherapy and paclitaxel + carboplatin).
What is the expected effect on the cost effectiveness estimates?	The analyses of erdafitinib versus individual comparators (i.e. paclitaxel monotherapy and paclitaxel + carboplatin) resulted in higher ICERs compared to the ICER versus the basket comparator.
What additional evidence or analyses might help to resolve this key issue?	A fully incremental analysis including all relevant comparators.
CS = company submission, EAG = Evidence Assessment Group, ICER = incremental cost-effectiveness ratio; UK = United Kingdom	

Table 1.9: Key issue 8: Lack of stopping rule for paclitaxel ± carboplatin

Report Section	4.2.4
Description of issue and why the EAG has identified it as important	As reported by existing guidelines, paclitaxel monotherapy and paclitaxel + carboplatin are recommended for the treatment of mUC in the UK with a stopping rule of 6 cycles of treatment. However, this was not applied in the economic model.
What alternative approach has the EAG suggested?	An updated economic model and scenario analysis in which patients on paclitaxel ± carboplatin (including paclitaxel monotherapy and paclitaxel + carboplatin), are treated up to a maximum of 6 cycles.
What is the expected effect on the cost effectiveness estimates?	Implementing the stopping rule for the comparator reduced its drug acquisition costs, and hence increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	N/A
EAG = Evidence Assessment Group, ICER = incremental cost-effectiveness ratio, mUC = metastatic urothelial carcinoma, N/A = not applicable; UK = United Kingdom	

Table 1.10: Key issue 9: Treatment effectiveness and extrapolation: the lack of PFS and TTD data for paclitaxel ± carboplatin in the UK RW mUC study

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	Due to the absence of PFS data for paclitaxel ± carboplatin in the UK RW mUC study, the company uses the PFS from Vaishampayan et al. 2005 as a proxy. Due to the absence of TTD data for paclitaxel ± carboplatin in the UK RW mUC study, the company made a simplifying assumption that TTD for paclitaxel ± carboplatin would be equivalent to the generated PFS. The EAG questions the plausibility of these assumptions.

Report Section	4.2.6
What alternative approach has the EAG suggested?	The EAG prefers to use TTNT of paclitaxel ± carboplatin from the UK RW mUC study as a proxy to inform PFS data for paclitaxel ± carboplatin. The EAG prefers a hard stop for paclitaxel ± carboplatin after 24 weeks (i.e. TTD for paclitaxel ± carboplatin in the economic model will be zero from week 25 onwards).
What is the expected effect on the cost effectiveness estimates?	Both alternative approaches increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	Additional scenario analyses using the PFS of taxanes in TA525 and TA692 as a proxy for paclitaxel ± carboplatin PFS would be informative.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; mUC = metastatic urothelial carcinoma; PFS = progression-free survival; RW = real-world; TA = technology appraisal; TTD = time to treatment discontinuation; TTNT = time to next treatment; UK = United Kingdom	

Table 1.11: Key issue 10: Treatment effectiveness and extrapolation: issues related to the assessment of the best-fitting parametric survival curves

Report Section	4.2.6
Description of issue and why the EAG has identified it as important	The EAG identified the following issues regarding the process of selecting the most suitable parametric survival curves: 1) A substantial part of the total observed data that was used for the extrapolation of outcomes was based on few patients, which adds uncertainty to the long-term extrapolations of the outcomes. 2) Jointly fitted parametric survival models were not explored in the economic model, despite the lack of evidence that the proportional hazards assumption was violated. 3) The standard parametric models for the extrapolation of erdafitinib OS, PFS, TTD and TTNT did not fit very well to the observed THOR data (underestimation of the observed data in the first few months and overestimation thereafter). 4) The validity of the extrapolated outcomes was not assessed based on external data.
What alternative approach has the EAG suggested?	1) Additional scenario analyses selecting the most pessimistic and optimistic parametric survival curves for PFS, TTNT, and TTD. 2) An updated economic model and scenario analysis including jointly fitted parametric survival models. 3) Explore using spline-based models as an alternative to standard parametric models (provided by the company in response to clarification). 4) Examine the validity of the extrapolated outcomes based on relevant external data (provided by the company in response to clarification).
What is the expected effect on the cost effectiveness estimates?	1) Selecting the most pessimistic and optimistic curves is expected to respectively increase and decrease the ICER. 2) Unclear. 3) Impact on the ICER depends on the selected spline-based model. 4) N/A.

Report Section	4.2.6
What additional evidence or analyses might help to resolve this key issue?	1) Additional scenario analyses selecting the most pessimistic and optimistic parametric survival curves for PFS, TTNT, and TTD. 2) An updated economic model and scenario analysis including jointly fitted parametric survival models.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; N/A = not applicable; OS = overall survival; PFS = progression-free survival; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; TTD = time to treatment discontinuation; TTNT = time to next treatment	

Table 1.12: Key issue 11: HRQoL: The approach used for the estimation of HSUVs in the economic model

Report Section	4.2.8
Description of issue and why the EAG has identified it as important	PF and PD HSUVs were estimated separately using linear MMRMs without including additional covariates. The EAG questions the estimation of the PF and PD utilities in separate models without inclusion of relevant covariates, which may result in potentially biased health state utility values.
What alternative approach has the EAG suggested?	The EAG prefers estimating the PF and PD health state utility values within a single model, including additional relevant covariates based on the company's best fitting multivariable regression model (i.e. model 1, including progression status and AEs).
What is the expected effect on the cost effectiveness estimates?	Using the multivariable regression model to estimate the PF and PD health state utility values increased the ICER.
What additional evidence or analyses might help to resolve this key issue?	N/A.
AE = adverse event; EAG = Evidence Assessment Group; HRQoL = health-related quality of life; HSUVs = health state utility values; ICER = incremental cost-effectiveness ratio; MMRM = mixed models for repeated measures; N/A = not applicable; PD = progressed disease; PF = progression-free	

Table 1.13: Key issue 12: Resource use and costs: Modelling different HCRU for erdafitinib and paclitaxel ± carboplatin based on expert opinion

Report Section	4.2.9
Description of issue and why the EAG has identified it as important	Different HCRU was modelled for erdafitinib and paclitaxel ± carboplatin, based on the assumption that patients receiving erdafitinib would need less outpatient visits compared to patients receiving paclitaxel ± carboplatin. This assumption was based on a single clinical expert comment during the advisory board. The EAG considers the company's evidence (a single expert opinion) insufficient to justify this assumption.
What alternative approach has the EAG suggested?	The EAG prefers assuming equal HCRU for erdafitinib and paclitaxel ± carboplatin.
What is the expected effect on the cost effectiveness estimates?	Assuming equal HCRU increased the ICER.

Report Section	4.2.9
What additional evidence or analyses might help to resolve this key issue?	Providing additional evidence based on relevant data to justify differences in HCRU between erdafitinib and paclitaxel ± carboplatin.
EAG = Evidence Assessment Group; HCRU = healthcare resource use; ICER = incremental cost-effectiveness ratio	

Table 1.14: Key issue 13: Uncertainty regarding which severity weight should be applied in the economic model

Report Section	4.2.10
Description of issue and why the EAG has identified it as important	The EAG is concerned about uncertainty in the modelled patient characteristics and treatment effectiveness of the comparators, which impact the estimated severity weight.
What alternative approach has the EAG suggested?	The EAG requested 1) to calculate the severity weight for each PSA iteration, and 2) to calculate the severity weight based on UK patient characteristics.
What is the expected effect on the cost effectiveness estimates?	Calculation of the severity weight based on UK patients from THOR resulted in a severity weight of x1.2, which increased the ICER substantially compared to applying a x1.7 severity weight.
What additional evidence or analyses might help to resolve this key issue?	Additional evidence and justification on which patient characteristics are reflective of UK clinical practice.
EAG = Evidence Assessment Group; ICER = incremental cost-effectiveness ratio; PSA = probabilistic sensitivity analysis; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; UK = United Kingdom.	

Table 1.15: Key issue 14: Company's cost effectiveness results: Majority of LYs and QALYs for erdafitinib were gained in the PD health state

Report Section	5.1
Description of issue and why the EAG has identified it as important	The majority of the LY and QALY gains for erdafitinib were acquired in the PD health state. The EAG is unsure whether this is plausible, as patients on erdafitinib were treated until disease progression (or unacceptable toxicity).
What alternative approach has the EAG suggested?	The EAG would like to see an explanation of the mechanism by which the economic model generated these results for erdafitinib.
What is the expected effect on the cost effectiveness estimates?	N/A
What additional evidence or analyses might help to resolve this key issue?	The EAG would like to see an explanation of the mechanism by which the economic model generated these results for erdafitinib.
EAG = Evidence Assessment Group; LY= life year; N/A = not applicable; PD = progressed disease; QALY= quality-adjusted life year	

1.6 Summary of the EAG's view

As discussed above, the EAG identified 14 key issues related to clinical effectiveness as well as cost effectiveness of this submission. These should be considered by the committee.

The estimated EAG base-case ICERs (probabilistic), based on the EAG preferred assumptions highlighted in Section 5.1, were £35,249, £50,581, and £37,765per QALY gained for erdafitinib versus the basket of paclitaxel ± carboplatin, paclitaxel monotherapy and paclitaxel + carboplatin respectively. For erdafitinib versus paclitaxel ± carboplatin, the probabilistic EAG base-case analyses indicated a cost effectiveness probability of 17% at a willingness-to-pay threshold of £30,000 per QALY gained. The most influential adjustments were applying the stopping rule of 6 cycles (i.e. 24 weeks) to paclitaxel monotherapy and paclitaxel + carboplatin, and assuming equal HRCU between erdafitinib and the comparators. The ICER increased most in the scenario analysis where patients with missing Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) and/or stage were omitted from the population adjustment.

There is large remaining uncertainty about the effectiveness and cost effectiveness of erdafitinib, of which the impact can be explored by conducting further analyses. This includes providing analyses using data imputation methods (e.g., multiple imputation) for dealing with missing data in the average treatment effect for the control (ATC), a fully incremental analysis including all relevant comparators, analyses using the progression-free survival (PFS) of taxanes in technology appraisal (TA) 525 and TA692 as a proxy for paclitaxel ± carboplatin PFS, analyses selecting the most pessimistic and optimistic parametric survival curves for PFS, time to next treatment (TTNT), and TTD, and analyses including jointly fitted parametric survival models. In addition, further evidence and justification could be provided regarding differences in healthcare resource use (HCRU) between erdafitinib and paclitaxel ± carboplatin, regarding which patient characteristics are reflective of UK clinical practice, and regarding the mechanism by which the economic model generated the life year (LY) and QALY gains for erdafitinib. Therefore, it is unclear to the EAG whether the company submission (CS) and the EAG report contain an unbiased ICER of erdafitinib compared with all relevant comparators.

Table 1.16: Summary of EAG's preferred assumptions and ICER

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
CS base-case							
Erdafitinib	[redacted]	[redacted]	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.856	[redacted]	0.927	[redacted]	26,487
Fixing violations (1- Stopping rule of 6 cycles (i.e. 24 weeks) to paclitaxel monotherapy and paclitaxel + carboplatin)							
Erdafitinib	[redacted]	[redacted]	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.856	[redacted]	0.927	[redacted]	30,657
Matter of judgment (2- TTNT of paclitaxel +carboplatin RW data for modelling of paclitaxel +carboplatin PFS)							
Erdafitinib	[redacted]	[redacted]	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.851	[redacted]	0.927	[redacted]	27,153
Matter of judgment (3- Multivariable regression model for estimation of health state utilities)							
Erdafitinib	[redacted]	[redacted]	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.829	[redacted]	0.927	[redacted]	28,683
Matter of judgment (4- Assuming equal HCRU between erdafitinib and comparators)							
Erdafitinib	[redacted]	[redacted]	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.856	[redacted]	0.927	[redacted]	29,255
Deterministic EAG base-case							
Erdafitinib	[redacted]	[redacted]	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.822	[redacted]	0.927	[redacted]	36,034
Probabilistic EAG base-case							
Erdafitinib	[redacted]	[redacted]	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.743	0.833	[redacted]	0.928	[redacted]	36,249

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-adjust life year; RW = real-world; TTNT = time to next treatment

2. Critique of company's definition of decision problem

Table 2.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE final scope	EAG comment
Population	People with metastatic or unresectable FGFR-altered UC	Adult patients with unresectable or metastatic UC, harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-(L)1 inhibitor in the unresectable or metastatic treatment setting.	To align with the final marketing authorisation.	The narrower population considered within the CS is in line with the anticipated marketing authorisation.
Intervention	Erdafitinib.	Erdafitinib.	N/A – in line with the NICE final scope.	The EAG is satisfied with the description of the intervention.
Comparator(s)	Established clinical management without erdafitinib, including but not limited to: • Chemotherapy (including docetaxel, paclitaxel) • Atezolizumab • BSC	Paclitaxel as a monotherapy, or in combination with carboplatin (paclitaxel ± carboplatin)	Clinical experts and RWE confirmed that the relevant comparator is paclitaxel ± carboplatin. Docetaxel's use is restricted to clinical trials and is not current SoC in England and Wales. Atezolizumab re-treatment is not considered established practice by UK-based clinicians due to the lack of evidence on the efficacy of re-treating with a PD-(L)1 inhibitor. Given the population of this appraisal focuses on those already treated with anti-PD-(L)1 therapy,	There are differences between the comparators considered by the company and those listed in the final NICE scope. The exclusion of some comparators (e.g., docetaxel, atezolizumab, BSC) raises concerns about the comprehensiveness of the assessment. The EAG's detailed critique of this approach is provided in Section 2.3.

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE final scope	EAG comment
			atezolizumab is not an appropriate comparator. For BSC, there is no evidence available in patients after exposure to PD-(L)1 inhibitors, and therefore a comparative analysis could not be conducted.	
Outcomes	The outcome measures to be considered include: • OS • PFS • Response rates (including type and DOR) • Adverse effects of treatment • HRQoL	• As per NICE scope.	N/A	While the company has included all outcomes specified in the NICE final scope, the EAG has some concerns regarding some limitations in the depth and quality of data provided for certain outcomes, particularly HRQoL as detailed in Section 2.4.
Subgroups to be considered	If evidence allows, the following subgroups will be considered separately: • FGFR alteration type • Previous anti-PD-(L)1 treatment	People with upper tract urothelial cancer	The proposed subgroups of FGFR alteration type and previous anti-PD-(L)1 treatment make up the relevant population, i.e., patients with FGFR3 alterations with disease progression during or following at least one line of therapy containing a PD-1 or PD-(L)1 inhibitor. Therefore, these subgroups do not need to be considered separately.	

	Final scope issued by NICE	Decision problem addressed in the CS	Rationale if different from the final NICE final scope	EAG comment
	• People with upper tract urothelial cancer			
Special considerations including issues related to equity or equality	None specified.	None identified.	N/A – in line with the NICE final scope.	

Based on Table 1 and pages 10 to 12 of the CS[1]

BSC = best supportive care; CS = company submission; DOR = duration of response; EAG = Evidence Assessment Group; FGFR = fibroblast growth factor receptor; FGFR3 = fibroblast growth factor receptor 3; HRQoL = health-related quality of life; N/A = not applicable; NICE = National Institute for Health and Care Excellence; OS = overall survival; PD-1 = programmed death receptor-1; PD-(L)1 = programmed death-(ligand)1; PFS = progression-free survival; RWE = real-world evidence; SoC = standard of care; UC = urothelial carcinoma; UK = United Kingdom

2.1 Population

The National Institute for Health and Care Excellence (NICE) scope for this assessment broadly defines the population as *"People with metastatic or unresectable fibroblast growth factor receptor (FGFR)-altered urothelial cancer".*[2] This definition encompasses a wide range of patients with various FGFR alterations, regardless of their specific genetic profile or treatment history. In contrast, the company submission (CS) delineates their population as: *"Adult patients with unresectable or metastatic urothelial carcinoma (UC), harboring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-(L)1 inhibitor in the unresectable or metastatic treatment setting".*[1] This is in line with the proposed marketing authorisation for the United Kingdom (UK), narrowing the focus by specifying fibroblast growth factor receptor 3 (FGFR3) alterations and requiring prior treatment with programmed death receptor-1 (PD-1) or programmed death-(ligand)1 (PD-(L]1) inhibitors, and aligning the population in the CS primary evidence for erdafitinib with Cohort 1 of the THOR (trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene abberations) trial: *"…erdafitinib versus chemotherapy (docetaxel or vinflunine) in patients who had progressed on or after one or two prior treatments`, one of which being an anti-PD-(L)1 agent".*[1] Whilst FDFR3 status is not specified, the company also stated: *"All patients with FGFR alterations had at least one FGFR3 alteration…"* (p. 41).[1]

EAG comment: In response to the request for clarification.[3] the company provide further details considering whether a) receiving at least one line of therapy containing a PD-1 or PD-(L)1 inhibitor and b) FGFR3 genetic alteration status, are disease/treatment effect modifiers as follows:

a) "As treatment with a PD-(L)1 inhibitor is a requirement of the marketing authorisation and thus the patient population relevant to this decision problem, considering whether a patient has received prior therapy with a PD-1 or PD-(L)1 inhibitor as a disease/treatment effect modifier becomes irrelevant, the evidence from THOR and UK RW mUC study align to the anticipated marketing authorisation, as all patients analysed have received a prior PD-(L)1."

b) "FGFR3 genetic alteration is a treatment effect modifier. Results from THOR Cohort 1 demonstrate that a targeted patient population harbouring positive FGFR3 alteration status have a statistically significant superior overall and progression-free survival to erdafitinib versus chemotherapy. Therefore, FGFR3 genetic alterations are predictive of response to erdafitinib."

The prognostic role of FGFR3 alterations was also considered: *"The prognostic role of FGFR3 alterations is not fully characterised in metastatic urothelial carcinoma. Understanding of the effect FGFR3 alterations have on clinical outcomes has been limited to real-world retrospective studies."*

Whilst it might be the case that both prior PD-1 or PD-(L)1 therapy and FGFR3 status might be treatment effect modifying, the Evidence Assessment Group (EAG) acknowledges that the decision problem aligns with the anticipated marketing authorisation and that the population considered in the THOR trial reflects the decision problem presented by the company. As such, this may not be regarded as a key issue if NICE can only make a recommendation for the licensed population and the indication is as proposed.

2.2 Intervention

The NICE final scope describes the intervention as erdafitinib, which concurs exactly with the decision problem.[2] In their submission, the company specifies that erdafitinib is administered orally, with a recommended starting dose of 8 mg once daily. The dose may be increased to 9 mg once daily based on serum phosphate levels and tolerability.[1, 4] The company noted that patients receiving erdafitinib were allowed certain concomitant medications and treatments deemed necessary for supportive care, except for those listed as prohibited. Allowed concomitant medications included symptomatic treatments, prophylactic medications, and localised palliative radiotherapy of short duration (e.g. ≤2 weeks) after discussion with the sponsor's medical monitor. The company provided details on permitted and prohibited concomitant medications in the clinical study protocol[5].

EAG comment: The EAG notes some uncertainty regarding whether palliative radiotherapy could have influenced the results of the study. While the company states that *"localised radiotherapy for symptomatic control was permitted, but should not have included definitive radiation to target lesions",* the impact of palliative radiotherapy on efficacy outcomes is not clear. To explore the influence of palliative radiotherapy, the EAG would need to see additional analyses exploring its effect on all relevant efficacy outcomes, not just the primary endpoints.

2.3 Comparators

The NICE final scope specified comparators as *"Established clinical management without erdafitinib, including but not limited to: Chemotherapy (including docetaxel, paclitaxel), Atezolizumab and Best supportive care"*.[2] The CS however, primarily compares erdafitinib to paclitaxel, either as monotherapy or in combination with carboplatin (paclitaxel ± carboplatin).[1] In response to the request for clarification, the company provided further rationale behind comparator selection, stating that *"the most important data sources are the RW UK mUC study, the clinical expert insights and the NICE guidelines. All these data sources combined led to our suggested base case and scenarios. From the RW UK mUC study, it became apparent that a variety of treatments were used after exposure to PD-(L)1 treatment"*.[3]

The company justified their choice of comparator based on a UK real-world (RW) mUC study of 198 patients who received treatment after PD-(L)1 exposure. This study showed that *"Paclitaxel ± carboplatin was the most frequently used treatment (36.4%, n=72)"*.[3] Additionally, clarification responses further detail the company's rationale for excluding other comparators summarised as follows:

- Docetaxel: The company argues its use is very limited in clinical practice and not recommended in NICE guidelines. They cite RW data showing only 2% of patients received docetaxel after PD-(L)1 treatment and highlight survey data indicating clinician preference for paclitaxel.
- Atezolizumab: The company states there's *"no evidence or clinical rationale for re-treating with PD-(L)1 inhibitors after progression on initial PD-(L)1 therapy"*. They additionally note this is not recommended in NICE, European Association of Urology (EAU), or European Society for Medical Oncology (ESMO) guidelines.
- Best supportive care (BSC): The company cites a lack of clinical evidence for BSC outcomes in patients previously treated with PD-(L)1 inhibitors. They state: *"There is no clinical evidence to model health outcomes for the use of best supportive care in patients who have been previously treated with PD-(L)1 inhibitors. The data source for the J&J UK RW mUC cohort study is the SACT dataset which details all NHS-funded systemic anti-cancer treatments administered to patients, therefore not being able to capture BSC data. As a result, accurately evaluating the cost-*

effectiveness of erdafitinib compared to best supportive care in this specific population is not feasible".

- Carboplatin + gemcitabine: The company argues this combination is not recommended as a second-line (2L) option in NICE guidelines, and there's limited evidence for re-challenging with platinum-based chemotherapy.

The clinical expert consulted by the EAG supports the company's focus on taxane-based chemotherapy as a relevant comparator in the 2L and third-line (3L) settings, stating that *"the current standard of care for patients with unresectable or metastatic UC in the 2L/3L setting is taxane-based chemotherapy."* More specifically, *"Weekly paclitaxel is commonly used in those whose performance status is good for further chemotherapy".* This aligns with the company's choice to focus on paclitaxel monotherapy or in combination with carboplatin. Additionally, the expert explains that patients with a long platinum-free interval (over 12 months) might be considered for platinum rechallenge, with taxol-carboplatin being the most preferred combination for rechallenge. This confirms the relevance of the company's paclitaxel ± carboplatin comparator.

EAG comment: The EAG raises the following potential concerns about the exclusion of other comparators from the CS:

- Although the company argues that docetaxel is rarely used in practice (citing RW data where only 2% of patients received it after PD-(L)1 treatment), the EAG considers that the low usage of docetaxel in current practice may not necessarily negate its relevance as a comparator. The clinical expert's input suggests that docetaxel is indeed less commonly used, but acknowledges the variability across centres and clinical scenarios. As the expert notes, *"patients with contraindications to immunotherapy might constitute a special category, although their numbers would likely be small and difficult to model".* This reinforces the EAG's view that while docetaxel usage may be limited, its inclusion would provide a more complete representation of treatment options.
- The company excludes atezolizumab, arguing that *"there's no evidence or clinical rationale for re-treating with PD-(L)1 inhibitors after progression on initial PD-(L)1 therapy."* The EAG, however, believes that excluding atezolizumab prematurely dismisses its potential role in certain scenarios, despite the lack of prospective trials. The clinical expert supports this exclusion, noting that "*immunotherapy-naive patients are a dwindling population"* and that the clinical role of erdafitinib is most appropriate in the *"2L/3L setting post-immunotherapy",* further diminishing the likelihood of re-treating with atezolizumab in this context.
- The company dismisses BSC as a comparator, citing a lack of evidence for BSC outcomes in patients treated with PD-(L)1 inhibitors. They argue that *"accurately evaluating the cost-effectiveness of erdafitinib compared to best supportive care in this specific population is not feasible."* The clinical expert consulted by the EAG also expresses doubt about the relevance of BSC in this context, stating that *"BSC is not a good comparator because it is typically valid only for patients whose performance status is poor and are unfit for further chemotherapy."* They further emphasise that *"patients who are physically fit prefer active treatment over BSC"*, underscoring that most patients would opt for further chemotherapy rather than supportive care if they remain eligible. The EAG acknowledges the difficulty of modelling BSC outcomes and expert's insights on BSC support the company's decision to exclude it as a comparator for the majority of patients, though the EAG still considers it a potential limitation for certain subpopulations.
- The company argues that the combination of carboplatin + gemcitabine is not recommended as a 2L option in NICE guidelines, and there is limited evidence for rechallenging with platinum-based chemotherapy. The clinical expert consulted concurs that platinum rechallenge may be relevant

only for patients with a long platinum-free interval, stating that when the interval exceeds 12 months, combinations like *"gem-cisplatin or taxol-carboplatin"* may be considered. This supports the company's decision to focus more narrowly on paclitaxel-based options for the majority of patients, with the caveat that certain subgroups may benefit from platinum-based combinations.

- Despite being included in the NICE final scope, comparators such as docetaxel, atezolizumab, and BSC were excluded from the main analyses. The CS justifies these exclusions based on perceived irrelevance or lack of data. For instance, docetaxel was excluded because *"its use is restricted to clinical trials and is not current standard of care (SoC) in England and Wales"*. Additionally, *"UK clinicians mentioned that patients who are currently receiving BSC or not receiving systemic treatment after prior exposure to anti-PD-(L)1 inhibitors may be eligible for erdafitinib if they have FGFR-positive disease. However, given the absence of evidence available following up BSC patients after exposure to PD-(L)1 inhibitors, a comparative analysis could not be conducted"* (CS, Section B.1.3.5.2).

The company provided a detailed summary of treatment patterns observed with *"the most important data sources the RW UK mUC study, the clinical expert insights and the NICE guidelines. All these data sources combined led to our suggested base case and scenarios. From the RW UK mUC study, it became apparent that a variety of treatments were used after exposure to PD-(L)1 treatment. The 198 relevant patients have been captured, and the treatments they received are detailed"* (Response to the request for clarification, Section B2)[3] supporting their choice of comparators, as shown in Table 2.2.

Table 2.2: Patients in the RW UK mUC study, treatments after PD-(L)1 treatment

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

Treatment	Patients (n)	Patients (%)	Included	Comments
1L = first-line; 3L = third-line; COVID-19 = coronavirus disease 2019; mUC = metastatic urothelial carcinoma; MVAC = methotrexate, vinblastine, doxorubicin, and cisplatin; N = number of patients; PD-(L)1 = programmed death-(ligand)1; RW = real-world; UK = United Kingdom				

The company's justification for excluding docetaxel and other comparators is based on the limited use of these treatments in RW UK clinical practice. The inclusion of paclitaxel ± carboplatin as the main comparator reflects the most common 2L treatment after PD-(L)1 inhibitors, as observed in the UK RW study.[6] The EAG recognises that while the company has provided evidence to support their comparator choices, the exclusion of certain comparators could still limit the comprehensiveness of the analysis.

While the company has provided additional justification for their comparator selection, the EAG maintains the consideration that focusing on paclitaxel ± carboplatin may limit the comprehensiveness of the assessment. This focus may not accurately reflect the complex decision-making process in RW clinical practice, where multiple treatment options are often considered. The choice of comparators may have a direct impact on the economic evaluation. By excluding potentially relevant comparators, the CS may not provide a complete picture of erdafitinib's cost effectiveness across all relevant treatment options. While the UK RW mUC study provided in the appendices offers valuable context on the use of different treatments in clinical practice, this data is not specific to the FGFR-altered population. This limits its applicability to the decision problem at hand and should be interpreted cautiously given the potential differences between the general mUC population and the FGFR-altered subgroup. A broader consideration of comparators, more closely aligned with the NICE final scope and reflective of current UK clinical practice, would provide a more robust basis for decision-making. The current approach may lead to an incomplete understanding of erdafitinib's relative efficacy and cost effectiveness, potentially hindering optimal decision-making regarding its use in clinical practice. This is therefore a key issue.

2.4 Outcomes

The NICE final scope specifies the following outcome measures to be considered: "*Overall survival (OS), Progression-free survival (PFS), Response rates (including type and duration of response), Adverse effects of treatment, Health-related quality of life (HRQL)"*.[2] The CS includes these outcomes but primarily focuses on: OS, PFS, objective response rate (ORR).[1] In response to the EAG's concerns about limited health-related quality of life (HRQoL) data, the company provided additional information, noting that *"the EQ-5D-5L questionnaires had missing data similar across trial arms, and that a mixed-effects regression analysis indicated no independent effect of treatment on utility"*.[3] The company provided some additional information on adverse effects, additionally noting *"The relationship between adverse events and HRQL is not fully explored, which is a notable omission in the context of advanced cancer treatment"*.[3]

EAG comment: The EAG raises concerns about the CS particularly the lack of detailed analyses regarding HRQoL outcomes, including time-to-deterioration and subgroup analyses. This gap limits the ability to fully understand the impact of erdafitinib on patients' overall well-being and daily functioning. Although the CS notes that *"HRQL was maintained on treatment, with few differences between treatment groups"* (CS, Section B.2.6.4),[1] it provides insufficient detail on these outcomes. The CS also underrepresents data from the Functional Assessment of Cancer Therapy – Bladder (FACT-Bl), another HRQoL measure. The company acknowledges that *"Results from the FACT-Bl assessment (domains and total scores) in Cohort 1 showed that HRQL was maintained on treatment across all five primary domains"* (CS, Section B.2.6.4),[1] but offers limited analysis of these findings.

2.5 Other relevant factors

Not applicable.

3. Clinical effectiveness

3.1 Critique of the methods of review(s)

3.1.1 Searches

The following paragraphs contain summaries and critiques of the searches related to clinical effectiveness presented in the CS.[1, 7] The Canadian Agency for Drugs and Technologies in Health (CADTH) evidence-based checklist for the Peer Review of Electronic Search Strategies (PRESS) was used to inform this critique.[8] The EAG has presented only the major limitations of each search strategy in the report.

Appendix D of the CS details the systematic literature review (SLR) conducted to identify relevant clinical evidence on treatments available in the UK for patients with locally advanced, metastatic or unresectable UC with progressive disease (PD) after receiving at least one prior systemic therapy.[7] The searches were conducted in March 2023 and updated in May 2024.

A summary of the sources searched is provided in Table 3.1.

Table 3.1: Data sources for the 2023 clinical effectiveness systematic review (as reported in CS)

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase	Ovid	2006-Current	Original:10.3.23
MEDLINE (inc. In Process & Other Non-Indexed Citations and Daily)	Ovid	2006-Current	Original:10.3.23
Embase & MEDLINE	Embase.com	2023/03/10-Current	Update: 1.5.24
CENTRAL (Cochrane Library)	Not reported	2006/01-Current	Original:10.3.23 Update: 1.5.24
CDSR (Cochrane Library)	Not reported	2006-Current	Original:10.3.23 Update: 1.5.24
Conferences			
ASCO ESMO ECO ISPOR Annual Meetings	Internet		Original:10.3.23 Update:1.5.24
Trials registries			
www.ClinicalTrials.gov EU-CTR WHO ICTRP Health Canada Clinical Trials Database	Internet		Original:10.3.23 Update:1.5.24

Based on CS and Appendices.[7, 9]
ASCO = American Society of Clinical Oncology; CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; ECO = European Cancer Organization; ESMO = European Society of Medical Oncology; EU-CTR = European Union-Clinical Trials Register; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; WHO ICTRP = World Health Organization International Clinical Trials Registry Platform

EAG comment:

- Searches were undertaken in March 2023 and updated in May 2024 to identify clinical evidence for existing and approved treatments for patients with locally advanced, metastatic, or surgically unresectable urothelial cancer (UC; Stage IV disease) who have received at least one prior line of chemotherapy. The initial reporting of search methods in the CS and accompanying documents was unclear and contained conflicting and inconsistent information. However, this was rectified at clarification and the company provided a revised Appendix D which provided sufficient detail for the EAG to fully appraise the searches.[9]
- A good range of bibliographic databases, conferences and trials registries were searched. Reference checking was conducted. The searches strategies provided were well structured and reproducible.
- The database searches for the clinical effectiveness SLR combined appropriate facets for urothelial cancer and named treatments. In the Embase and MEDLINE searches, this was then combined with a study design filter for clinical trials. Animal-only studies were excluded. Searches made good use of both subject headings and free text terms. Database searches were limited to studies from 2006-current. No language limit was applied to the searches.
- For the 2024 update the EAG asked the company to clarify whether the reported MEDLINE/Embase strategy was a single search conducted simultaneously over both the Embase and MEDLINE individual databases, or a single search of Embase conducted on the understanding that it now contains all records from MEDLINE. The company responded that "*Since the Embase platform can integrate both MEDLINE and Embase databases using a common search syntax, a single search strategy was used for both the databases, as depicted in Table 4 in the Appendix. Nevertheless, search syntax used in Ovid for original (2023) SLR were accurately mapped and translated into search syntax used in Embase.com before running the searches for updated (2024) SLR*".[3]
- The EAG noted that the interventions facet in the 2024 update appeared more limited than in the original searches. The company explained that "*the updated (2024). SLR was focused on informing clinical evidence specific to the UK treatment landscape as part of the NICE submission. Therefore, instead of conducting an SLR update on all treatment comparators, we limited the 2024 SLR update to only the following comparators that are currently available in the UK*".[3]
- The EAG queried the omittance of erdafitinib from the update searches, the company confirmed that this was an error and that they "*reran the searches after including erdafitinib. 18 additional records were retrieved from Embase while no new studies were found in other databases, including Cochrane. None of the 18 records were relevant as per the 2024 SLR PICOS criteria and. These 18 records have been excluded at abstract screening stage in an updated PRISMA flow diagram."*[3]
- The full list of grey literature resources searched for the 2024 update was confirmed at clarification. Whilst individual search strategies per resource were not provided, details of keyword combinations were given. It is unclear if these were the same keywords used for the 2023 search.
- Separate adverse events (AEs) searches were not reported. The clinical effectiveness searches incorporated a methodological filter intended to limit the search to specific study designs, namely randomised controlled trials (RCTs). Guidance by the Centre for Reviews and Dissemination (CRD)[10] recommends that if searches have been limited by a study design filter, additional searches should be undertaken to ensure that AEs that are long-term, rare or unanticipated are not missed. Whilst an additional top up search for observational studies was performed on Biosis, Derwent drug file, Embase and MEDLINE for the terms "urothelial cancer + UK + real World/Observational", the EAG considered that due to the restrictive nature of this strategy it was possible that some relevant safety evidence may not have been identified.

3.1.2 Inclusion criteria

A SLR was conducted to identify relevant clinical evidence. Full details of the SLR search strategy, study selection process and results were reported in Appendix D of the CS.[7]

The eligibility criteria used in the search strategy is presented in Table 3.2.

Table 3.2: Eligibility criteria used in search strategy for RCT and non-RCT evidence

Inclusion criteria	Description	Justification
Population	Patients aged 18+ with locally advanced (T3b and T4a), metastatic, or surgically unresectable urothelial cancer (Stage IV disease) who have received one prior line of systemic therapy.	The population is much narrower than the final scope and does not match the decision problem addressed in the CS (see Table 2.1).
Interventions	Erdafitinib.	Consistent with the final scope.
Comparators	Carboplatin + gemcitabine Cisplatin + gemcitabine Paclitaxel Docetaxel Pembrolizumab Atezolizumab BSC (author defined)	The comparators are much broader and does not match the final scope or the decision problem addressed in the CS (see Table 2.1).
Outcomes	OS PFS ORR DOR AEs PROs (FACT-Bl, PGI-S, EORTC QLQ C30 and EQ-5D-5L/EQ-5D-3L)	Consistent with the final scope.
Study design	All Phase II, III, or IV RCTs in the patient population of interest	No justification offered.

Based on Table 1 of the Appendix D[7]
AE = adverse event; BSC = best supportive care; CS = company submission; DOR = duration of response; EORTC QLQ C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-3L = EQ-5D-5L = EuroQol 5-Dimensions 3-Level; EQ-5D-5L = EuroQol 5-Dimensions 5-Level; FACT-Bl = functional assessment of cancer therapy-bladder; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PGI-S = Patient Global Impression of Severity scale; PRO = patient-reported outcome; RCT = randomised control trial

EAG comment:

- The eligible population and comparator for this SLR are misaligned with that described in the NICE final scope and the decision problem. These areas of mismatch may mean that the clinical effectiveness evidence generated by the SLR does not fully address either the NICE final scope or the decision problem.
- No exclusion criteria were reported, and the inclusion criteria did not have a restriction on language, but five studies were excluded in screening for "Non-English". The company did not provide specific details of the excluded studies and therefore it was not possible for the EAG to determine

the impact of these omissions on clinical effectiveness estimates. This means that the potential impact of language bias cannot be discounted.

3.1.3 Critique of data extraction

Two reviewers, with a third party for disputes or consensus, were used for screening and data extraction. An appropriate Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) diagram outlined the inclusion and exclusion of studies.

EAG comment: While noting some independent verification (of an unknown proportion), the CS absence of clarity regarding the extent of independent checks suggests a reliance on a single reviewer for initial extraction which introduces the potential risk of bias.[11] This issue is compounded by the lack of author communication to fill data gaps and lack of a clear protocol for resolving reviewer discrepancies raises questions about the consistency of the final dataset. While these methodological issues do not necessarily indicate pervasive errors or bias, they do increase the likelihood of such problems, potentially affecting the review's comprehensiveness and reliability.[12] The strategy, therefore, while demonstrating strong foundational elements, requires refinement to fully ensure the robustness, overall integrity and value of the review process.

3.1.4 Quality assessment

A risk of bias analysis was conducted for the one included study - THOR trial using the NICE 7-item checklist. No details of the process of quality assessment were reported.

EAG comment: It is not clear by which manner the assessment was conducted. An optimal approach would be two independent reviewers each conducting an appraisal, with any disagreements then resolved through consensus or by the arbitration of a third independent reviewer.

3.1.5 Evidence synthesis

The company stated that no meta-analysis was performed, given that there were no other relevant studies supporting the use of erdafitinib or relevant comparators. Additional data were provided from a registry study initiated by Johnson & Johnson within the context of the decision problem for this appraisal requiring the conduct of an indirect treatment comparison (ITC). Further details of the ITC are provided in Section 3.4.

3.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

The CS details two sources of evidence for the use of erdafitinib for the treatment of adults with unresectable or UC harbouring susceptible [redacted].[1] The first pivotal evidence is the THOR trial, an ongoing, international, Phase III, randomised, open-label trial comparing erdafitinib versus chemotherapy (vinflunine or docetaxel) in patients with advanced UC and susceptible FGFR alterations who had progressed on or after one or two prior treatments, including an anti-PD-(L)1 agent (Cohort 1).[13] Supportive evidence is found in the BLC2001 study, a Phase II single-arm trial of erdafitinib in patients with metastatic or surgically unresectable UC with FGFR alterations. The methodology of the supportive Phase II BCL2001 trial is presented in CS Appendix N.[7] Additional efficacy and safety data

are supplied from this trial. The following Sections will provide summary of the primary trial included in this submission.

3.2.1 Design of THOR trial

The THOR trial is an ongoing global, Phase III, randomised, open-label, multicentre, confirmatory registrational trial evaluating erdafitinib in patients with advanced UC and susceptible FGFR alterations who had progressed on or after one or two prior treatments. Primary efficacy endpoint was OS with secondary endpoints being PFS, ORR, duration of response (DOR) and HRQoL. It consists of two cohorts:

- Cohort 1: erdafitinib versus chemotherapy (docetaxel or vinflunine) in patients who had progressed on or after one or two prior treatments, one of which being an anti-PD-(L)1 agent.
- Cohort 2: erdafitinib versus pembrolizumab in patients who had progressed on or after one prior treatment not containing an anti-PD-(L)1 agent

The CS emphasises that to align with "*with the decision problem and marketing authorisation…this submission will focus on Cohort 1 only"*[1]. Details are provided below.

The trial consists of three phases: screening, treatment and follow-up. The screening phase comprised molecular and full-study screening. Patients were then randomly assigned at a 1:1 ratio to either:

- Treatment Group 1: 8 mg erdafitinib once daily for 21 days in a 21-day cycle (with pharmacodynamically guided up-titration to 9 mg)
- Treatment Group 2: chemotherapy (320 mg/m2 vinflunine administered as a 20-minute intravenous (IV) infusion, or 75 mg/m^2 docetaxel administered as a 1-hour IV infusion, once every 3 weeks).

The decision to administer either vinflunine or docetaxel was made at site level by the investigator prior to the enrolment of patients. Participants were stratified by region (North America versus the rest of the world), Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) (0 or 1 versus 2) and disease distribution (presence versus absence of visceral metastases: lung, liver, or bone). The CS confirms that '*During treatment phase, patients continued to receive treatment until disease progression, intolerable toxicity, withdrawal of consent or a decision taken by the investigator to discontinue treatment. The post-treatment follow-up phase extended from the end-of-treatment visit until the patient died, withdrew consent, was lost to follow-up, or the end of study, whichever came first.*') (CS Section B2.3.1.1).[1] An overview of the trial methodology and flow is described in Table 3.3 and Figure 3.1 below.

Table 3.3: Summary of the THOR trial methodology

Trial name:	THOR
Trial design:	Phase III, randomised, open-label, multicentre trial
Locations:	One hundred and twenty-one (121) sites in 23 countries, including: Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, France, Germany, Greece, Hungary, Israel, Italy, Japan, Netherlands, Russia, the Republic of Korea, Spain, Taiwan, Turkey, the UK and the US
Key eligibility criteria for patients	**Inclusion criteria:** Histological demonstration of transitional cell carcinoma of the urothelium. Metastatic or surgically unresectable UC.

	Documented progression of disease, defined as any progression that requires a change in treatment prior to randomisation. Prior treatment with an anti-PD-(L)1 agent as monotherapy or as combination therapy; no more than two prior lines of systemic treatment. Prior treatment with an anti-PD-(L)1 agent could have been given as neoadjuvant, adjuvant, or in the metastatic line of treatment as frontline or maintenance therapy. Patients must meet appropriate molecular eligibility criteria, as determined by central laboratory screening or by local historical test results. Tumours must have at least one of the following fusions: FGFR2-BICC1, FGFR2-CASP7, FGFR3-TACC3, FGFR3-BAIAP2L1; or one of the following FGFR3 mutations: R248C, S249C, G370C, Y373C. ECOG PS Grade 0, 1, or 2. **Exclusion criteria:** Treatment with any other investigational agent or participation in another clinical study with therapeutic intent within 30 days prior to randomisation. Active malignancies (that is, requiring treatment change in the last 24 months). The only allowed exceptions are UC, skin cancer treated within the last 24 months that is considered completely cured, localised prostate cancer with a Gleason score of 6 (treated within the last 24 months or untreated and under surveillance) and localised prostate cancer with a Gleason score of 3+4 that has been treated more than 6 months prior to full study screening and considered to have a very low risk of recurrence. Symptomatic CNS metastases. Received prior FGFR inhibitor treatment. Known allergies, hypersensitivity or intolerance to erdafitinib or its excipients. Corneal or retinal abnormality likely to increase the risk of eye toxicity. History of uncontrolled cardiovascular disease. Impaired wound healing capacity defined as skin/decubitus ulcers, chronic leg ulcers, known gastric ulcers, or unhealed incisions. History of severe hypersensitivity reaction to either docetaxel, or to other drugs formulated with polyoxyethylated castor oil, or to vinflunine or other vinca alkaloids. The full eligibility criteria can be found in Appendix M.
Settings and locations where the data were collected	A total of 266 patients were enrolled and treated at one of the 121 trial sites.
Trial drugs	Intervention: erdafitinib (8 mg oral tablet administered once daily for 21 days in a 21-day cycle). Comparator: vinflunine (320 mg/m2 as a 20-minute IV infusion every 3 weeks) or docetaxel (75 mg/m2 as a 1-hour IV infusion every 3 weeks).
Permitted and disallowed concomitant medication	The following concomitant medications were permitted during the study: Symptomatic treatment: supportive care, such as antibiotics, analgesics, transfusions, diet, etc., and concomitant medications for the symptomatic treatment of related toxicities (Grade 1–4) could be administered according to the SoC at the site, and the treating physician's discretion, as clinically indicated.

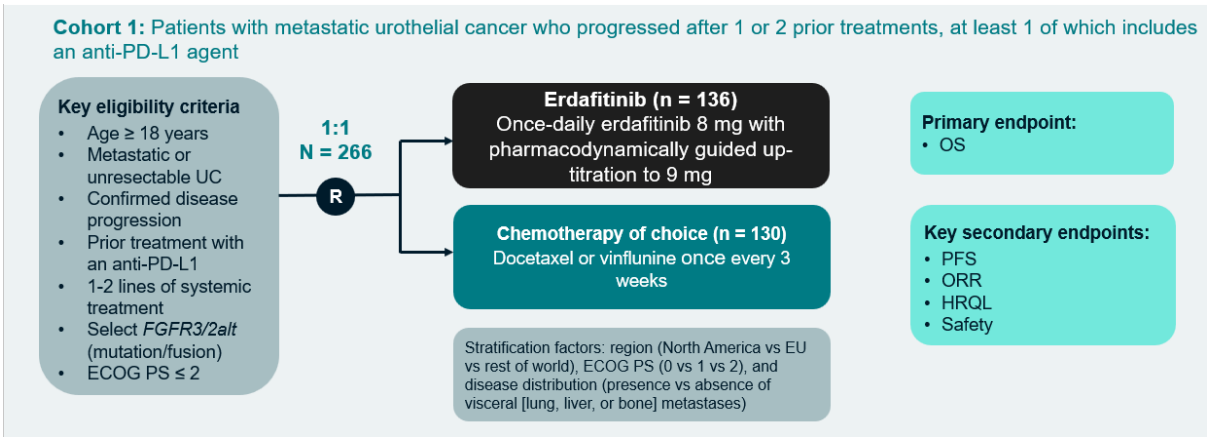
	Prophylactic medication: appropriate prophylactic antiemetic regimens could be provided if required, in accordance with institutional practice and current ESMO guidelines. Chronic supportive therapies: ongoing bisphosphonates and denosumab or other supportive therapies were permitted. Palliative radiotherapy: localised radiotherapy for symptomatic control was permitted but should not have included definitive radiation to target lesions. The following medications were prohibited during the study: - Concurrent investigational agents. - Concurrent antineoplastic agents or hormonal anticancer therapy For patients receiving erdafitinib: - Medications known to increase serum levels of calcium and serum phosphate levels. For patients receiving chemotherapy (vinflunine or docetaxel): - Strong inhibitors of the CYP3A4 enzymes. For patients receiving vinflunine: - Strong inducers of CYP3A4 enzymes. - QT/QTc prolonging drugs.
Primary endpoints	OS, defined as the date of randomisation to the date of the patient's death.
Key secondary endpoints	PFS, assessed per RECIST v1.1 by the investigator, or death, whichever is reported first; defined as duration in days from the date of randomisation to the date of disease progression. ORR, assessed per RECIST v1.1 by the investigator; defined as the proportion of patients who achieved CR or PR. DOR, defined as duration in days from the date of initial documentation of a response to the date of first documented evidence of PD or death (for responders) PROs: change from baseline in HRQoL as assessed by the FACT-Bl, EQ-5D-5L questionnaire, and PGI-S, and time until urinary bladder cancer symptom deterioration (subset of FACT-Bl items). Safety.
Subgroup analyses	FGFR alteration type PD-(L)1 status Tumour location Visceral metastases Prior therapy Type of chemotherapy (docetaxel or vinflunine) Demographic and baseline characteristics (gender, age, race, ethnicity, region, baseline creatine clearance, baseline haemoglobin level, baseline ECOG PS) Please see Appendix E for full list. The subgroup analyses was not powered to assess treatment effect within subgroups.

Based on Table 5, CS[1]

CNS = central nervous system; CR = complete response; CS = company submission; CYP3A4 = Cytochrome P450 3A4; DOR = duration of response; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ESMO = European Society of Medical Oncology; FACT-Bl = Functional Assessment of Cancer Therapy – Bladder; FGFR = fibroblast growth factor receptor; HRQoL = health-related quality of life; IV = intravenous; ORR = objective response rate; OS = overall survival; PD = progressive disease; PD-(L)1 =

programmed death-(ligand)1; PFS = progression-free survival; PGI-S = Patient Global Impression of Severity scale; PR = partial response; PRO = patient-reported outcome; RECIST = Response Evaluation Criteria In Solid Tumours; SoC = standard of care; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; UC = urothelial carcinoma; UK = United Kingdom; US = United States

Figure 3.1: THOR trial design, Cohort 1



Based on Figure 3, CS[1]

Alt = alterations; CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FGFR = fibroblast growth factor receptor; HRQoL = health-related quality of life; ORR = objective response rate; OS = overall survival; PD-(L)1 = programmed death-(ligand)1; PFS = progression-free survival; UC = urothelial carcinoma

The CS[1] summarises the patient flow of all randomised patients enrolled in Cohort 1 of the trial and provides additional detail in appendix D.2[7]. Briefly, of 266 enrolled participants, 136 were randomly assigned to receive erdafitinib and 130 to receive chemotherapy. Of these patients, 135 and 112 patients received at least one dose of erdafitinib or chemotherapy, respectively. By the point of clinical cut-off (January 2023), 29 patients in the erdafitinib arm and 10 in the chemotherapy arm were still receiving treatment within the trial. Discontinuation was typically due to disease progression (erdafitinib: n=81; chemotherapy: n=62) and AEs (erdafitinib: n=17; chemotherapy: n=19). Fifty-seven patients in the erdafitinib arm and 37 in the chemotherapy arm were continuing in the trial. The primary reason for discontinuation of the trial was death (erdafitinib n=77; chemotherapy: n=78).

3.2.2 Statistical analysis of THOR trial

The analysis sets of the trial are presented in Table 3.4. The intention-to-treat (ITT) set was utilised to summarise the study population and baseline characteristics, efficacy and PRO data. The CS confirms that the per protocol population was not utilised for efficacy analysis as the protocol population was not <95% of the ITT population. Table 3.5 provides an overview on the statistical considerations. Briefly, data is presented from the interim analysis (clinical cut-off date of 15 January 2023). The interim analysis occurred after 155 death events had been observed (at approximately 75% information fraction). The efficacy boundary p-value was predetermined to be 0.019 (two-sided) based on the O'Brien–Fleming alpha-spending function[1]. Following the interim analysis, the independent data monitoring committee made a recommendation to stop Cohort 1 due to superiority of erdafitinib over chemotherapy and allowed cross-over of six patients in the chemotherapy group to the erdafitinib group. The CS clarifies that due to the small number of patients who crossed over, no adjustment analyses were performed.

Table 3.4: THOR analysis sets

Analysis set	Definition	Number of patients		
		Erdafitinib	Chemotherapy	Total
Cohort 1 ITT analysis set	All randomised patients in Cohort 1. Patients in this population will be analysed according to the treatment to which they are randomised.	136	130	266
Safety	All randomised patients who received at least one dose of the study drug. Safety data will be analysed according to the actual treatment received.	135	112	247

Based on Table 9, CS[1]
CS = company submission; ITT = intention-to-treat; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations

Table 3.5: Summary of statistical analyses in THOR

Hypothesis objective	Erdafitinib treatment prolongs OS in patients with advanced UC harbouring selected FGFR alterations following one or two prior line(s) of systemic therapy, with at least one line containing anti-PD-(L)1, compared with the OS of those treated with chemotherapy (docetaxel or vinflunine).
Statistical analysis	For the primary efficacy analysis, the KM method was used to estimate the distribution of OS for each treatment group within each cohort. The stratified log-rank test was used to compare survival curves of OS between the two treatment arms. The Type 1 error was controlled at 5% (two-sided) for the primary endpoint. All tests were conducted at a two-sided alpha level of 0.05, and a 95% CI was provided, unless stated otherwise. Secondary endpoints were assessed at the same significance levels as specified for testing the primary endpoint (OS) to protect the overall Type 1 error rate. The testing order of these endpoints was as follows: PFS, ORR, time to urinary bladder cancer symptom deterioration. PFS was analysed the same as OS. The ORR was analysed by the Cochran–Mantel–Haenszel chi-squared test. For time to urinary bladder cancer symptom deterioration, the median time to deterioration was estimated using a KM method. Additionally, HR and associated 95% CIs were estimated by stratified Cox's proportional hazards model with stratification variables. The KM method was used to estimate the distribution of DOR.
Sample size, power calculation	Approximately 280 patients (approximately 140 patients per arm) were planned to be enrolled in Cohort 1. The final analysis was planned when approximately 208 death events occurred. The study had at least 85% power to detect an HR of 0.65 at a statistical significance level of 5% (two-sided), with one interim analysis for efficacy at an approximately 65% information fraction (approximately 136 deaths) and a final analysis.
Data management, patient withdrawals	A patient who discontinues study treatment continued to participate in the study for follow-up of survival status, subsequent anticancer therapy, EQ-5D-5L questionnaire completion, and resolution of any ongoing drug-related AEs. For patients who discontinue treatment before disease progression, every effort should be made to continue to monitor their disease status according to the Time and Events Schedule. If a patient discontinued treatment, an end-of-treatment visit was conducted 30 (+7) days after the patient's last dose of the study drug. The primary reason for treatment discontinuation was clearly documented in the patient's medical record

	and recorded in the eCRF. Once a patient discontinued treatment with the study drug, the patient was not permitted to be retreated. When a patient withdrew consent before completing the study, the reason for withdrawal was documented in the eCRF and in the source document. In addition, patients who withdrew consent had to complete and sign a withdrawal of consent form to specify if they agreed to have survival data collected or not. The study drug assigned to the withdrawn patient was not assigned to another patient. Patients were replaced only if the patient withdrew prior to the study drug administration.
Based on Table 10, CS[1] AE = adverse event; CI = confidence interval; CS = company submission; DOR = duration of response; eCRF = electronic case report form; EQ-5D-5L = European Quality of Life-5 Dimension, 5-Level; FGFR = fibroblast growth factor receptor; HR = hazard ratio; KM = Kaplan-Meier; ORR = objective response rate; OS = overall survival; PD-(L)1 = programmed death-(ligand)1; PFS = progression-free survival; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; UC = urothelial carcinoma	

EAG comment: The EAG consider the analysis to be generally well conducted with appropriate methods utilised and noted below.

- The use of stratified log-rank tests for time-to-event outcomes
- Cox proportional hazards models for estimating hazard ratios (HRs)
- The Cochran-Mantel-Haenszel test for comparing response rates
- Pre-specified interim analysis with appropriate alpha spending function

The EAG highlights the risk of the introduction of bias for subjective outcomes as a consequence of the open label design. However, while the EAG draw attention to this, we do note this is of less concern for the primary endpoint of OS.

3.2.3 Baseline characteristics

The baseline characteristics for the Cohort 1 ITT populations are shown in Table 3.6. The CS emphasises that 'Most patients were male (71.4%), white (54.1%), and from Europe (60.9%). The median age at full-study screening was 67.5 years (range: 32, 86 years). Most patients were aged 65 and over. The patient population enrolled in THOR is considered broadly representative of that seen within UK clinical practice, as confirmed by UK clinicians (CS Section B.2.3.1.3)1.

Table 3.6: Baseline demographics and disease characteristics (Cohort 1 ITT population)

Characteristic	Erdafitinib (n=136)	Chemotherapy (n=130)
Age, years		
Median (range)	66.0 (32-85)	69.0 (35-86)
<65 years, n (%)	59 (43.4)	45 (34.6)
65–69 years, n (%)	30 (22.1)	23 (17.7)
70–74 years, n (%)	21 (15.4)	32 (24.6)
≥75 years, n (%)	26 (19.1)	30 (23.1)
Gender, n (%)		
Male	96 (70.6)	94 (72.3)
Female	40 (29.4)	36 (27.7)

Characteristic	Erdafitinib (n=136)	Chemotherapy (n=130)
Race, n (%)		
Asian	37 (27.2)	40 (30.8)
Black or African American	0	1 (0.8)
White	81 (59.6)	63 (48.5)
Multiple	0	1 (0.8)
Not reported	18 (13.2)	25 (19.2)
Geographic region, n (%)		
North America	8 (5.9)	5 (3.8)
Europe	82 (60.3)	80 (61.5)
Rest of the world	46 (33.8)	45 (34.6)
Primary tumour location, n (%)		
Lower tract	95 (69.9)	82 (63.1)
Bladder	90 (66.2)	74 (56.9)
Urethra	5 (3.7)	8 (6.2)
Prostate	0	0
Upper tract	41 (30.1)	48 (36.9)
Renal Pelvis	19 (14.0)	20 (15.4)
Ureter	22 (16.2)	28 (21.5)
Baseline ECOG PS, n (%)		
0	63 (46.3)	51 (39.2)
1	61 (44.9)	66 (50.8)
2	12 (8.8)	13 (10.0)
Disease distribution at study entry, n (%)		
Presence of visceral metastases[a]	101 (74.3)	97 (74.6)
Lung	71 (52.2)	67 (51.5)
Liver	31 (22.8)	38 (29.2)
Bone	36 (26.5)	39 (30.0)
Absence of visceral metastases (lung, liver, or bone)	35 (25.7)	33 (25.4)
PD-(L)1 status, n (%)		
N	96	79
CPS ≥1	38 (39.6)	38 (48.1)
CPS <1	58 (60.4)	41 (51.9)
PD-(L)1 status, n (%)		
N	96	79
CPS ≥10	7 (7.3)	11 (13.9)
CPS <10	89 (92.7)	68 (86.1)
***FGFR3* alterations, n (%)**		
n	135	129

Characteristic	Erdafitinib (n=136)	Chemotherapy (n=130)
Mutations	108 (79.4)	107 (82.3)
Fusions	25 (18.4)	19 (14.6)
Mutations and fusions	2 (1.5)	3 (2.3)

Based on Table 6, CS[1]
Notes: Percentages are based on the number of patients in a specified group with non-missing values for the relevant parameter. [a] Number and percentages for lung, liver, and bone are based on patients marked with 'Yes' in the eCRF question 'Are there currently any metastatic disease sites involving liver, lung, and/or bone?
CPS = combined positive score; CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eCRF = electronic case report form; FGFR3 = fibroblast growth factor receptor 3; ITT = intention-to-treat; PD-(L)1 = programmed death-(ligand)1

EAG comment: Both treatment arms were similar and generally well balanced across baseline characteristics. While median ages overall were similar between the two arms, differences at the >5% level were present in the age range categorisation of <65 years (erdafitinib: 43.4% versus 34.6%) and at 70-74 years (erdafitinib: 15.4% versus 24.6%. Additionally, location of primary tumours was different at the >5% level between arms with bladder cancer being more frequent (erdafitinib: 66.2% versus 56.9%) and cancer of the ureter less frequent (erdafitinib: 16.2% versus 21.5%) in experimental arm. Presence of visceral metastasis to liver also differed between groups at >5% level, although not at the overall level of visceral metastasis. There was less liver metastasis in the erdafitinib arm (22.8% versus 29.2%). It should also be noted that distribution of ECOG PS was different between arms at the >5% level with 46.3 of erdafitinib arm having a score of '0' versus 39.2 of the chemotherapy arm. PD-(L)1 status was also different between the groups, with a combined positive score (CPS) ≥1 at 39.8% and CPS <1 at 60.4% in the erdafitinib arm versus 48.1 and 51.9% respectively in the chemotherapy arm. The CPS ≥10 was also different between arms with 7.3% in the erdafitinib arm versus 13.9% in the chemotherapy arm, and indeed at CPS <10 with 92.7% in the erdafitinib versus 86.1% in the chemotherapy arms. The EAG does not highlight such differences to necessarily suggest that this may impact on any clinical outcomes but draws attention for consideration. The EAG do note that some of these differences reflect small subgroup numbers rather than differences in characteristics.

The EAG noted that only 60.9% of patients were from Europe and 54.1% were white. To seek further information on the generalisability of this population to the relevant population in England and Wales, we asked the company to provide the data for UK based participants. In their response to the request for clarification[3] the company provided the following data (see Tables 3.6 and 3.7). Only [redacted] participants were UK based and the EAG noted that the starting age selected by the company was [redacted]. The EAG highlighted that the clinical experts cited by the company also argued that most patients would be [redacted]. Additionally, the EAG considered that the [redacted].

Table 3.7: Summary of demographics and baseline characteristics data: UK subjects

[redacted]	[redacted]	[redacted]	[redacted]
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Based on Table 7, response to the request for clarification.[3] ITT = intention-to-treat; SD = standard deviation; UK = United Kingdom			

Table 3.8: Summary of disease characteristics at baseline: UK subjects

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Based on Table 8, response to the request for clarification[3]
[redacted]
[redacted]CPS = combined positive score; eCRF = electronic case report form; [redacted]; ITT = intention-to-treat; PD-(L)1 = programmed death-(ligand)1; SD = standard deviation; UK = United Kingdom

In their response to this, the company stated that, based on a clinical expert report: '*General perception is that clinical trial populations are younger than patients in real practice. However, clinicians agreed that the age ranges of patients in THOR and RW UK mUC study were similar, with a median age of 66.5 and 68.8, respectively. Additionally, the erdafitinib population was weighted to match the proportion of age categories (< 65 and ≥ 65) in NCRAS (a dataset that reflects UK clinical practice). A subgroup analysis of the erdafitinib arm in THOR showed a median survival of approximately 11 months for patients ≥ 65 years versus 14 months for patients < 65 years (Figure 4, CSR page 61). In addition, previous appraisals in mUC were based on IMvigor211 (TA525) and KEYNOTE-045 (TA692) trials which had median patient ages of 67.0 and 66.0 years, respectively, which were deemed generalisable to the UK patient population initiating second-line treatment* '(Response to the request for clarification, Section B1c).[3] The EAG highlights that in the same clinical expert report provided, it is noted that RW patients tend to be older and less fit.[14] [redacted]. This discrepancy may raise concerns about the applicability of

trial results to routine National Health Service (NHS) practice. This limitation is further compounded by differences in race and fitness between the trial population and the RW UK population i.e. underrepresentation of patients who are of Black or African American race, an overrepresentation of Asian patients, and a predominance of patients with an ECOG PS of 0-1, indicating a healthier population than might be seen in UK clinical practice, where patients might have poorer PS (e.g., ECOG PS 2+).

The EAG acknowledges the company's effort to address these concerns within the reweighting approach taken, which aims to partially address the issue, however, maintain that concerns may persist about the representativeness of the trial population for the UK setting. Lack of generalisability therefore remains a key issue. This also has implications for the ITC in terms of comparability with the UK real-world evidence (RWE; see Sections 3.3 and 3.4).

3.2.4 Risk of bias assessment

3.2.4.1.1 Risk of bias assessment of the THOR trial

The quality assessment of the THOR trial was conducted using the NICE Single Technology Appraisal (STA) tool. Overall, the CS states the THOR study was assessed to have a low risk of bias[1, 5]. Full results of this assessment are presented in Appendix D.3[7] whereby:

"The THOR study adequately described the methods for randomisation of patients and allocation concealment.[515] *The demographic and clinical characteristics of the patients were balanced between the two treatment groups at baseline. Details on random allocation and concealment were also adequate, and the independent data monitoring committee made a recommendation to unblind the data only after interim analysis to allow crossover of patients from chemotherapy to erdafitinib. Clinical endpoints were evaluated in an ITT population, and the authors reported all outcomes described in the study methods".*

3.2.5 Efficacy results of the included studies

3.2.5.1 Overall survival

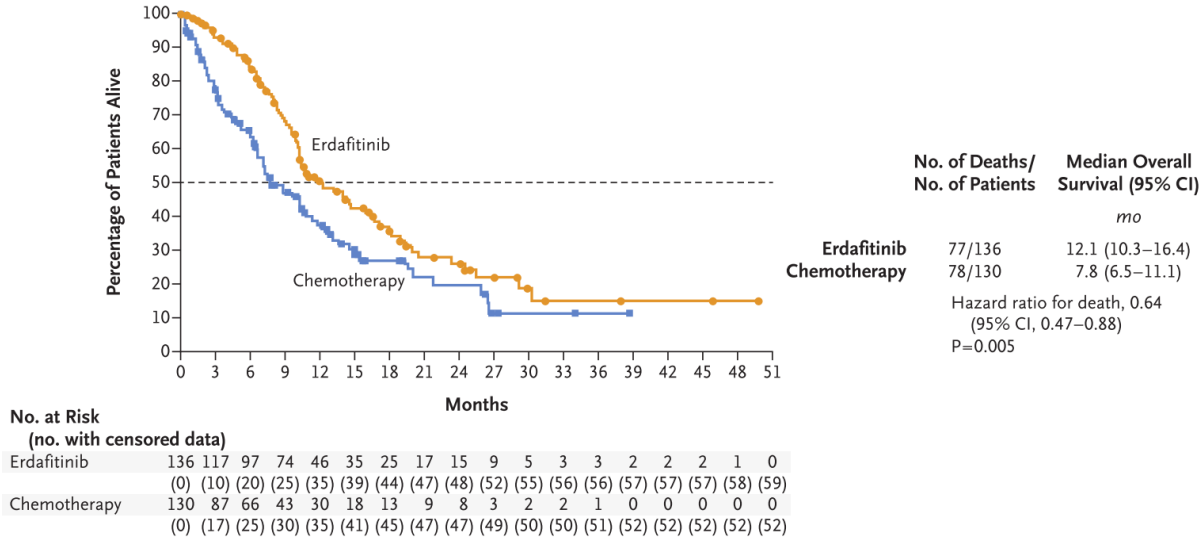
The OS results for Cohort 1 ITT analysis set of the THOR trial comparing erdafitinib with chemotherapy within the CS are presented in Table 3.9 with accompany survival curve (Figure 3.2).

Table 3.9: Analysis of OS in the THOR trial (Cohort 1 ITT analysis set)

	Erdafitinib (n=136)	**Chemotherapy (docetaxel or vinflunine; n=130)**
Number of events (%)	77 (56.6)	78 (60.0)
Median OS, months (95% CI)	12.06 (10.28, 16.36)	7.79 (6.54, 11.07)
OS HR (95% CI)[a]	0.64 (0.47, 0.88)	
p-value[b]	0.005	
6-month survival rate (95% CI)	0.85 (0.77, 0.90)	0.66 (0.56, 0.74)
9-month survival rate (95% CI)	[redacted]	[redacted]
12-month survival rate (95% CI)	0.51 (0.41, 0.60)	0.38 (0.28, 0.47)
24-month survival rate (95% CI)	[redacted]	[redacted]

	Erdafitinib (n=136)	Chemotherapy (docetaxel or vinflunine; n=130)
Based on Table 11, CS[1] [a] HR and 95% CI are estimated using a Cox proportional hazards regression model, with treatment as the only explanatory variable. An HR <1 indicates longer survival time in the erdafitinib arm compared with the chemotherapy (vinflunine or docetaxel) arm; [b] p-value is two-sided and based on a log-rank test CI = confidence interval; CS = company submission; FGFR = fibroblast growth factor receptor; HR = hazard ratio; ITT = intention-to-treat; OS = overall survival; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations		

Figure 3.2: Kaplan-Meier plot of OS (Cohort 1 ITT analysis set)



Based on CS Figure 4.[1]
CI = confidence interval; CS – company submission; ITT = intention-to-treat; OS = overall survival

3.2.5.2 Subsequent Therapies

The proportion of patients who received subsequent therapies was similar in both treatment groups (32.4% in the erdafitinib group and 36.9% in the chemotherapy group). The subsequent therapies used include chemotherapy (erdafitinib group: 15.4%; chemotherapy group: 16.2%), and antibody-drug conjugates (ADCs) (erdafitinib group: 16.2%; chemotherapy group: 10.8%). Of these, the most commonly used ADC was enfortumab vedotin (erdafitinib group: 14.0%; chemotherapy group: 10.0%). Patients also received subsequent immunotherapy, specifically CPIs (erdafitinib group: 6.6%; chemotherapy group: 6.9%), and FGFR inhibitors (erdafitinib group: 2.2%; chemotherapy group: 7.7%). Of these, six patients in the chemotherapy group received erdafitinib.

Table 3.10: Summary of the subsequent therapies used for patients in Cohort 1 ITT analysis set of the THOR trial

Subsequent therapy, n (%)	Erdafitinib (n=136)	Chemotherapy (n=130)
Any subsequent therapy[a]	**44 (32.4)**	**48 (36.9)**
Number of subsequent therapy lines		
1	33 (24.3)	40 (30.8)
2	9 (6.6)	8 (6.2)
3	0 (0.0)	0 (0.0)
>3	2 (1.5)	0 (0.0)

Subsequent therapy, n (%)	Erdafitinib (n=136)	Chemotherapy (n=130)
Chemotherapy	**21 (15.4)**	**21 (16.2)**
Carboplatin	8 (5.9)	9 (6.9)
Gemcitabine	6 (4.4)	10 (7.7)
Paclitaxel	8 (5.9)	6 (4.6)
Docetaxel	4 (2.9)	2 (1.5)
Vinflunine	4 (2.9)	0
Cisplatin	0	2 (1.5)
Methotrexate	0	2 (1.5)
Pemetrexed	2 (1.5)	0
Doxorubicin	0	1 (0.8)
Vinblastine	0	1 (0.8)
Immunotherapy	**9 (6.6)**	**9 (6.9)**
Pembrolizumab	4 (2.9)	4 (3.1)
Atezolizumab	2 (1.5)	2 (1.5)
Tislelizumab	1 (0.7)	2 (1.5)
Nivolumab	1 (0.7)	1 (0.8)
Avelumab	1 (0.7)	0
FGFR inhibitors	**3 (2.2)**	**10 (7.7)**
Erdafitinib	0	6 (4.6)
Derazantinib	3 (2.2)	2 (1.5)
Pemigatinib	0	2 (1.5)
Antibody-drug conjugate	**22 (16.2)**	**14 (10.8)**
Enfortumab vedotin	19 (14.0)	13 (10.0)
Sacituzumab govitecan	3 (2.2)	0
Disitamab vedotin	0	1 (0.8)
Other systemic therapy	**2 (1.5)**	**1 (0.8)**
Sitravatinib	1 (0.7)	1 (0.8)
Lenvatinib	1 (0.7)	0
Investigational systemic therapy	**0**	**3 (2.3)**

Based on CS Table 15[1]
[a] Patients may have received >1 subsequent therapy
CS = company submission; FGFR = fibroblast growth factor receptor; ITT = intention-to-treat; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations

3.2.5.3 Progression-free survival

Progression-free survival, a key secondary endpoint, also showed a statistically significant improvement for erdafitinib, see Table 3.11.

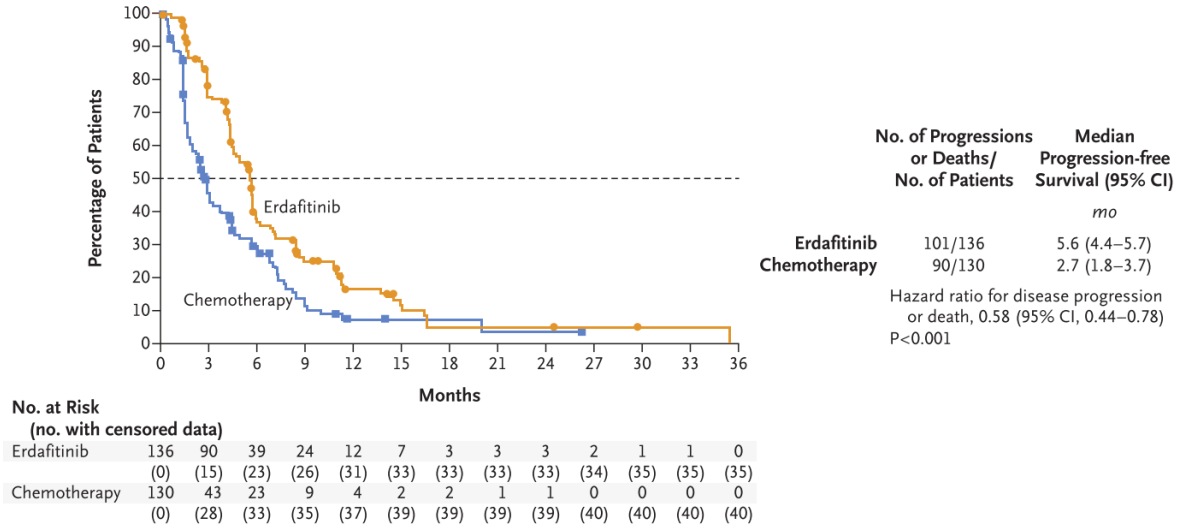
Table 3.11: Analysis of PFS in the THOR trial (Cohort 1 ITT analysis set)

	Erdafitinib (n=136)	Chemotherapy (n=130)
Number of events, n (%)	101 (74.3)	90 (69.2)
Median PFS, months (95% CI)	5.55 (4.40, 5.65)	2.73 (1.81, 3.68)
PFS HR (95% CI)[a]	0.58 (0.44, 0.78)	
p-value[b]	0.0002	
6-month survival rate, n (95% CI)	[redacted]	[redacted]
9-month survival rate (95% CI)	[redacted]	[redacted]
12-month survival rate (95% CI)	[redacted]	[redacted]
24-month survival rate (95% CI)	[redacted]	[redacted]

Source: Table 12, CS[1]
[a] HR and 95% CI are estimated using a Cox proportional hazards regression model with treatment as the explanatory variable. An HR <1 indicates longer survival time in the erdafitinib arm compared with the chemotherapy (vinflunine or docetaxel) arm; [b] p-value is two-sided and is based on a log-rank test.
CI = confidence interval; CS = company submission; FGFR = fibroblast growth factor receptor; HR = hazard ratio; ITT = intention-to-treat; PFS = progression-free survival; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations

The KM curves for PFS separated early and remained separated until around 16 months.

Figure 3.3: Kaplan-Meier plot of PFS (Cohort 1 ITT analysis set)



Based on CS Figure 5.[1]
CI = confidence interval; CS = company submission; ITT = intention-to-treat; PFS = progression-free survival

EAG comment: The OS benefit for erdafitinib appears clinically meaningful and statistically significant. The 4.3-month improvement in median OS (12.06 versus 7.79 months) and 36% reduction in risk of death (HR: 0.64; 95% confidence interval [CI]: 0.47, 0.88) are notable in this treatment setting. The Kaplan-Meier (KM) curves demonstrate early and sustained separation, suggesting a consistent OS benefit throughout the study period. However, longer-term follow-up data would be valuable to assess the durability of this survival benefit, particularly given the continued separation of curves at later time points. This is therefore a key issue.

The PFS benefit is statistically significant and clinically meaningful, more than doubling the median PFS, however as PFS was investigator-assessed in an open-label trial, there is potential for bias. Independent radiological review of PFS would have strengthened the robustness of this endpoint.

While the open-label design may introduce some bias in treatment decisions that could impact OS, this is less of a concern for this objective endpoint. Nevertheless, the potential impact of this design and subsequent treatment choices should be considered. The company has provided detailed information on subsequent therapies received by patients in both arms. The distribution appears to be relatively balanced between arms, which may mitigate potential confounding effects on OS. However, the company should clarify if any statistical adjustments or sensitivity analyses were performed to account for these subsequent therapies in the OS analysis.

Given the importance of OS as the primary endpoint, a more detailed discussion of the maturity of the OS data and the number of patients at risk at key time points would be helpful for interpreting the reliability of the long-term OS estimates. The plateau of the curves at later timepoints should be interpreted cautiously due to small numbers of patients at risk.

3.2.5.4 Objective response rate (ORR)

The ORR showed a substantial improvement with erdafitinib, see Table 3.12.

Table 3.12: Analysis of ORR in the THOR trial (Cohort 1 ITT analysis set)

	Erdafitinib (n=136)	Chemotherapy (n=130)
ORR, n (%)	**62 (45.6)**	**15 (11.5)**
Relative risk (95% CI)	3.94 (2.37, 6.57)	
p-value[a]	<0.001	
BOR, n (%)		
CR	[redacted]	[redacted]
PR	[redacted]	[redacted]
SD[b]	[redacted]	[redacted]
PD	[redacted]	[redacted]
NE	[redacted]	[redacted]
DCR, n (%)	[redacted]	[redacted]
Relative risk (95% CI)	[redacted]	
p-value[a]	<0.001	

Based on CS Table 13.[1]
[a] All p-values are two-sided.
[b] Minimum duration requirement for SD is 6 weeks from the date of randomisation. SD includes patients with no measurable disease at baseline and their best response was non-CR/non-PD. ORR: RR >1 indicates that the probability of achieving an objective response (PR or CR) is higher on the erdafitinib arm compared with the chemotherapy arm. DCR: relative risk >1 indicates that the probability of achieving a response of SD or better is higher on the erdafitinib arm compared with the chemotherapy arm.
BOR = best overall response; CI = confidence interval; CR = complete response; CS = company submission; DCR = disease control rate; FGFR = fibroblast growth factor receptor; ITT = intention-to-treat; NE = not evaluable; ORR = objective response rate; PD = progressive disease; PR = partial response; RR = relative risk; SD = stable disease; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations

3.2.5.5 Duration of response

The results are presented in Table 3.13.

Table 3.13: Analysis of DOR in the THOR trial (Cohort 1 ITT analysis set)

	Erdafitinib (n=62)	Chemotherapy (n=15)
DOR		
Number of events, n (%)	[redacted]	[redacted]
Number censored, n (%)	[redacted]	[redacted]
Started subsequent anticancer therapy	[redacted]	[redacted]
No progression until data cut-off	[redacted]	[redacted]
Kaplan–Meier estimates (months)		
25% percentile (95% CI)	[redacted]	[redacted]
Median (95% CI)	4.86 (3.84, 7.46)	5.55 (2.14, 6.01)
75% percentile (95% CI)	[redacted]	[redacted]
Min, max	[redacted]	[redacted]
6-month survival rate (95% CI)	[redacted]	[redacted]
9-month survival rate (95% CI)	[redacted]	[redacted]
12-month survival rate (95% CI)	[redacted]	[redacted]
24-month survival rate (95% CI)	[redacted]	[redacted]
HR (95% CI)[a]	0.85 (0.43, 1.66)	
p-value[b]	0.6222	

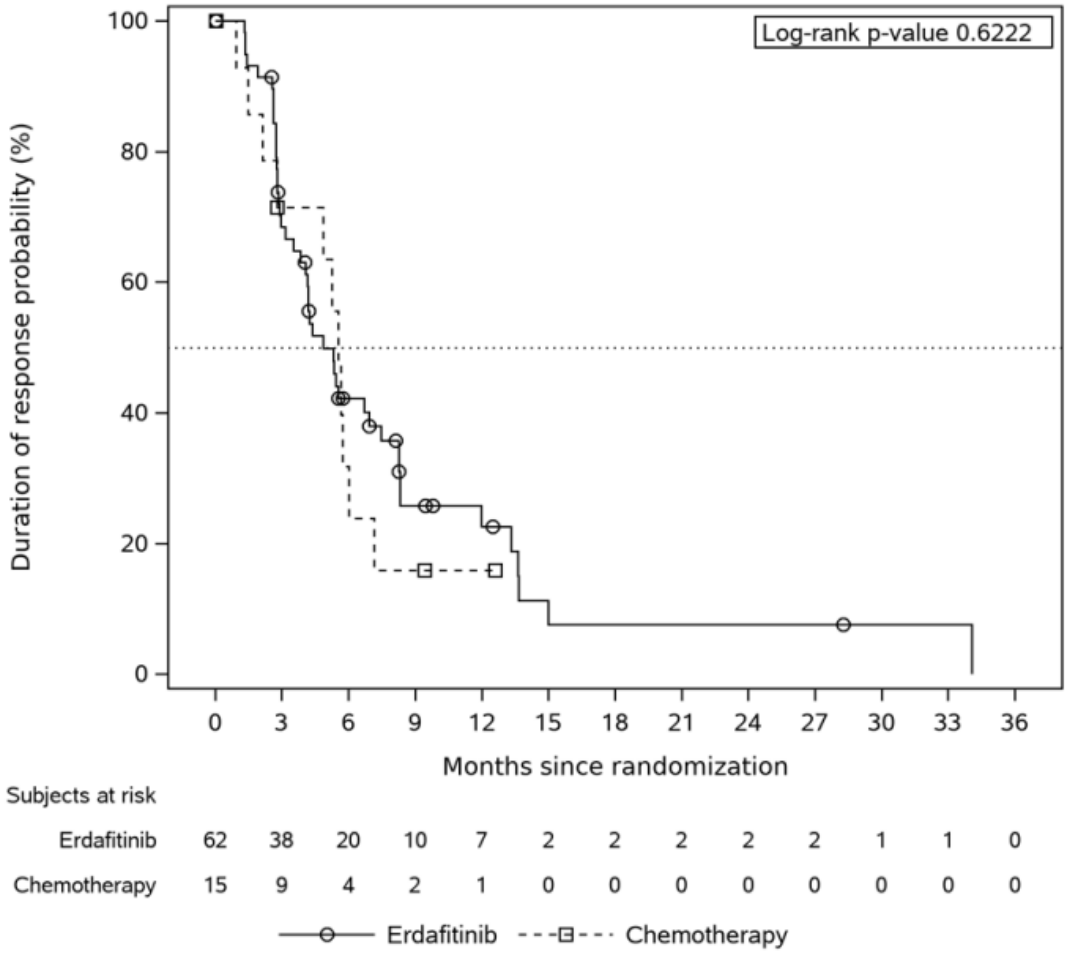
Based on CS Table 14.[1]

[a] HR and 95% CI are estimated using a Cox proportional hazards regression model with treatment as the explanatory variable. A HR <1 indicates longer DOR in the erdafitinib arm as compared with the chemotherapy (vinflunine or docetaxel) arm; [b] p-value is two-sided and is based on a log-rank test.

+ Indicates censored observation.

CI = confidence interval; CS = company submission; DOR = duration of response; FGFR = fibroblast growth factor receptor; HR = hazard ratio; ITT = intention-to-treat; max = maximum; min = minimum; NE = not evaluable; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations

Figure 3.4: Kaplan-Meier plot of DOR (Cohort 1 ITT analysis set)



Based on CS Figure 7[1]
CS = company submission; DOR = duration of response; ITT = intention-to-treat

EAG comment: The ORR difference is striking and statistically significant. The higher complete response (CR) rate for erdafitinib is particularly notable. As with PFS, the open-label design may introduce bias in investigator-assessed responses. Independent review of responses would have been valuable to confirm these findings. The company should provide details on the timing of response assessments and confirmation of responses. The similar DOR between arms is somewhat unexpected given the PFS and ORR advantages for erdafitinib. This could suggest that while erdafitinib induces more responses, the durability of these responses may not be superior to chemotherapy. However, the wide CIs and the small number of responders in the chemotherapy arm (n=15 versus n=62 for erdafitinib) make interpretation challenging. Further investigation into the nature and quality of responses in both arms may be warranted.

3.2.6 Adverse events

The CS reports that in the THOR trial, most patients experienced AEs that were manageable. The safety analyses presented in the CS are based on 247 patients who received at least one dose of the study drug (135 patients receiving erdafitinib, 112 patients receiving chemotherapy). In the trial, treatment-emergent adverse events (TEAEs) were categorised with the use of the Medical Dictionary for Regulatory Activities Version 24.1; the severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03.

3.2.6.1 Treatment Exposure

The median duration of exposure was longer for erdafitinib than with chemotherapy (4.8 months versus 1.4 months, respectively). In the erdafitinib treatment group, 104 (77.0%) patients were up-titrated from 8 mg to 9 mg daily. Of these, 57 (42.2%) of patients maintained the 9 mg up-titrated dose or the 8 mg starting dose. Sixty-six (48.9%) maintained a dose of 8 mg or more without a dose reduction.

Table 3.14 summarises treatment exposure and duration of treatment for both treatment arms.[13, 15]

Table 3.14: Summary of treatment exposure

	Erdafitinib (n=135)	Chemotherapy (n=112)
Extent of exposure (days)		
Median	146.0	43.0
Range	(5, 1162)	(1, 820)
Number of chemotherapy cycles		
Median	NA	3.0
Range	NA	(1, 35)
Based on CS Table 18[1] CS = company submission		

3.2.6.2 Treatment-emergent adverse events

Almost all patients experienced TEAEs in both groups (98.5% erdafitinib, 97.3% chemotherapy). The frequency of Grade 3-4 TEAEs was generally well balanced between treatment groups; 85 patients (63.0%) receiving erdafitinib and 72 patients (64.3%) receiving chemotherapy experienced at least one Grade 3-4 TEAE. The most frequently reported Grade 3-4 TEAEs (>8%) in the erdafitinib arm were palmar-plantar erythrodysesthesia syndrome (9.6%) and stomatitis (8.1%). In the chemotherapy arm, these were neutropenia (14.3%), leukopenia (8.9%), and anaemia (8.0%).

A summary of TEAEs in the THOR trial is presented in Table 3.15.

Table 3.15: Summary of AEs in THOR; Cohort 1 safety analysis set

Event, n (%)	Erdafitinib (n=135)	Chemotherapy (n=112)
AEs	133 (98.5)	109 (97.3)
TRAEs[a]	131 (97.0)	97 (86.6)
AEs leading to death[b]	6 (4.4)	7 (6.3)
TRAEs[a] leading to death	1 (0.7)	6 (5.4)
SAEs	56 (41.5)	47 (42.0)
Treatment-related SAEs	18 (13.3)	27 (24.1)
AEs leading to discontinuation of study agent	19 (14.1)	20 (17.9)
TRAEs[a] leading to discontinuation of study agent	11 (8.1)	15 (13.4)
AEs leading to dose reduction of study agent	93 (68.9)	27 (24.1)
TRAEs[a] leading to dose reduction of study agent	89 (65.9)	24 (21.4)

Event, n (%)	Erdafitinib (n=135)	Chemotherapy (n=112)
AEs leading to dose interruption of study agent	97 (71.9)	35 (31.3)
TRAEs[a] leading to dose interruption of study agent	89 (65.9)	22 (19.6)
Grade 3-4 AEs	85 (63.0)	72 (64.3)
Grade 3-4 TRAEs[a]	62 (45.9)	52 (46.4)
Grade 3-4 SAEs	52 (38.5)	41 (36.6)
Grade 3-4 treatment-related SAEs[a]	16 (11.9)	23 (20.5)
COVID-19 TRAEs	12 (8.9)	5 (4.5)
COVID-19 treatment-related SAEs	1 (0.7)	0 (0.0)

Based on CS Table 19.[1]
[a] An AE is categorised as related if assessed by the investigator as 'possibly', 'probably', or 'very likely' related to study agent. [b] AEs leading to death are based on whether the AE outcome was fatal.
AE = adverse event; COVID-19 = coronavirus disease 2019; CS = company submission; FGFR = fibroblast growth factor receptor; SAE = serious adverse event; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; TRAE = treatment-related adverse event

Table 3.16: Any Grade TEAEs occurring in ≥10% of patients in either treatment arm, and corresponding Grade ≥3 TEAEs occurring in ≥2% of patients

	Erdafitinib (n=135)		Chemotherapy (n=112)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
No. of patients, n (%)				
Diarrhoea	84 (62.2)	4 (3.0)	19 (17.0)	3 (2.7)
Stomatitis	65 (48.1)	11 (8.1)	14 (12.5)	2 (1.8)
Constipation	36 (26.7)	-	31 (27.7)	-
Dry mouth	53 (39.3)	-	4 (3.6)	-
Nausea	20 (14.8)	-	27 (24.1)	-
Vomiting	13 (9.6)	2 (1.5)	16 (14.3)	3 (2.7)
Hyperphosphataemia	108 (80.0)	7 (5.2)		
Decreased appetite	36 (26.7)	4 (3.0)	23 (20.5)	3 (2.7)
Hyponatraemia	16 (11.9)	10 (7.4)	4 (3.6)	2 (1.8)
Asthenia	20 (14.8)	2 (1.5)	28 (25.0)	4 (3.6)
Fatigue	20 (14.8)	0	21 (18.8)	4 (3.6)
Pyrexia	20 (14.8)	-	14 (12.5)	-
Oedema peripheral	8 (5.9)	-	13 (11.6)	-
Alopecia	34 (25.2)	-	27 (24.1)	-
Palmar-plantar erythrodysesthesia syndrome	41 (30.4)	13 (9.6)	1 (0.9)	0
Dry skin	31 (23.0)	-	5 (4.5)	-
Onycholysis	31 (23.0)	8 (5.9)	1 (0.9)	0
Onychomadesis	28 (20.7)	-	2 (1.8)	-
Nail discolouration	24 (17.8)	-	2 (1.8)	-

	Erdafitinib (n=135)		Chemotherapy (n=112)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
No. of patients, n (%)				
Nail disorder/dystrophy	19 (14.1)	3 (2.2)	2 (1.8)	0
Urinary tract infection	15 (11.1)	6 (4.4)	8 (7.1)	3 (2.7)
Paronychia	16 (11.9)	-	0	-
Anaemia	35 (25.9)	10 (7.4)	36 (32.1)	9 (8.0)
Neutropenia	0	0	22 (19.6)	16 (14.3)
Leukopenia	1 (0.7)	0	15 (13.4)	10 (8.9)
Dysgeusia	37 (27.4)	-	8 (7.1)	-
Alanine aminotransferase increased	37 (27.4)	4 (3.0)	4 (3.6)	1 (0.9)
Weight decreased	30 (22.2)	3 (2.2)	3 (2.7)	0
Aspartate aminotransferase increased	29 (21.5)	3 (2.2)	3 (2.7)	0
Blood creatinine increased	19 (14.1)	-	7 (6.3)	-
Blood alkaline phosphatase increased	14 (10.4)	3 (2.2)	4 (3.6)	1 (0.9)
Arthralgia	14 (10.4)	-	9 (8.0)	-
Dry eye	23 (17.0)	-	2 (1.8)	-
Epistaxis	17 (12.6)	-	3 (2.7)	-
Haematuria	16 (11.9)	3 (2.2)	10 (8.9)	2 (1.8)

Based on CS Table 20.[1]
CS = company submission; TEAE = treatment-emergent adverse event

EAG comment: The CS provides a comprehensive overview of AEs from the THOR trial. The use of standardised categorisation and grading systems strengthens the reliability of the safety data. However, the open-label design of the trial may introduce potential bias in AE reporting, particularly for subjective events.

The longer exposure time to erdafitinib compared to chemotherapy complicates direct comparisons of AE rates. The high rate of dose up-titration and maintenance suggests that the treatment was generally tolerable, but also highlights the importance of dose optimization in managing the safety profile.

The similar rates of Grade 3-4 TEAEs between arms is reassuring. However, the nature of these events differs significantly, with skin toxicities and mucosal events predominating with erdafitinib, contrasting with haematological toxicities seen with chemotherapy. This distinct safety profile may require different management strategies and patient education approaches.

3.2.6.3 Treatment-related adverse events

The most frequently reported TRAEs in the erdafitinib group were hyperphosphatemia (78.5%), diarrhoea (54.8%), stomatitis (45.9%) and dry mouth (38.5%), whereas in the chemotherapy group, anaemia (27.7%), alopecia (21.4%) and nausea (19.6%) were the most frequently reported TRAEs.

Table 3.17 presents the most frequently reported TRAEs for any Grace (≥10%) for both erdafitinib and chemotherapy treatment groups. The most frequently reported TRAEs in the erdafitinib group were hyperphosphatemia (78.5%), diarrhoea (54.8%), stomatitis (45.9%) and dry mouth (38.5%), whereas in

the chemotherapy group, anaemia (27.7%), alopecia (21.4%) and nausea (19.6%) were the most frequently reported TRAEs.[13, 15]

Table 3.17: Any Grace TRAEs occurring in ≥10% of patients in either treatment arm

	Erdafitinib (n=135)	Chemotherapy (n=112)
No. of patients, n (%)		
Diarrhoea	74 (54.8)	12 (10.7)
Stomatitis	62 (45.9)	13 (11.6)
Dry mouth	52 (38.5)	3 (2.7)
Nausea	14 (10.4)	22 (19.6)
Constipation	12 (8.9)	21 (18.8)
Vomiting	9 (6.7)	15 (13.4)
Hyperphosphataemia	106 (78.5%)	-
Decreased appetite	28 (20.7)	20 (17.9)
Alopecia	32 (23.7)	24 (21.4)
Palmar-plantar erythrodysesthesia syndrome	41 (30.4)	1 (0.9)
Dry skin	30 (22.2)	4 (3.6)
Onycholysis	31 (23.0)	1 (0.9)
Onychomadesis	27 (20.0)	2 (1.8)
Nail discolouration	24 (17.8)	2 (1.8)
Nail disorder	18 (13.3)	2 (1.8)
Fatigue	18 (13.3)	17 (15.2)
Asthenia	11 (8.1)	21 (18.8)
Anaemia	16 (11.9)	31 (27.7)
Neutropenia	0	21 (18.8)
Leukopenia	0	13 (11.6)
Dysgeusia	34 (25.2)	7 (6.3)
Dry eye	22 (16.3)	2 (1.8)
Alanine aminotransferase increased	29 (21.5)	3 (2.7)
Aspartate aminotransferase increased	25 (18.5)	1 (0.9)
Weight decreased	14 (10.4)	3 (2.7)
Paronychia	16 (11.9)	0 (0.0)

Based on CS Table 21.[1]
CS = company submission; TRAE = treatment-related adverse event

EAG comment: The most frequent TRAEs with erdafitinib reflect its mechanism of action as an FGFR inhibitor. The high incidence of hyperphosphatemia (78.5%) is particularly notable and requires careful monitoring and management in clinical practice. The CS could benefit from more detailed information on the clinical consequences of Hyperphosphataemia and strategies for its long-term management.

3.2.6.4 Serious adverse events

Serious adverse events (SAEs) were experienced by 56 (41.5%) patients in the erdafitinib group and 47 (42.0%) patients in the chemotherapy group. Of these, 18 (13.3%) patients in the erdafitinib group and

27 (24.1%) patients in the chemotherapy group had SAEs considered by the investigator to be related to the study drug. The most frequently reported SAEs (>3%) in the erdafitinib group were urinary tract infection (4.4%) and haematuria (3.7%). In the chemotherapy group, they were febrile neutropenia (6.3%) and febrile bone marrow aplasia (3.6%).

Table 3.18 presents the most frequently reported SAEs for both treatment arms.[13, 15]

Table 3.18: SAEs occurring in ≥2% of patients in either treatment arm

Event, n (%)	Erdafitinib (n=135)	Chemotherapy (n=112)
Patients with ≥1 SAE	56 (41.5)	47 (42.0)
Urinary tract infection	6 (4.4%)	2 (1.8%)
Febrile neutropenia	0	7 (6.3%)
Febrile bone marrow aplasia	0	4 (3.6%)
Neutropenia	0	3 (2.7%)
Pyrexia	2 (1.5%)	3 (2.7%)
Haematuria	5 (3.7%)	1 (0.9%)
Acute kidney injury	3 (2.2%)	0
Hyponatraemia	3 (2.2%)	1 (0.9%)

Based on CS Table 22.[1]
Patients are counted only once for any given event, regardless of the number of times they actually experienced the event. AEs are coded using the Medical Dictionary for Regulatory Activities Version 24.1.
AE - adverse event; CS = company submission; SAE = serious adverse event

EAG comment: The similar overall incidence of SAEs between arms is reassuring. However, the lower rate of treatment-related SAEs with erdafitinib is a positive finding that supports its overall tolerability. The differing nature of SAEs between arms however will have implications for patient monitoring and supportive care needs.

3.2.6.5 Adverse event of special interest

Central serous retinopathy, an adverse event of special interest (AESI) and a known class effect of FGFR inhibitors, occurred in 23 patients (17%) receiving erdafitinib. These events were manageable with dose modifications. In patients with any Grade central serous retinopathy, 70% of the events were resolved by the clinical cut-off date; of the ongoing events, 71% were Grade 1. No patients experienced blindness due to central serous retinopathy.

Hyperphosphataemia, a common drug-induced toxicity for FGFR-targeted agents, was experienced by 108 (80.0%) patients in the erdafitinib group. Most events were Grade 1 or 2 (74.8%), with 5.9% experiencing a Grade 3 or 4 event. No patients had serious TEAEs of hyperphosphatemia or discontinued erdafitinib due to hyperphosphatemia. Full details on AEs of interest and central serous retinopathy events are available in Appendix F[7].

EAG comment: The reporting of FGFR inhibitor class-specific AEs is valuable. The incidence of central serous retinopathy (17%) is concerning, though it appears to be manageable with dose modifications. Long-term follow-up data on ocular events would be beneficial to assess any potential chronic effects. The company's framing of hyperphosphatemia as a pharmacodynamic marker rather than solely an AE is interesting but requires further validation. More information on the relationship between hyperphosphatemia and efficacy outcomes would be valuable.

3.2.6.6 Adverse events leading to treatment discontinuation

A lower number of patients had TRAEs leading to treatment discontinuation in the erdafitinib group (n=11; 8.1%) compared with the chemotherapy group (n=15; 13.4%). Full details on AEs leading to treatment discontinuation is available in Appendix F[7].

EAG comment: The lower rate of TRAEs leading to discontinuation with erdafitinib is encouraging and may contribute to its efficacy advantage by allowing for longer treatment duration. However, the high rates of dose reductions (65.9%) and interruptions (65.9%) due to TRAEs with erdafitinib raise questions about the optimal dosing strategy and potential impacts on drug exposure and efficacy.

3.2.6.7 Deaths

As of the clinical cut-off for the analysis, 77 patients (56.6%) in the erdafitinib treatment group and 78 patients (60.0%) in the chemotherapy treatment group had died during the study. The primary reason for death in both treatment groups was progression of disease (46.3% and 48.5% respectively). In the erdafitinib group, eight (5.9%) patients died due to an AE; the event was considered to be related to erdafitinib for one (0.7%) patient. In the chemotherapy group, 10 (7.7%) patients died due to an AE; the event was considered to be related to the study drug in six of those patients (4.6%).

The similar overall mortality rates between arms suggest that erdafitinib does not increase mortality risk compared to chemotherapy. The lower rate of treatment-related deaths with erdafitinib is noteworthy and supports its safety profile. However, more details on the nature of treatment-related deaths would be valuable for a full assessment of their clinical implications.

3.2.6.8 BLC2001

A summary of safety data from BLC2001 is provided in Appendix N of the CS.[7] These data were consistent with those observed during the THOR trial, and the known safety profile of erdafitinib.[15]

3.2.6.9 Hyperphosphatemia as a pharmacodynamic marker

Hyperphosphatemia is a common on-target effect of FGFR inhibitors and serves as a pharmacodynamic marker of erdafitinib activity. In the THOR trial, 80.0% of patients in the erdafitinib group experienced hyperphosphatemia, with a median time to onset of 15.0 days. Most events (74.8%) were Grade 1-2 in severity. Hyperphosphatemia was managed through dose modifications and phosphate binders, with 20.0% of patients receiving sevelamer. No patients discontinued erdafitinib due to hyperphosphatemia. The occurrence of hyperphosphatemia indicates target engagement and may be associated with clinical benefit, though this relationship requires further study.

EAG comment: Regarding safety, erdafitinib's profile appears distinct from chemotherapy but is generally manageable. Strengths of the safety data include comprehensive reporting of AEs, the use of standardised grading systems, and the inclusion of class-specific AEs of interest. The lower rates of treatment-related SAEs, deaths, and discontinuations associated with erdafitinib are also encouraging.

Several limitations and areas of uncertainty remain regarding the use of erdafitinib. Firstly, the longer exposure time to erdafitinib compared to traditional chemotherapy complicates direct comparisons of AE rates. Moreover, the high incidence of specific AEs associated with erdafitinib, such as hyperphosphatemia and skin toxicities, necessitates careful monitoring and management in clinical practice. The long-term safety data, especially concerning ocular events and other cumulative toxicities, are also limited. The open-label design of the THOR trial may introduce bias in the reporting of AEs, particularly those that are subjective. Furthermore, there is a need for more detailed information on the

management of AEs, including supportive care measures and how dose modifications might impact efficacy, to aid in clinical decision-making. The relationship between AEs and HRQoL is another area that remains underexplored, which is a significant omission given the advanced stage of cancer being treated. To complement the clinical trial data and inform its optimal use within the NHS, further RWE on the safety profile of erdafitinib in routine clinical practice would be beneficial. Additionally, longer-term follow-up data are needed to assess potential chronic or late-onset AEs, particularly in light of erdafitinib's novel mechanism of action.

The safety profile of erdafitinib differed from chemotherapy but was generally manageable with dose modifications. Key erdafitinib-related AEs included hyperphosphatemia (80.0%), diarrhoea (54.8%), and stomatitis (45.9%). Despite these events, HRQoL was maintained on treatment, suggesting that the side effects were tolerable for most patients. The incidence of Grade 3-4 TRAEs was similar between erdafitinib (45.9%) and chemotherapy (46.4%). Importantly, fewer patients discontinued treatment due to AEs with erdafitinib (14.1%) compared to chemotherapy (17.9%), which may have contributed to the maintained HRQoL, and improved efficacy outcomes observed with erdafitinib.

3.2.7 Health-related quality of life

The THOR trial assessed HRQoL using the FACT-Bl, European Quality of Life-5 Dimension, 5 Level (EQ-5D-5L), and Patient Global Impression of Severity scale (PGI-S) instruments. There was high compliance (>80%) for PRO assessments at baseline and through most treatment cycles up to Cycle 10 for both treatment groups. Mixed models for repeated measures (MMRM) analyses showed that HRQoL was maintained on treatment across all five primary domains (physical, social, emotional, functional well-being, and total scores). For the physical well-being domain, the mean change from baseline to Cycle 11 was -0.2 (95% CI: -1.1, 0.7) for erdafitinib and -0.5 (95% CI: -1.6, 0.6) for chemotherapy, indicating no clinically meaningful difference between groups. The MMRM analyses of the EQ-5D-5L health utility index showed that general HRQoL was maintained on treatment. The mean change from baseline to Cycle 11 in the health utility index was 0.01 (95% CI: -0.03, 0.05) for erdafitinib and -0.02 (95% CI: -0.07, 0.03) for chemotherapy. For the visual analogue scale (VAS), mean changes were 1.2 (95% CI: -2.5, 4.9) for erdafitinib and -1.8 (95% CI: -6.2, 2.6) for chemotherapy.

The proportion of patients reporting improvement or no change from baseline in PGI-S score at Cycle 11 was 68% for erdafitinib and 62% for chemotherapy.

There was no statistically significant difference in time to first clinically meaningful urinary symptom deterioration between erdafitinib and chemotherapy (HR: 1.47; 95% CI: 0.98, 2.21; p = 0.064). The median time to deterioration was 1.5 months (95% CI: 0.82, 2.83) for erdafitinib versus 2.8 months (95% CI: 1.51, 5.32) for chemotherapy. This endpoint was impacted by heavy and imbalanced censoring in the chemotherapy group.

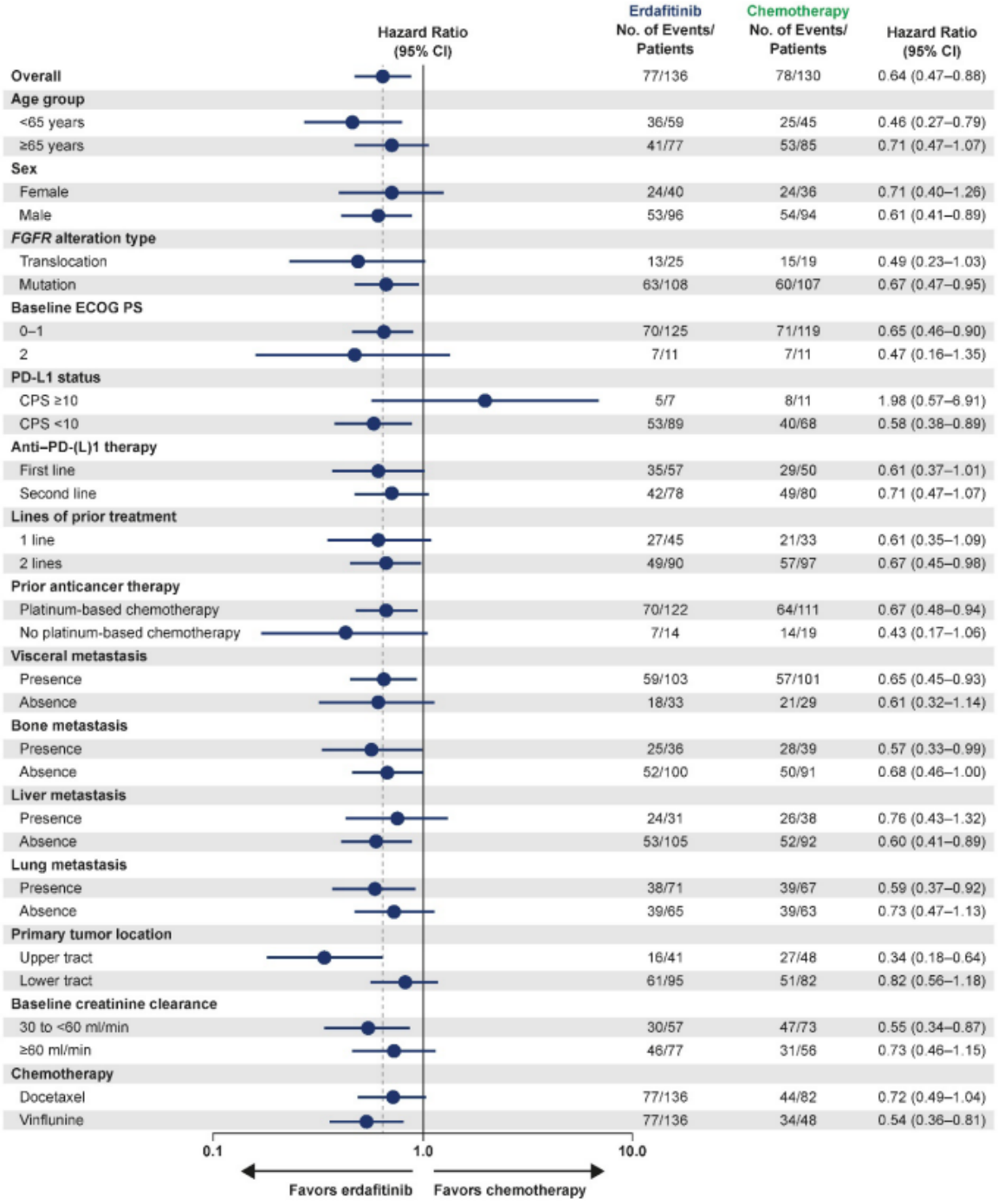
EAG comment: The maintenance of HRQoL in the erdafitinib arm is encouraging, particularly given the observed benefits in survival and response rates. However, the lack of improvement in HRQoL despite these efficacy outcomes is noteworthy and merits further investigation. The open-label design of the study may have influenced PROs, potentially introducing bias. Additionally, the heavy censoring in the chemotherapy arm concerning the urinary symptom deterioration endpoint complicates interpretation. To enhance the robustness of the findings, the company should provide more detailed results for all HRQoL measures, including mean changes from baseline and proportions of patients experiencing clinically meaningful changes.

3.2.8 Subgroup analysis

Subgroup analyses for OS were generally consistent with the primary analysis, showing benefits for erdafitinib across various prespecified subgroups including:

- Prior lines of therapy
- Prior anti-PD-(L)1 therapy
- Prior platinum-based chemotherapy
- Primary tumour location
- FGFR alteration type
- Type of chemotherapy (docetaxel or vinflunine)

Figure 3.5: Forest plot of OS HR by subgroup factors



Based on CS Figure 10.[1]

CI = confidence interval; CPS = combined positive score; CS = company submission; ECOG PS = Eastern Cooperative Oncology Group Performance Status; FGFR = fibroblast growth factor receptor; OS = overall survival; PD-(L)1 = programmed death-(ligand)1

EAG comment: The CS asserts that the results from subgroup analyses are consistent with the main analyses for erdafitinib compared with chemotherapy, regardless of various factors such as the number of prior lines of therapy, prior anti-PD-(L)1 therapy, prior treatment with platinum-based chemotherapy, FGFR alteration type, and type of chemotherapy (docetaxel or vinflunine). This claim implies no evidence of effect modification, suggesting a uniform treatment effect for erdafitinib. However, the

EAG contends that this interpretation oversimplifies the data and potentially overlooks significant effect modification, particularly in underpowered subgroups.

The EAG highlights several trends in the forest plot provided in the CS that suggest possible effect modification. Although these trends are not statistically significant, they indicate differences in treatment outcomes across key subgroups that the company has not fully acknowledged. For instance, the HR for patients under 65 years of age (HR: 0.46, 95% CI: 0.27–0.79) indicates a stronger benefit from erdafitinib compared to chemotherapy, while the HR for patients aged 65 or older (HR: 0.71, 95% CI: 0.47–1.07) suggests a potentially smaller benefit. Also, the HR for patients with prior platinum-based chemotherapy is 0.67 (95% CI: 0.48–0.94), while for those without prior platinum-based chemotherapy, the HR is 0.43 (95% CI: 0.17–1.06). Although both subgroups suggest a benefit for erdafitinib, the wider CI for the non-platinum group introduces significant uncertainty. The company's focus on statistical significance might downplay clinically meaningful trends. Even non-significant results in underpowered subgroups could indicate important treatment effects, and such trends should be carefully considered in clinical decision-making. Despite overlapping CIs, the substantial difference in HR values points to a trend that warrants further exploration. Additionally, the forest plot reveals variations in response based on factors like baseline PS (ECOG 0-1 versus ECOG 2) and FGFR alteration type (translocation versus mutation), further suggesting potential effect modification. The EAG is concerned about the underpowered nature of the subgroup analyses, as acknowledged by the company. The small sample sizes in these subgroups increase the risk of Type II errors, where real differences in treatment effects may not be detected due to insufficient statistical power.

The company's assertion that results from subgroup analyses are consistent with the main analyses fails to acknowledge these trends, which could have significant implications for clinical practice, where factors like age, prior therapy, and PS are often considered. Of course, the treatment effect of interest in this appraisal is not that in the trial given that the comparators of interest are not the same as those THOR. However, evidence of treatment effect modification between erdafitinib and any chemotherapy might still be indicative of treatment effect modification with the comparators of interest. These potential subgroup effects are therefore informative for the key issue relating to the ITC (see Sections 3.3 and 3.4).

3.3 Critique of trials identified and included in the ITC and/or multiple treatment comparison

The CS acknowledged the absence of direct head-to-head trial data comparing erdafitinib with paclitaxel ± carboplatin, prompting the use of various ITCs and matching-adjusted indirect comparisons (MAICs). The CS states: *"A total of six studies were identified globally for patients with locally advanced, metastatic, or surgically unresectable (stage IV) UC who have received one prior line of systemic therapy…However, none of these six RCTs, except for THOR, are relevant for inclusion in the indirect treatment comparisons (ITCs) necessary for this appraisal (i.e.* [redacted] *). To resolve this evidence gap, Johnson & Johnson initiated an RW study conducted in England that provides a strong source of data for clinical outcomes for patients treated with SoC in the UK, utilised in an ITC…"*.[1] The company justified using the UK RW mUC study in the base-case ITC, citing its relevance to UK clinical practice given paclitaxel ± carboplatin was identified as the most relevant comparator for UK clinical practice *"To provide a more accurate representation of the current clinical management for patients with advanced UC in England, Johnson & Johnson conducted a UK RW mUC study using datasets available through the NCRAS. This UK RW mUC study provides insight into England-specific data on*

comparators to erdafitinib and patient profiles in the NHS and reflects the RW population likely to receive erdafitinib in clinical practice in England" (Section B.2.9)[1].

The company also included the PLUTO trial for use in a MAIC as an exploratory analysis.[16] The trial EV-301 was also included in a MAIC, but between the chemotherapy arm of THOR and that trial.[17, 18] Given the lack of FGFR mutation status for the RW data, the results of this comparison were used to demonstrate the lack of treatment modification of FGFR3 mutation on chemotherapy (as opposed to erdafitinib) because mutation status was also unknown in the EV-301 trial.[1] See Section 3.4 for further details as to how these studies were used in the various ITCs.

EAG comment: The primary trials and data sources used in the company's analyses with key limitations are summarised in Table 3.19. More details are provided in Section 3.4.

Table 3.19: Overview of trials included in the ITCs

Trial Name	Phase	Purpose	Comparator (s)	Population	Sample size	Key outcomes	Role in analysis	Key limitations
THOR	III	To evaluate erdafitinib's efficacy in FGFR-altered mUC, compared to vinflunine or docetaxel	Vinflunine, docetaxel	FGFR-altered mUC, progressed after 1-2 treatments including PD-(L)1	266	OS, PFS, ORR	Primary evidence source for IPD ITCs and MAICs; compared with RW data and other trials	Limited UK population (only 12 patients), differences in trial population versus UK RW population
BLC2001	II	To provide supplementary efficacy and safety data for erdafitinib in previously treated FGFR-altered mUC patients	Single-arm	FGFR-altered mUC, previously treated	99	ORR, safety	Pooled with THOR data for more robust IPD ITCs and MAICs	Single-arm trial, potential heterogeneity when pooled with THOR data
UK RW mUC Study	N/A	To provide RWE on outcomes of mUC patients treated with paclitaxel ± carboplatin in the UK	Paclitaxel ± carboplatin	Patients diagnosed with mUC in England between 2016-2021	10,787	OS, TTD, PFS (derived)	Primary comparator in IPD ITCs against erdafitinib	Significant missing data (ECOG), lack of direct PFS data, small sample sizes for some subgroups
PLUTO	III	To compare paclitaxel monotherapy to pazopanib	Paclitaxel monotherapy	Patients with mUC who had received prior platinum-based chemotherapy	140 (70 in paclitaxel arm)	OS, PFS	Used in exploratory MAICs to compare	Population had only received prior platinum-based treatment, no prior exposure to PD-(L)1 inhibitors; not

Trial Name	Phase	Purpose	Comparator (s)	Population	Sample size	Key outcomes	Role in analysis	Key limitations
		in mUC patients					erdafitinib with paclitaxel	generalisable to erdafitinib target population
EV-301	III	To compare chemotherapy regimens (vinflunine, docetaxel, paclitaxel) in mUC patients previously treated with platinum-based chemotherapy and PD-(L)1 inhibitors	Vinflunine, docetaxel, paclitaxel (chemotherapy of choice)	Adults with locally advanced or mUC previously treated with platinum-based chemotherapy and PD-(L)1 inhibitors	608 (301 in enfortumab vedotin arm, 307 in chemotherapy arm)	OS, PFS, ORR	Included in MAICs to assess comparative efficacy of chemotherapy regimens	Different patient population compared to THOR, limited to ECOG PS 0-1, no information on FGFR mutation status (although this was used to test the effect of FGFR3 mutation status on the effectiveness of chemotherapy in the THOR trial)

Based on THOR[13, 15]; BLC2001[19, 20]; UK RW mUC study[6]; PLUTO[16]; EV-301 details[21] presented within the CS[1]
CS = company submission; ECOG PS: Eastern Cooperative Oncology Group Performance Status; FGFR = fibroblast growth factor receptor; IPD = individual patient data; ITC = indirect treatment comparison; MAIC = matching-adjusted indirect comparison; mUC = metastatic urothelial carcinoma; N/A = not applicable; OS = overall survival; ORR = objective response rate; PD-(L)1 = programmed death-(ligand)1; PFS = progression-free survival; RW = real-world; RWE = real-world evidence; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; TRAE = treatment-related adverse event; TTD = time to treatment discontinuation; UK = United Kingdom

3.4 Critique of the ITC and/or multiple treatment comparison

The company conducted several ITC analyses, which are summarised with EAG comments in the following sections:

- 3.4.1 – base-case individual patient data (IPD) ITC
- 3.4.2 – exploratory MAIC as alternative to the base-case IPD ITC
- 3.4.3 – MAIC between chemotherapy arms in THOR and the EV-301 trial to test for the treatment effect modification of FGFR alteration status

3.4.1 Base-case analysis –IPD ITC

In the absence of direct head-to-head clinical trial data comparing erdafitinib to paclitaxel ± carboplatin, an IPD ITC of OS and time to next treatment (TTNT) (in the absence of PFS) was conducted between the THOR trial and a UK RW mUC study. This approach was in line with NICE Decision Support Unit (DSU) Technical Support Documents (TSD) 17 and 18.[22, 23] The company identified four relevant trials (including THOR and BLC2001) through a SLR. However, none of the trials, except THOR, were deemed directly applicable to the population of interest - patients with FGFR alterations who progressed on or after PD-1/PD-(L)1 therapy. Thus, the UK RW mUC study became the primary data source for the comparator arm in the ITC, particularly for paclitaxel ± carboplatin. The company applied three methods to adjust for differences in baseline characteristics between the two datasets:

- Regression adjustment: This method used a Cox proportional hazard regression model to account for baseline differences, estimating treatment effects by adjusting for patient-level covariates.
- Inverse probability weighting (IPW): Using propensity scores, this method reweighted patient cohorts to balance baseline characteristics between the treatment groups. The UK RW mUC paclitaxel cohort served as the control group, with weights applied based on treatment assignment probability. The analysis estimated the average treatment effect for the control (ATC).
- Doubly robust estimator: This method combined the regression model for outcomes with the exposure model, providing additional protection against model misspecification

Sensitivity analyses were conducted to explore different weighting formulas (average treatment effect for the treated [ATT], ATC, and average treatment effect [ATE]).

The following seven patient characteristics were available for the analysis from the UK RW mUC study[1]:

- Number of prior lines of therapy: categorised as 1 line or 2 lines.
- ECOG PS: 0 or 1-2
- Tumour location: upper or lower
- Age group at diagnosis: <65 or ≥65 years of age
- Sex
- Tumour stage at diagnosis: 1-2 or 3-4
- Cisplatin ineligibility

The THOR trial (erdafitinib arm) and the UK RW mUC study (paclitaxel ± carboplatin arm) showed notable differences in baseline characteristics. The THOR cohort had a higher proportion of patients with two prior lines of therapy (66.7% in THOR versus 50% in the UK RW study) and better PS (45.2% of THOR patients had ECOG PS 0 compared to 29.2% in the UK RW study).

Other characteristics, such as age, sex, tumour location, stage at diagnosis, and cisplatin eligibility, were considered comparable between the two cohorts. However, significant missing data were noted, particularly for ECOG PS in the UK RW cohort (missing for 56.9% of patients). To account for this, the analysis assumed all missing ECOG PS scores were in the worst category (1-2), introducing a suggested conservative bias that may overestimate the severity of the paclitaxel cohort. This conservative assumption was explored in sensitivity analyses by restricting the analysis to patients with complete ECOG PS data, though it reduced the sample size.

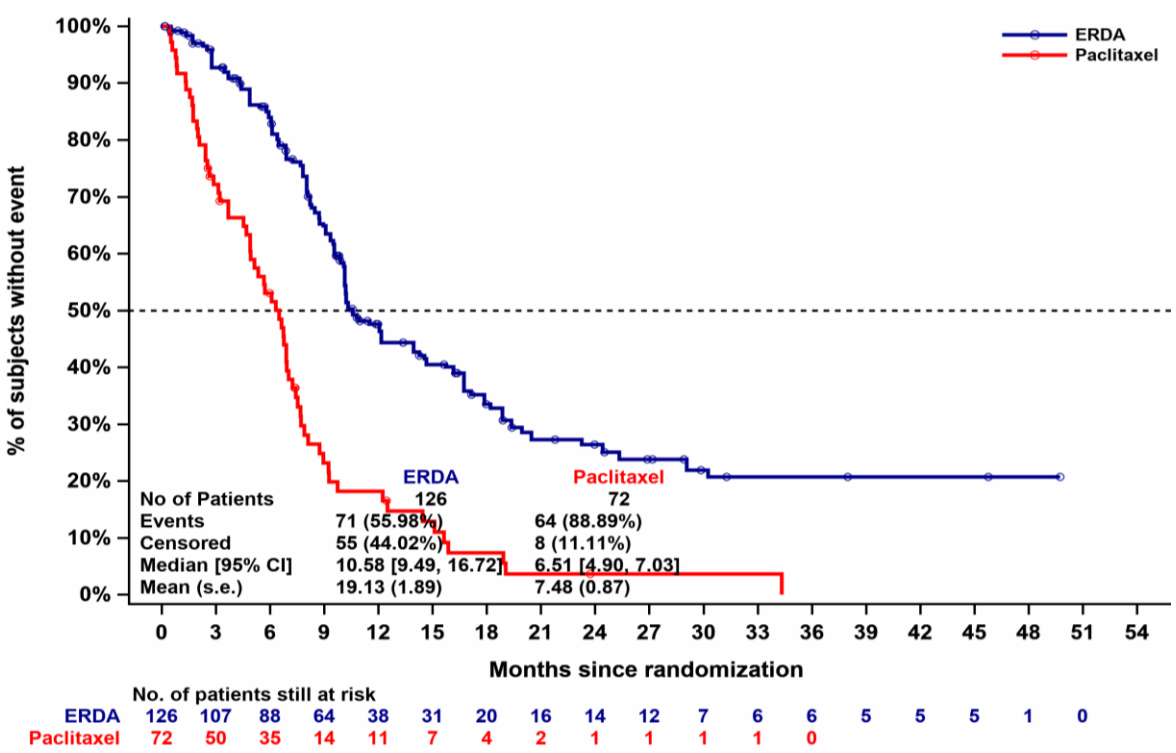
The results are shown in Table 3.20. Note that all TTNT values have been 'greyed out' to recognise that there was a correction to the TTNT analysis (original CS defined TTNT as OS) in the response to clarification, but only the base-case values.[3]

Table 3.20: Results of ITC between THOR and UK RW mUC study

Comparison	OS HR (95% CI)	p-value	TTNT HR (95% CI)	p-value
Unadjusted comparison	0.33 (0.24 to 0.47)	<0.0001	0.32 (0.23 to 0.45)	<0.0001
Adjusted comparisons				
Covariate adjustment	0.37 (0.26 to 0.54)	<0.0001	0.34 (0.23 to 0.48)	<0.0001
Weighting				
ATT	0.32 (0.21 to 0.48)	<0.0001	0.31 (0.20 to 0.48)	<0.0001
ATC (base-case)	0.35 (0.23 to 0.52)	<0.0001	0.33 (0.22 to 0.48) 0.53 (0.37 to 0.76)*	<0.0001 <0.0005*
ATO	0.36 (0.24 to 0.52)	<0.0001	0.35 (0.24 to 0.52)	<0.0001
ATE	0.33 (0.22 to 0.48)	<0.0001	0.34 (0.23 to 0.48)	<0.0001

Based on Table 17, CS[1] except *Table 58, response to clarification.[3]
Note: All TTNT values have been 'greyed out' to recognise that there was a correction to the TTNT analysis (original CS defined TTNT as OS) in the response to clarification, but only the base-case values.[3]
ATE = average treatment effect; ATC = average treatment effect for the control; ATO = average treatment effect for overlap; ATT = average treatment effect for the treated; CI = confidence interval; CS = company submission; HR = hazard ratio; ITC = indirect treatment comparison; mUC = metastatic urothelial carcinoma; OS = overall survival; RW = real-world; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; TTNT = time to next treatment; UK = United Kingdom

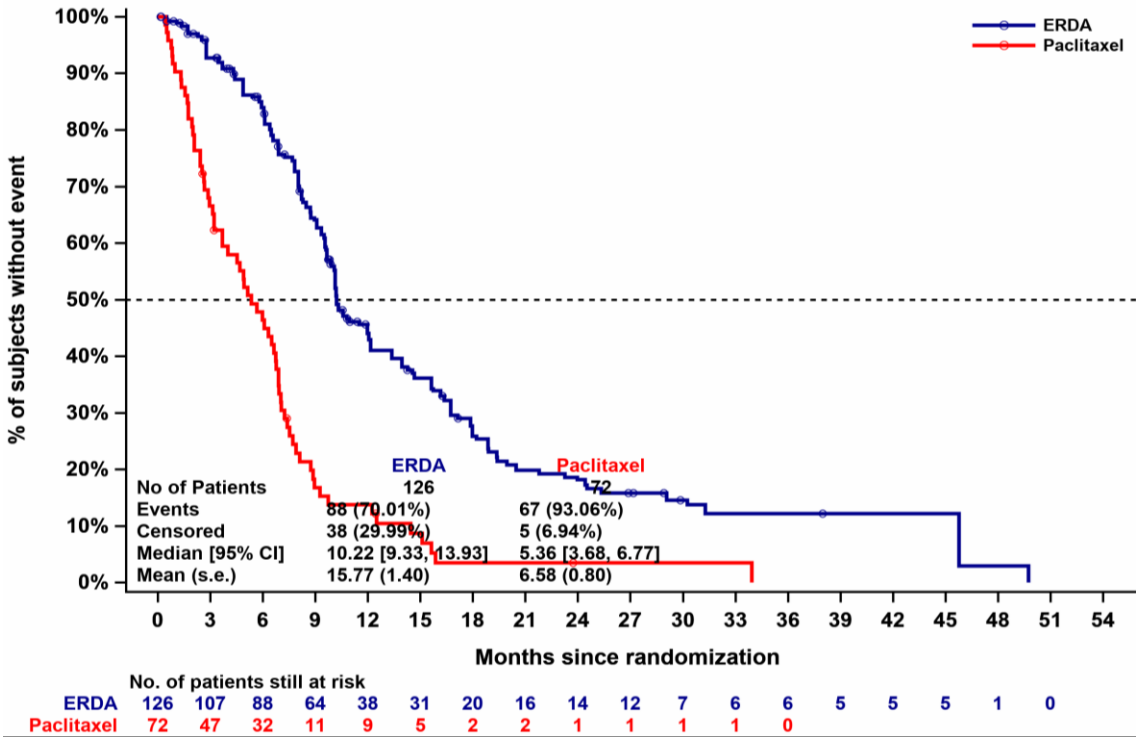
Figure 3.6: Kaplan-Meier curve for ATC-adjusted OS comparison for erdafitinib versus paclitaxel



Based on CS Figure 11[1]

ATC = average treatment effect for the control; CS = company submission; OS = overall survival

Figure 3.7: Kaplan-Meier curve for ATC-adjusted TTNT comparison for erdafitinib versus paclitaxel



Based on CS Figure 12[1]

ATC = average treatment effect for the control; CS = company submission; TTNT = time to next treatment

3.4.1.1 Missing data from UK RW study

The UK RW study, which forms a key part of the company's evidence base, as well as lacking information on FGFR alteration status, had significant missing data for ECOG PS (57% missing).[6] This limitation could compromise the utility of the study for robust comparisons. The company addressed this in their response, stating that *"ECOG PS scores are not routinely submitted by NHS Trusts to the cancer registry, therefore a number of patients in the UK RW mUC study have missing values"* (Appendix P).[7]

To handle the missing data, the company adopted a worst-case scenario approach, where patients with missing ECOG PS or tumour stage were assigned the less favourable patient outcome characteristics available. The rationale behind this approach, as explained by the company, includes the following points:

- **Initial exploratory analyses** did not show major differences in outcomes between the missing category and the other categories.
- **Data was assumed to be missing at random**, and no significant association with treatment outcomes was identified.
- **Alternative imputation methods**, such as multiple imputation, were not considered feasible due to the limited number of variables available and the high percentage of missing data.

To assess the robustness of this approach, the company conducted sensitivity analyses with different scenarios for handling missing data, as shown in Table 3.21.

Table 3.21: Results of ITC between THOR and UK RW mUC study under different missing data scenarios

Scenario	Erdafitinib	Paclitaxel ± carboplatin	HR (OS)	Median OS (months)	Median TTNT (months)	HR (TTNT)
Base-case (worst case)	126	72	0.35 (0.23-0.52)	10.6 (9.5, 16.7)	8.0 (6.5, 9.0)	0.53 (0.37, 0.76)
Missing excluded	92	31	0.22 (0.12-0.39)	13.9 (8.9, 19.4)	10.9 (8.3, 15.7)	0.34 (0.21, 0.58)
Best-case	126	72	0.35 (0.23-0.52)	15.7 (10.2, 19.4)	10.2 (7.7, 14.7)	0.38 (0.25, 0.59)

Based on response to the request for clarification, Table 10[3]
FGFR = fibroblast growth factor receptor; HR = hazard ratio; ITC = indirect treatment comparison; mUC = metastatic urothelial carcinoma; OS = overall survival; RW = real-world; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; TTNT = time to next treatment; UK = United Kingdom

EAG comment: The IPD ITC allowed the company to compare erdafitinib with paclitaxel ± carboplatin, despite the absence of direct comparative data. The estimates of the relative effectiveness were consistent across all adjusted analyses against erdafitinib, irrespective of the adjustment method used (covariate adjustment or inverse probability of treatment weighting) and irrespective of the weighing approach applied if using inverse probability of treatment weighting. Moreover, the HRs remained consistent when either ATT weights or ATC weights were applied. This suggests that there is no significant interaction between the treatment effect and the characteristics of the population under

investigation. The observed consistency demonstrates limited uncertainty associated with the choice of methods.

Specifically, missing ECOG PS data in the UK RW study and the assumption that patients with missing values were in the worst category may skew the results. The worst-case scenario was intended to be conservative, as it up-weighted the less favourable patients in the erdafitinib group, potentially leading to more conservative estimates of the treatment-outcome association. However, the company acknowledges that this approach might introduce bias, as not all missing patients necessarily belong to the less-favourable group. The sensitivity analyses showed comparable results across different scenarios, which the company argues supports the robustness of their conclusions. During clarification, the EAG requested that the company perform data imputation using a multiple imputation method and provide an updated economic model and scenario analysis using this method. The company, however, noted that "*other imputation approaches, like multiple imputation, were not considered due to the limited number of variables available in the UK RW mUC study relative to the percentage of missing data"* and *"it could be that the pattern of missingness might be dependent on specific patients' characteristics in the RWE cohort which are not captured/available in the dataset. Unfortunately, this is an inherited characteristic of RWE data, and it cannot be tackled in this analysis. However, the exploratory analyses with all important characteristics included in the dataset did not indicate any dependency with the missing values."* (Response to the request for clarification, Section B1(d)).[3] This statement raises a critical concern, if the data is insufficient for multiple imputation, it may also be insufficient to confidently adjust for differences between the populations, potentially undermining the reliability of the ITC findings. Furthermore, the company's assertion that exploratory analyses did not indicate any dependency with the missing values suggests that the pattern of missingness might not be as complex as initially presumed. This finding could imply that multiple imputation might still have been a feasible option. The decision not to pursue multiple imputation, despite the lack of detected dependency, seems contradictory and warrants further explanation. This therefore forms part of the key issue regarding the ITC.

The company also acknowledged that TTNT was probably not a good proxy for PFS: *"TTNT curves for both erdafitinib and paclitaxel ± carboplatin were close to the OS curves. This led to the conclusion that TTNT alone may not serve as a suitable proxy for PFS in this context."* (p. 110)[1] It might be useful to compare TTNT outcomes with those for PFS in the THOR trial, notwithstanding the difference in comparator. However, the unadjusted HRs are so different to those from the trial for OS i.e. 0.33 (0.24 to 0.47) versus 0.64 (0.47 to 0.88) that this is likely to be not very informative. However, the company admitted that TTNT had been incorrectly defined in the CS as OS, which leads the EAG to wonder whether indeed TTNT actually is such a poor proxy.[3] Therefore, this remains part of the key issue regarding the ITC.

3.4.2 Matching-adjusted indirect comparisons AIC analyses (erdafitinib versus paclitaxel)

As an exploratory analysis, the company conducted a MAIC to compare erdafitinib to paclitaxel using the PLUTO trial.[1] They acknowledged the limitations of this analysis: *"Importantly, the PLUTO trial population had only been exposed to platinum-based chemotherapy, without any prior exposure to PD-(L)1 inhibitors. The outcomes experienced by these patients are not likely to be generalisable to the population relevant in this appraisal, and they would not be eligible to receive erdafitinib. Nonetheless, we included this broader evidence base to understand the range of uncertainty associated with choice of comparative data."* (p. 73) The results included a base-case (matching of the important characteristics: ECOG score, liver metastases, primary site bladder, and time since last platinum therapy) OS HR of 0.59 (95% CI: 0.42 to 0.85). This was in contrast to the unadjusted (observed) HR

of 0.46 (0.34, 0.64). There was no significant difference for PFS: base-case (matching of the important characteristics: ECOG score, liver metastases, primary site bladder, and time since last platinum therapy) HR of 0.81 (95% CI: 0.59, 1.11). This was in contrast to the unadjusted HR of 0.66 (0.50, 0.89).

However, the company also stated that these results: *"…represent the upper bounds of relative efficacy between erdafitinib and paclitaxel. These patients had been recently diagnosed with mUC (median time from diagnoses of 15 months) and had only received prior platinum-based treatment, making their treatment less intensive compared to patients in the erdafitinib arm in THOR. As a result, patients receiving paclitaxel monotherapy in the PLUTO trial were expected to have better outcomes than patients who would be treated with erdafitinib in a clinical setting."* (p. 73)

EAG comment: The EAG acknowledges that, all things being equal, the IPD ITC should be more accurate than the MAIC. However, as described above, there were significant limitations to the IPD ITC, including missing data and the use of TTNT as a proxy for PFS. In addition, there is also lack of reporting of FDFR alterations status in the RW mUC study, which also applies to the PLUTO trial, the importance of which is explored in Section 3.4.3. Nevertheless, there is evidence to suggest that the matching was successful (see Table 40 of Appendix Q).[9] It is also a concern that the direction of change of HR not the same for OS as for PFS, which does call into question the company's assertion of these results being an "upper bound". The MAIC results therefore inform the key issue regarding the ITC.

3.4.3 Matching-adjusted indirect comparisons analyses exploring the efficacy of chemotherapies in the THOR and EV-301 trials

The company also conducted a MAIC to address the uncertainty due to the lack of FGFR mutation status data in the UK RW mUC study.[1] This analysis compared the efficacy of chemotherapy regimens in the THOR trial (vinflunine or docetaxel) with those in the EV-301 trial (vinflunine, docetaxel, or paclitaxel). The purpose was to explore whether chemotherapy had different outcomes in patients with FGFR alterations (in THOR) compared to an all-comers mUC population (in EV-301), where prior exposure to anti-PD-(L)1 inhibitors was common.

EV-301 is a phase3, RCT with the efficacy of chemotherapies (vinflunine, docetaxel and paclitaxel) in an allcomers mUC patient population with prior exposure to anti-PD-(L)1 inhibitors. To explore whether chemotherapy works differently in patients with FGFR - alterations and those without, we use the comparator arms in THOR (vinflunine and docetaxel) and EV-301 (vinflunine, docetaxel and paclitaxel) to assess their comparative efficacy.[13, 15, 21] There were 25% of the patients who received vinflunine and 75% received a taxane (docetaxel or paclitaxel) in EV-301. In THOR, 38% received vinflunine and 62% received docetaxel.

Baseline differences between the trials are presented in Table 3.22.

Table 3.22: Key differences between THOR and EV-301 trials

	THOR (FGFR-altered la/mUC)	EV-301 (la/mUC)
Patient population	Adults with metastatic or surgically unresectable UC with at least one FGFR alteration.	Adults with locally advanced or mUC, regardless of genetic alteration status.
Prior treatment	Up to two prior systemic therapies allowed, including one prior line of anti-PD-(L)1.	Up to three prior lines of systemic therapy allowed, including at least one anti-PD-(L)1 agent and no more than one prior chemotherapy regimen in

	THOR (FGFR-altered la/mUC)	EV-301 (la/mUC)
		advanced disease. Platinum-based and an anti-PD-(L)1 therapy required.
ECOG PS	Scores of 0 to 2 accepted	Scores of 0 to 1 accepted.

Based on CS Appendices, Table 34[7]
CS = company submission; FGFR = fibroblast growth factor receptor; PD-(L)1 = programmed cell death protein (ligand)1; mUC = metastatic urothelial carcinoma; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; UC = urothelial carcinoma

3.4.4 Methodology and statistical adjustments

- **Data matching**: Patients from THOR who did not meet the inclusion criteria of EV-301 (e.g., ECOG 2, no prior platinum-based chemotherapy) were excluded. After applying these criteria, the baseline characteristics of the remaining THOR patients were weighted to match the EV-301 population.
- **Reduction in sample size**: After applying exclusion criteria, the effective sample size (ESS) of the THOR chemotherapy arm decreased by 58%, from 130 to 55 patients, which limited the power of the analysis but was considered acceptable for efficacy comparisons.
- **Endpoints considered**: The analysis focused on three efficacy endpoints - **OS**, **PFS**, and **ORR**.

Both trials are considered sufficiently comparable in design and outcome measures. However, baseline patient characteristics differ, such as ECOG score and prior therapies. To account for these differences, the company employed the MAIC method, a population-adjusted ITC approach. MAIC cannot fully adjust for all differences between patient populations, particularly when comparing FGFR mutation status between trials.

OS: The MAIC results showed no significant difference between the chemotherapy arms of THOR and EV-301. The HR of 1.05 (95% CI: 0.69–1.60) indicated that chemotherapy in THOR (vinflunine or docetaxel) was 5% more likely to result in death compared to chemotherapy in EV-301 (vinflunine, docetaxel, or paclitaxel). The KM curves suggested a slight potential benefit for chemotherapy in EV-301 during the early follow-up period, but the curves converged after 9 months.

PFS: Similar to OS, PFS showed no significant differences between the two trials after adjustments. The HR for chemotherapy from THOR compared to EV-301 was 1.13 (95% CI: 0.68–1.88), indicating a small reduction in PFS benefit, but the wide CI encompassed the possibility of equivalent efficacy.

ORR: Chemotherapy in EV-301 demonstrated a slight numerical advantage over chemotherapy in THOR, with an odds ratio (OR) of 0.64 (95% CI: 0.30–1.40), but this difference was not statistically significant. Sensitivity analyses consistently produced results close to 1, indicating that the covariate adjustments had minimal impact on the outcomes.

EAG comment: The CS presented evidence from the THOR and BLC2001 trials, which specifically targeted patients with FGFR3-altered mUC.[13, 15, 19, 20] In contrast, the UK RW study and PLUTO were not limited to FGFR alterations.[1] This discrepancy in patient populations introduces an underlying difference that may bias the indirect comparisons made between these datasets. The company acknowledged this issue, stating that *"details on FGFR alterations were not available as the registry cohort includes an untested population"* (CS, Section B.2.9)[1]. The lack of FGFR mutation data in the UK RW study is a significant limitation, as it prevents a tailored assessment of erdafitinib's efficacy within the targeted FGFR3-altered subgroup. Erdafitinib's efficacy is strongly linked to the presence of FGFR alterations, but the question is what might be the effect of FGFR3 alterations on the effectiveness

of the comparators. The company did address this by performing a MAIC for three outcomes, OS, PFS and ORR, between the chemotherapy arms of THOR and the EV-301 trial where FDFR status was also unknown. The MAIC analysis concluded that, despite key differences in trial design, the efficacy of chemotherapies (vinflunine and docetaxel) in THOR was similar to those in EV-301 (vinflunine, docetaxel, or paclitaxel) across all endpoints (OS, PFS, and ORR). This suggests that chemotherapy performs similarly in patients with or without FGFR alterations. However, the substantial reduction in sample size, reliance on retrospective data, and limitations in the matching process highlight the need for caution when interpreting these findings, noting that:

- Little difference does not imply no difference, and adjustment might mean insufficient power to detect differences.
- Lack of information on FGFR status does not imply lack of FGFR alterations.
- Little difference between the chemotherapy regimen mixes in THOR and EV-301 does not imply generalisability to only paclitaxel ± platinum or indeed any of the comparators from the scope or UK clinical practice not included in the ITC such as docetaxel or gemcitabine. It is possible that FGFR3 alterations might be treatment effect modifying for only some forms of chemotherapy. It also does not imply generalisability to atezolizumab.

Therefore, this remains part of the key issue regarding the ITC.

3.5 Additional work on clinical effectiveness undertaken by the EAG

Not applicable.

3.6 Conclusions of the clinical effectiveness section

The CS[1, 7] and response to the request for clarification[3, 9] provided sufficient details for the EAG to appraise the literature searches conducted to identify relevant clinical evidence for existing and approved treatments for patients with locally advanced, metastatic, or surgically unresectable urothelial cancer (UC; Stage IV disease) who have received at least one prior line of chemotherapy. Searches were conducted in March 2023 and updated in May 2024. The revised searches provided at clarification were clear and reproducible, and comprehensive strategies were used. Bibliographic databases, conference proceedings and trials registers were searched. Whilst the EAG feels that a separate search for AEs data may have been beneficial, overall, the EAG has no major concerns about the literature searches conducted.

The evidence submitted is largely consistent with the decision problem outlined in the final scope, particularly in terms of the population and intervention. However, some discrepancies arise in the comparators and the extent to which the submission fully captures the NICE final scope's requirements. The NICE final scope for this assessment broadly defines the population *as "People with metastatic or unresectable fibroblast growth factor receptor (FGFR)-altered urothelial cancer"* which includes a wide range of patients with various FGFR alterations. In contrast, the CS focuses specifically *on "Adult patients with unresectable or metastatic urothelial carcinoma (UC), harboring susceptible* [redacted] *in the unresectable or metastatic treatment setting"*. This narrower population aligns with the marketing authorisation for erdafitinib and the primary evidence from Cohort 1 of the THOR trial, but limits generalisability to broader FGFR-altered populations. The company highlights that NICE's appraisal should adhere to the marketing authorisation and clarifies that the population definition is consistent with regulatory approvals. Thus,

this may not be regarded as a key issue if NICE is limited to recommending the treatment for this licensed population.

The CS focuses on paclitaxel ± carboplatin as the primary comparator, justified by RW data suggesting this is the most relevant treatment in UK clinical practice (Section 2.3). However, the exclusion of other comparators specified in the NICE final scope, such as docetaxel, atezolizumab, and BSC, limits the comprehensiveness of the assessment. The RW data used for the ITC also shows that there are treatments that could be considered as UK clinical practice, which have not been included such as gemcitabine. This could affect the understanding of erdafitinib's relative effectiveness and cost effectiveness. Moreover, the [redacted] (Section 3.2).

The CS incorporates RWE from the UK RW mUC study, which strengthens the relevance of the findings for NHS decision-makers. However, the RWE introduces significant uncertainties due to the absence of FGFR status data, missing data on patient characteristics such as ECOG PS and the use of TTNT as a proxy for PFS. These gaps increase the risk of residual confounding, despite the company's use of advanced statistical techniques such as covariate adjustment, IPW, and doubly robust estimators to adjust for differences between the trial and RW populations. While the ITC results consistently favour erdafitinib over paclitaxel ± carboplatin in OS and TTNT, uncertainty about the robustness of these findings remains.

Concerns also remain regarding the long-term effectiveness of erdafitinib, as the short median follow-up in the THOR trial (15.9 months) limits confidence in the durability of the treatment. This introduces uncertainty in extrapolating long-term survival outcomes, particularly since KM curves rather than parametric survival models were used for survival analysis, which may lead to biased projections. These factors raise doubts about the reliability of the long-term cost effectiveness estimates and highlight the need for further data and more sophisticated modelling approaches. The company should also rigorously evaluate the censoring patterns and reasons for censoring in both trial arms to determine if censoring rates differ, and whether informative censoring could bias the results.

The inclusion of HRQoL outcomes in the CS is also limited. The available EQ-5D-5L data and the analysis does not sufficiently explore the relationship between AEs and quality of life (QoL). The absence of in-depth analysis on the DOR and its correlation with long-term benefits weakens the robustness of the HRQoL findings. Additionally, while erdafitinib shows a superior ORR compared to chemotherapy (45.6% versus 11.5%), the CS does not fully explore the DOR or its implications for patient outcomes.

In conclusion, the submission offers a comprehensive and well-supported analysis of erdafitinib's clinical effectiveness but must be interpreted with caution due to key uncertainties - particularly around comparator selection, data limitations, long-term efficacy, and the generalisability of findings to the UK NHS population. These uncertainties limit the ability to derive a fully unbiased estimate of erdafitinib's treatment effect in relation to the relevant populations, interventions, comparators, and outcomes. Further RW data, longer-term follow-up, and more robust handling of missing data in future analyses would be necessary to supplement the CS.

4. Cost effectiveness

4.1 EAG comment on company's review of cost effectiveness evidence

This Section pertains mainly to the review of CEA studies. However, the search Section (4.1.1) also contains summaries and critiques of other searches related to cost effectiveness presented in the CS. Therefore, the following Section includes searches for the CEA review, measurement and evaluation of health effects as well as for cost and healthcare resource identification, measurement and valuation.

4.1.1 Searches performed for CE Section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness, HRQoL and resource use identification presented in the CS.[1, 7] The CADTH evidence-based checklist for the PRESS, was used to inform this critique.[8] The EAG has presented only the major limitations of each search strategy in the report.

Appendix E of the revised CS appendices provided at clarification, provides details of searches conducted to identify relevant studies on cost effectiveness and cost/health care resource use in adult patients with locally advanced (T3b and T4a), metastatic, or surgically unresectable urothelial cancer (Stage IV disease) who have received at least one prior line of chemotherapy.[9] The searches were conducted in January 2018 and subsequently updated in November 2021, March 2023 and April 2024.

A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources searched for economic evaluations

Resource	Host/source	Date ranges (combined for all searches)	Date searched
Electronic databases			
Embase	Ovid	2000-Current	Original: 18.1.18 Update: 10.11.21 Update: 18.5.23
MEDLINE	Ovid	2000-Current	Original: 18.1.18 Update: 10.11.21 Update: 18.5.23
Embase & MEDLINE	Embase.com		Update 19.4.24
MEDLINE in Process	Pubmed.com	2000-Current	Original: 18.1.18 Update: 10.11.21 Update: 18.5.23
EconLit	Not stated	All	Original: 18.1.18 Update: 10.11.21 Update: 18.5.23 Update: 31.4.24
CENTRAL (Cochrane Library)	Not reported	2000-Current	Original: 18.1.18 Update: 10.11.21 Update: 18.5.23 Update 10.4.24

Resource	Host/source	Date ranges (combined for all searches)	Date searched
CDSR (Cochrane Library)	Not reported	2000-Current	Original: 18.1.18 Update: 10.11.21 Update: 18.5.23 Update 10.4.24
Additional resources			
CEA Registry (Tufts)	Internet		Original: 3.11.21 Update: 24.5.23 Update 8.5.24
ClinicalTrials.gov			
EU Trials			
HTA websites			
• CADTH • NICE • PBAC • SMC • INAHTA • HAS • IQWiG	Internet		Original: 3.11.21 Update: 24.5.23 Update 8.5.24
Conferences			
• ASCO • ESMO • ECO • ISPOR	Internet		Original: 4.11.21 Update: 24.5.23 Update 8.5.24

As reported in the CS[1, 9]
ASCO = American Society of Clinical Oncology; CADTH = Canadian Agency for Drugs and Technology in Health; CDSR = Cochrane Database of Systematic Reviews; CEA Registry = Cost-Effectiveness Analysis Registry; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; ECO = European Cancer Organization; ESMO = European Society of Medical Oncology; EU-CTR = European Union-Clinical Trials Register; HAS = Haute Autorité de santé; HTA = Health Technology Assessment; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; INAHTA = International Network of Agencies for Health Technology Assessment; IQWiG = Institut für Qualität und Wirtschaftlichkeit Im Gesundheitswesen; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium

EAG comment:

- A single set of searches was used to identify relevant studies on cost effectiveness and cost/HCRU in in adult patients with locally advanced (T3b and T4a), metastatic, or surgically unresectable urothelial cancer (Stage IV disease) who have received at least one prior line of chemotherapy. Searches were run in January 2018 and subsequently updated in November 2021, March 2023 and April 2024. The initial reporting of search methods in the CS and accompanying documents was unclear and contained conflicting, missing and inconsistent information (including missing strategies for grey literature and missing update searches). Whilst an amended appendix was provided, some confusion remained which may affect the reproducibility of searches, however the searches that were provided appear appropriate.[9]

- In addition to bibliographic database searches, a good range of HTA organisation websites, grey literature resources and conferences proceedings were searched. Reference checking was conducted.
- Database searches were limited to studies published since 2000. Searches were not limited by language of publication.
- The full list of grey literature resources searched for the 2024 update was confirmed at clarification, although the EAG noted some reporting errors in Table 30, E1.3. of the revised appendices regarding the inclusion of ECCO (which the EAG believe should read ECO), and also an abbreviation for IMWG (International Myeloma Working Group), which the EAG believes may have been included in error. Whilst individual search strategies per resource were not included, details of keyword combinations for each year were provided.[3, 9]
- In the response to clarification the company stated "*Due to a lack of subscription/access to the CEA registry during 2024 SLR update, the Tufts Medical Center Cost-Effectiveness Analysis registry database was not searched. Instead, HTAD and NHS EED databases were searched, which did not yield any records of interest between May 2023 and April 2024 (see Appendix G.1.1).*"[3] However, the EAG was unable to locate these searches in appendix G.1.1.[9] The EAG also note that both HTAD and NHS EED are archival only and have not had any new references added since 2018, therefore a search with the stated date limit would not have been appropriate. However, given the other resources searched this is unlikely to have affected the overall recall of results.

Table 4.2: Data sources searched for HRQoL

Resource	Host/Source	Date Ranges	Date searched
Electronic databases			
Embase & MEDLINE	Embase.com	2023/05-2024/04	10.4.24
EconLit	Not reported	All	31.4.24
CENTRAL (Cochrane Library)	Not reported	2023/05-2024/04	10.4.24
CDSR (Cochrane Library)	Not reported	2023/05-2024/04	10.4.24

As reported in the CS[1, 9]
CDSR = Cochrane Database of Systematic Reviews; CENTRAL = Cochrane Central Register of Controlled Trials; CS = company submission; HRQoL = health-related quality of life

EAG comment:

- A single set of searches was reported for HRQoL data conducted in April 2024 and covering the period from May 2023 to April 2024, see Table 4.2. The EAG queried if these were the only searches conducted for HRQoL[7]. Whilst the company responded that they had now "*now added search strategies and results for each iteration of the HRQoL SLRs in Appendix E*",[3] the only strategies specifically for HRQoL in the revised appendices were for the same 2023-2024 search. The PRISMA flowchart (Figure 7: Appendix F) reported an additional 94 included records located through previous versions of the review, but it is unclear which searches these refer to. Appendix F also contains a second flow chart for utility studies up to 2023, but no strategies are provided, therefore EAG is unable to comment on their appropriateness.[9] As the reporting of the searches for this Section remains confused and incomplete, it is unclear to the EAG whether the searches would have retrieved all appropriate data.
- The company confirmed that the grey literature sources described in Appendix G were also used to inform the HRQoL section, which may have mitigated against some loss of recall.

4.1.2 Inclusion/exclusion criteria

The in- and exclusion criteria used by the company are presented in Appendices G, H and I of the CS, Tables 8, 11 and 13.[7]

EAG comment: The EAG agrees that the eligibility criteria are suitable to fulfil the company's objective to identify cost effectiveness studies and evidence on HRQoL and costs related to the disease.

4.1.3 Conclusions of the cost effectiveness review

The CS provides an overview of the included cost effectiveness, utility and resource use and costs studies, but no specific conclusion was formulated.

EAG comment: A single set of searches was run in January 2018 to identify relevant studies on cost effectiveness and cost/health care resource and subsequently updated in November 2021, March 2023 and April 2024. The initial reporting of search methods in the CS and accompanying documents was unclear and contained conflicting, missing and inconsistent information. Whilst an amended appendix was provided, some confusion remained which may affect the reproducibility of the searches, however, those searches that were provided appear appropriate. A second set of searches to identify HRQoL data conducted in 2024 was reported in the CS, and while the strategies appeared appropriate, they only covered a limited time period from May 2023 to April 2024. The PRISMA flowcharts provided at clarification suggest that other searches were performed, but no additional strategies were provided. The EAG therefore remains unsure about how these were sourced and cannot provide a full critique of the appropriateness of the searches for this element of the submission.

4.2 Summary and critique of company's submitted economic evaluation by the EAG

4.2.1 NICE reference case checklist

Table 4.3: NICE reference case checklist

Element of HTA	Reference case	EAG comment on CS
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	In line with reference case.
Perspective on costs	NHS and PSS.	In line with reference case.
Type of economic evaluation	Cost utility analysis with fully incremental analysis.	In line with reference case.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	In line with reference case.
Synthesis of evidence on health effects	Based on systematic review.	In line with reference case.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQoL in adults.	In line with reference case.
Source of data for measurement of HRQoL	Reported directly by patients and/or carers.	In line with reference case.

Element of HTA	Reference case	EAG comment on CS
Source of preference data for valuation of changes in HRQoL	Representative sample of the UK population.	In line with reference case.
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	In line with reference case.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	In line with reference case.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	In line with reference case.

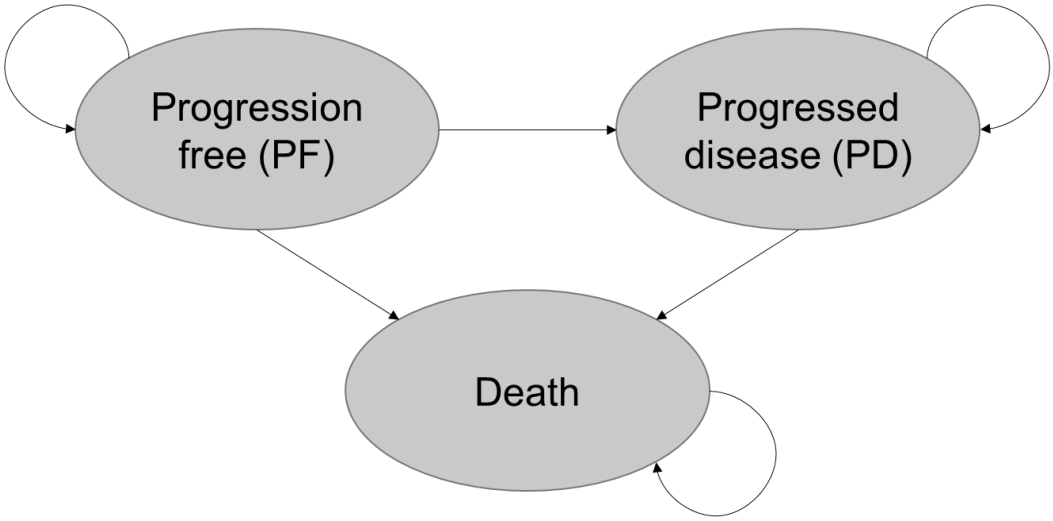
CS = company submission; EAG = Evidence Assessment Group; EQ-5D = EuroQol-5D; HRQoL = health-related quality of life; HTA = Health Technology Assessment; NHS = National Health Service; PSS = Personal Social Services; QALY = quality-adjusted life year; UK = United Kingdom

4.2.2 Model structure

The company developed a de novo partitioned survival model (PSM) in Microsoft® Excel, including three health states: PF, PD, and death (Figure 4.1).[1] The PSM approach was selected by the company as, amongst other considerations, it allowed the direct use of clinical trial evidence from the THOR trial[24] (e.g., OS and PFS) and had been used in previous NICE TAs in mUC.[1] Patients entered the model in the PF state, in which they could stay or move to the PD or death state. Patients in the PD state could stay there or move to the death state. Death was considered an absorbing state. Treatment-dependent costs and health outcomes associated with each arm were captured for each mutually exclusive health state.

Mortality risk in each cycle was bound by age-matched general population predictions.[25] A limit was applied to the per-cycle hazard of progression and the hazard of death to ensure that PFS could not exceed OS.

Figure 4.1: Model structure



Based on Figure 13 of the CS[1]
CS = company submission; PD = progressed disease; PF = progression free

EAG comment: The main concerns of the EAG relate to: a) lack of a state transition model to verify the plausibility of the PSM extrapolations and b) use of 2017-2019 mortality risk data despite more recent mortality risk data being available.

a) The NICE DSU TSD19 recommends state transition modelling to be performed alongside PSM to assist in verifying the plausibility of the extrapolations and to explore key clinical uncertainties in the extrapolation period.[26] However, in response to clarification question B5, the company argued that the partitioned survival analysis approach is likely the simplest and most suitable modelling structure to capture the relevant disease outcomes, given the collected data and the approach used in similar TA (e.g., TA525, TA530, TA692, TA739, and TA788).[27] Although the EAG acknowledges that conducting a state transition model approach would require significant resource and time, this would be especially informative in the current submission given the uncertainty in the extrapolated curves due to the long tails of observed data including low patient numbers at risk as discussed in Section 4.2.6.
b) In the CS[1], mortality risk at each cycle was bound by age-matched general population predictions. The company stated that the mortality risk estimates were sourced from the *"latest available Office for National Statistics"*. However, the data used in the economic model represented mortality risks from 2017 to 2019, despite more recent data being available (2020-2022).[25] The EAG expects this to have a minor impact on the cost effectiveness results.

4.2.3 Population

The population included in the company's model was [redacted]. This population was narrower than the population defined in the NICE scope (i.e., people with metastatic or unresectable FGFR-altered UC) (CS, Table 1).[1] The company narrowed the population to align with the final marketing authorisation of erdafitinib. Marketing authorisation had not yet been obtained at the date of the CS (expected in [redacted]).

The modelled population for erdafitinib was based on cohort 1 from the THOR trial[24], an ongoing global, phase III, randomised, open-label, multicentre, confirmatory registrational trial evaluating erdafitinib in patients with advanced UC and susceptible FGFR alterations who had progressed on or after one or two prior treatments[24]. To ensure consistency between intervention and comparator, the modelled population characteristics were based on the THOR cohort 1 population but adjusted through ATC to align with the RW patient population in the UK. The company followed a worst-case approach to deal with missing data for the population adjustment between THOR[24] and the UK RW mUC dataset[6]. The THOR ATC-adjusted baseline patient characteristics that were used to inform the economic model are listed in Table 4.4 below. The company also provided the patient characteristics of the ATD adjusted population excluding the missing data, the unadjusted THOR ITT population, and the UK subjects of the THOR trial (Table 4.4).

Table 4.4: Key THOR ATC-adjusted patient characteristics used in the economic model

	Economic model base-case (ATC-adjusted) (n=126)		ATC adjusted excluding missing data (n=92)		Unadjusted THOR ITT (n=266)		THOR UK subjects (n=12)	
	Mean	**Standard deviation**	**Mean**	**Standard deviation**	**Mean**	**Standard deviation**	**Mean**	**Standard deviation**
Age at model start	66.5	10.4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average patient weight (kg)	75.0	20.6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average BSA (m²)	1.9	0.3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Average creatinine clearance (mL/min)	64.0	24.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportion male	73.7%	N/A	[redacted]	N/A	[redacted]	N/A	[redacted]	N/A
Source	THOR trial, erdafitinib arm (ATC-adjusted)[7] UK RW mUC study[6]		THOR trial, erdafitinib arm (ATC-adjusted)[7]		THOR trial[24]		THOR trial[24]	

Based on CS Table 28[1], clarification response Table 9[3], company model sheet Controls!H36:K44

ATC = average treatment effect of the control; BSA = body surface area; CS =company submission; ITT = intention-to-treat; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; UK = United Kingdom

EAG comment: The main concerns of the EAG relate to: a) the worst-case scenario approach used for dealing with missing data in the population adjustment, and b) the modelled patient characteristics not being representative of the UK.

a) The modelled population for the CEA was based on the THOR population, but was adjusted towards the comparator (ATC) to ensure comparability with the UK RW mUC study.[6] However, disease stage data was missing in 27% of patients in the THOR trial, and ECOG PS data was missing in 57% of patients in the UK RW. To deal with the missing data for the ATC-adjustment, the company followed a worst-case approach assuming the worst value possible: diagnosis stage 3-4 and ECOG PS 1-2, respectively.[7] The company stated that the worst-case approach was a conservative approach, as it would upweight the less favourable patients in erdafitinib. Moreover, this was expected to improve the alignment with UK clinical practice, as it would ensure patient baseline characteristics from the UK RW mUC study[6] and would allow retaining all the data available from both studies, increasing sample size and robustness.[3] The company did also provide two additional scenarios (Table 4.4), one in which patients with missing PS or stage were omitted and one using the unadjusted THOR ITT population. However, the EAG noted that the company's worst-case approach resulted in shorter erdafitinib PFS, i.e. patients moving faster from the PF to the PD health state in the economic model. As a result, erdafitinib treatment costs were lower, leading to a substantially lower ICER ([redacted]/quality-adjusted life year (QALY) compared to the scenarios excluding missing data ([redacted]/QALY) and using the THOR ITT unadjusted population ([redacted]/QALY). In addition, the EAG would like to highlight that when comparing erdafitinib versus paclitaxel + carboplatin (Table 6.7), the probabilistic scenario analysis in which population with missing ECOG PS and/or stage were omitted resulted in an error in the excel model, and it would be helpful if the company could fix this. The EAG noted that using the worst-case approach, the majority of LYs and QALYs for erdafitinib were gained in the PD health state. As discussed in more detail in Section 5.1, it is unclear to the EAG whether this is plausible. As discussed in Section 3.4.1.1 of this report, the company's worst-case approach may lead to bias and could misrepresent the actual population that will be treated with erdafitinib in UK clinical practice especially as it assumes that missing criteria of the data were not missing at random. It is unclear to the EAG why the missing data was deemed not missing at random and the company should provide further evidence for this. Despite being asked in clarification response B1[3], the company did not provide updated analyses using any form of data imputation (e.g., multiple imputation), arguing that the multiple imputation would not lead to robust estimates, as it might have missed some important variables. However, as discussed in Section 3.4.1.1, *'if the data is insufficient for multiple imputation, it may also be insufficient to confidently adjust for differences between the populations, potentially undermining the reliability of the ITC findings'* and, given that the pattern of missingness might not be as complex as presumed, multiple imputation could still have been a feasible option. Due to the before-mentioned arguments, this is a key issue and the EAG would like to see a scenario analysis where the company handles the missing data using an alternative data imputation method (e.g., multiple imputation). In addition, a best-case scenario analysis could be informative to quantify the impact of assumptions regarding handling missing patients in the population adjustment on the cost-effectiveness results.

b) The company's modelled patient characteristics were obtained through an ATC of the THOR cohort 1 population that had been adjusted to reflect the population on the UK RW mUC study, as the THOR trial had limited UK participants (n=[redacted]). Nonetheless, some of the modelled patient characteristics did not align with the expected patient characteristics in UK clinical practice. Some of the clinical experts consulted by the company argued, despite the ages being comparable, most

patients would be [redacted] (i.e., [redacted] years) than the starting age selected by the company (i.e., 66 years):

[redacted]

[14]. Although the EAG agrees with the company that the mean age of the THOR trial and UK RW mUC study were similar (66.5 and 68.8, respectively), it is unclear why these deviate substantially from clinical expert inputs. Nonetheless, the EAG expects that using the clinical experts preferred age (i.e., [redacted] years) will have a limited impact on the ICER.

4.2.4 Intervention and comparators

The intervention considered in the CS was erdafitinib, administered at a dose of 8 mg, once daily for 21 days, according to the anticipated MHRA. Consistent with the draft Summary of Product Characteristics (SmPC) and the THOR trial, erdafitinib treatment was continued until disease progression, withdrawal or unacceptable toxicity.

The main comparator considered in the CS was paclitaxel ± carboplatin, implemented as a basket of paclitaxel monotherapy and paclitaxel in combination with carboplatin, weighted 3:1, respectively. The company stated that this basket of comparators was based on consensus from a UK advisory board,[14,28] which was confirmed by results from the company's UK RW mUC study.[6] Paclitaxel monotherapy was administered at a dose of 80 mg/m^2 as a 1-hour IV infusion in 250 ml sodium chloride on days 1, 8 and 15 every 28 days until progression, withdrawal, or intolerable toxicity. For paclitaxel in combination with carboplatin, the dose of paclitaxel was 175 mg/m² over a period of 3 hours, alongside carboplatin, which was dosed to a targeted area under the curve (AUC) of 6 mg/ml as a 30-minute IV infusion over 30 minutes every 3 weeks in 500 ml glucose 5%. In the CS economic model, the comparators of the THOR[24] and PLUTO trials[16] were included and used in scenario analyses to explore the efficacy profile of the treatment used in those trials. In the CS economic model docetaxel and vinflunine prescribed doses were derived from the THOR trial. For docetaxel, the modelled dose was 75 mg/m^2 as a 1-hour IV infusion every 3 weeks until progression. For vinflunine, the modelled dose was 320 mg/m^2 as a 20-minute IV infusion once every 3 weeks. Both drugs were administered until disease progression, withdrawal, or intolerable toxicity. In addition, a scenario analysis was performed in the CS model, using the paclitaxel monotherapy arm in the PLUTO trial as a comparator with a dose of 80 mg/m² once every week.

The NICE scope for comparators included established clinical management without erdafitinib, including but not limited to chemotherapy (including docetaxel, paclitaxel), atezolizumab, and BSC. The company justified the omission of comparators mentioned in the NICE scope by stating that 1) docetaxel use was restricted to clinical trials and was not current standard of care (SoC) in England and Wales; 2) evidence on the efficacy of atezolizumab being used for re-treating with a PD-(L)1 inhibitor was lacking; and 3) there was no evidence available of BSC in patients after exposure to PD-(L)1 inhibitors.[1]

EAG comment: The main concerns of the EAG relate to a) the modelling of paclitaxel ± carboplatin as a treatment basket, b) lack of stopping rule for paclitaxel and carboplatin, c) omitting comparators that were included in the NICE scope, and d) lack of modelling up titration to a 9 mg dose for erdafitinib.

a) The main comparator considered in the CS was paclitaxel ± carboplatin, implemented as a basket of paclitaxel monotherapy and paclitaxel in combination with carboplatin, weighted 3:1, respectively. The 3:1 ratio was derived from the UK RW mUC study, in which 75% patients

received paclitaxel monotherapy and 25% received paclitaxel + carboplatin. However, according to the clinical expert consulted by the EAG, despite a ratio of 3:1 being reasonable, this ratio would be hugely variable between centres.[29] The inclusion of paclitaxel ± carboplatin as a basket, rather than modelling the two comparators individually, may also bias the overall effectiveness of the comparator, as the OS HR for erdafitinib versus paclitaxel monotherapy (i.e., 0.38) substantially differed from the OS HR of erdafitinib versus paclitaxel + carboplatin (0.22).[3] In fact, when modelling paclitaxel monotherapy and paclitaxel + carboplatin separately, the ICER increases for both comparisons compared to the basket approach (basket approach: £26,487/QALY; paclitaxel monotherapy: £36,034/QALY; paclitaxel +carboplatin: £29,454/QALY). In addition, as discussed in Section 2.3 of this report, it is unclear whether this basket of treatment is consistent with UK clinical practice and the exclusion of relevant comparators may not provide a complete picture of erdafitinib's cost effectiveness across all relevant treatment options. Therefore, the inclusion of the basket of treatment is considered a source of uncertainty by the EAG, potentially underestimating the ICERs. Although the EAG acknowledges the limitation of lower patient numbers when modelling paclitaxel monotherapy and paclitaxel + carboplatin separately, the EAG presents the results of its base-case and scenario analyses for both erdafitinib versus the basket comparator and the individual comparators (i.e. paclitaxel monotherapy and paclitaxel + carboplatin).

b) Paclitaxel monotherapy and paclitaxel + carboplatin are recommended for the treatment of mUC in the UK for a maximum of six treatment cycles, as reported by the EAG's clinical expert, company clarification response B4, and existing guidelines.[30-32] However, this was not implemented in the economic model, as modelled patients were treated until disease progression. In clarification response B9h, the company agreed that a hard stop at 24 weeks could improve alignment with UK clinical practice. Therefore, the EAG, in line with the existing guidelines and other relevant TA's (i.e. TA530 and TA692), applied a stopping rule to paclitaxel monotherapy and paclitaxel ± carboplatin at 24 weeks in its EAG base-case.
c) The company omitted comparators that were listed in the NICE decision scope from their analyses (CS, Table 1).[1] The company's main comparator in the economic model is paclitaxel ± carboplatin, modelled as a basket comparator. However, the NICE scope also mentioned chemotherapy (including docetaxel), atezolizumab, and BSC, which were not included in the economic model. The EAG disagrees on the omission of relevant comparators specified in the NICE final scope, as discussed in Section 2.3, and considers that these should be included in the economic model and all analyses. In addition, the company should provide a fully incremental analysis including all relevant comparators (as was requested in clarification question B28, but not provided by the company).
d) Erdafitinib was modelled at an 8 mg dose once daily for 21 days, based to the anticipated MHRA and the THOR trial. In the THOR trial, however, 77% (n=104) of patients were up titrated to 9 mg of erdafitinib, while 17% of doses were skipped (based on a mean duration of exposure of 206.8 days and a sample size of N=135). The company did correct for skipped doses in its economic model, based on the proportion of doses that were skipped in the THOR safety population (17.07%, based on a mean duration of exposure of 206.8 days and a sample size of N=135).. However, up titration to 9 mg seems not incorporated in the economic model, and the modelled erdafitinib dose (and potentially also treatment costs) is therefore likely to be underestimated.

4.2.5 Perspective, time horizon and discounting

The analysis is performed from the NHS and Personal Social Services (PSS) perspective. Discount rates of 3.5% are applied to both costs and benefits. The model cycle length is one week with a lifetime time horizon (40 years).

EAG comment: The company stated that a half-cycle correction was not applied in the CS economic model, given its short cycle length (7 days), however, it was included in its base-case. The company acknowledged this discrepancy in the clarification letter and the EAG agrees on the half-cycle correction being applied in the economic model despite the relatively short cycle length.

4.2.6 Treatment effectiveness and extrapolation

An overview of the main sources of evidence on treatment effectiveness used for intervention and comparators are presented in Table 4.5. THOR trial data[24] was used for clinical data inputs to model outcomes for the erdafitinib arm and chemotherapy arm of that trial, which has been adjusted to the UK RW mUC study.[6] For paclitaxel ± carboplatin, outcomes were estimated based on the ITC using the UK RW mUC study. Treatment effectiveness of paclitaxel monotherapy from the PLUTO trial[16] was informed by an unanchored MAIC as described in CS Appendix Q.[7]

Table 4.5: Overview of the data sources informing the economic model (company base-case)

Model input	Data source	Company's justification
Baseline characteristics		
Median age (years)	THOR, adjusted to UK RW mUC study population[24]	Appropriately reflects the modelled population for this decision problem; validated by clinical experts.
Proportion male (%)		
Average BSA (m2)		
Average patient weight (kg)		
FGFR3+ prevalence (%)	THOR[24]	
Erdafitinib		
OS	THOR, adjusted to UK RW mUC study population[24]	Most appropriate source of clinical evidence for erdafitinib that is consistent with the comparative analysis for paclitaxel ± carboplatin in the UK
TTNT*		
PFS		
TTD		
Paclitaxel ± carboplatin		
OS	UK RW mUC study	Most appropriate source of clinical data for paclitaxel ± carboplatin, reflective of the UK population (in the absence of direct head-to-head evidence)
TTNT		
PFS	Assumption: ratio of TTNT and PFS for erdafitinib applied to derive the extrapolation for paclitaxel ± carboplatin PFS	
TTD	Assumption: equivalent to PFS	
Chemotherapy (THOR)		
OS	THOR[24]	Not explicitly mentioned

Model input	Data source	Company's justification
TTNT		
PFS		
TTD		
Paclitaxel (PLUTO)		
OS	HR based on unadjusted MAIC among patients treated with erdafitinib (BLC2001 and THOR) versus paclitaxel (PLUTO)	Not explicitly mentioned
TTNT	N/A	
PFS	HR based on unadjusted MAIC among patients treated with erdafitinib (BLC2001 and THOR) versus paclitaxel (PLUTO)	
TTD	Assumption: equivalent to PFS	

Based on CS Table 29[1]
* TTNT is included in the model for the purpose of approximating PFS
BSA = body surface area; CS = company submission; FGFR3 = fibroblast growth receptor 3; HR = hazard ratio, MAIC = matching-adjusted indirect comparison, N/A = not applicable, OS = overall survival, PFS = progression-free survival, THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; TTD = time to treatment discontinuation, TTNT = time to next treatment, UK RW mUC study population = United Kingdom real world metastatic urothelial carcinoma study population

To model OS, TTNT, PFS and TTD for erdafitinib, paclitaxel ± carboplatin, and chemotherapy (THOR) over a lifetime horizon, parametric survival curves were fitted to the observed THOR and UK RW mUC study data based on NICE DSU TSD14.[33] Seven distributions were considered, including the exponential, Weibull, gamma, generalised gamma, Gompertz, log-logistic and log-normal.

Assessment of the best-fitting curves for use in the base-case and scenario analyses was based on the following criteria:

- Statistical goodness-of-fit based on the Akaike information criterion (AIC) and the Bayesian information criteria (BIC) for each arm
- Visual inspection to assess the fit of the extrapolation to the Kaplan–Meier curve
- Visual inspection for plausibility of the underlying hazard functions
- Clinical plausibility of survival estimates, based on estimates of survival after 3, 5 and 10 years derived from a structured approach to clinical expert validation

Details of the company's assessment of the best fitting curves for use in their base-case are provided in Table 4.6.

Table 4.6: Company's assessment of the best fitting curves to extrapolate OS, TTNT, PFS and TTD

	OS	TTNT	PFS	TTD
General considerations	N/A	N/A	**Paclitaxel ± carboplatin** TTNT curves for both erdafitinib and paclitaxel ± carboplatin were close to the OS curves. This led to the conclusion that TTNT alone may not serve as a suitable proxy for PFS in this context	**Paclitaxel ± carboplatin** TTD data were not available from the UK RW mUC study.
Statistical goodness-of-fit based on AIC BIC for each arm	**Erdafitinib** Differences across AIC and BIC statistics were generally small, though the log-logistic, log-normal and generalised gamma provided the best statistical fits **Paclitaxel ± carboplatin** All model extrapolations had similar statistical fits **Chemotherapy (THOR)** All the curves provide similarly good fits, except the BIC value for the generalised gamma	**Erdafitinib** Assessment of the statistical fits showed only small differences between models, with the log-logistic considered to be the most appropriate distribution **Paclitaxel ± carboplatin** Based on AIC and BIC statistics, the curve that matches very closely to the data is the log-normal	**Erdafitinib** Based on AIC and BIC statistics, the log-logistic and log-normal extrapolations provided the best fitting curves **Paclitaxel ± carboplatin** Not explicitly discussed **Chemotherapy (THOR)** Log-logistic, log-normal, and generalised gamma models provide similarly adequate fits	**Erdafitinib** The statistical fits show log-logistic and generalised gamma with better statistical fits **Paclitaxel ± carboplatin** Not explicitly discussed **Chemotherapy (THOR)** The log-logistic has the lowest AIC and BIC, with values for the log-normal and generalised gamma not too different
Visual inspection to assess the fit of the extrapolation to the Kaplan–Meier curve	**Erdafitinib** The extrapolated curves show fairly small differences in modelled survival over time	**Erdafitinib** Not explicitly discussed **Paclitaxel ± carboplatin**	**Erdafitinib** Based on visual assessment, the log-logistic and log-normal extrapolations provided the best fitting curves	**Erdafitinib** Visual assessment of model fits to the observed TTD data

	OS	TTNT	PFS	TTD
	Paclitaxel ± carboplatin Not explicitly discussed **Chemotherapy (THOR)** All seven curves provide a good visual fit, with the log-logistic and log-normal curves providing more optimistic long-term projections	Not explicitly discussed	**Paclitaxel ± carboplatin** Not explicitly discussed **Chemotherapy (THOR)** Most of the curves provide plausible representation of the data	shows relatively good fits for all models **Paclitaxel ± carboplatin** Not explicitly discussed **Chemotherapy (THOR)** All parametric models provided a reasonable fit to the KM curve
Visual inspection for plausibility of the underlying hazard functions	PH assumption is not valid based on non-parallel lines in the log-cumulative hazard plot **Erdafitinib** Shape of log-logistic, log-normal and generalised gamma distributions most similar to the OS hazard plot **Paclitaxel ± carboplatin** The log-logistic curve has a hazard function that closely resembled the observed hazard **Chemotherapy (THOR)** All distributions appear plausible except the log-logistic and log-normal	**Erdafitinib** Not explicitly discussed **Paclitaxel ± carboplatin** Not explicitly discussed	**Erdafitinib** The log-logistic, log-normal and generalised gamma distributions appear plausible **Paclitaxel ± carboplatin** Not explicitly discussed **Chemotherapy (THOR)** Not explicitly discussed.	**Erdafitinib** Not explicitly discussed **Paclitaxel ± carboplatin** Not explicitly discussed

	OS	TTNT	PFS	TTD
Clinical plausibility of survival estimates, based on estimates of survival after 3, 5 and 10 years derived from a structured approach to clinical expert validation	**Erdafitinib** The log-logistic and log-normal provided plausible likely estimates of long-term survival probability **Paclitaxel ± carboplatin** All model extrapolations had similar long-term survival outcomes. The log-logistic curve closely aligned with the most likely estimates provided by clinical experts **Chemotherapy (THOR)** Not explicitly discussed	**Erdafitinib** Not explicitly discussed **Paclitaxel ± carboplatin** Not explicitly discussed	**Erdafitinib** The PFS data was mature such that no clinical validation was sought **Paclitaxel ± carboplatin** Not explicitly discussed **Chemotherapy (THOR)** Log-logistic closely aligns with the estimates reported in KEYNOTE-045	**Erdafitinib** Not explicitly discussed **Paclitaxel ± carboplatin** Not explicitly discussed **Chemotherapy (THOR)** Not explicitly discussed
Base-case approach	**Erdafitinib** Log-logistic **Paclitaxel ± carboplatin** Log-logistic **Chemotherapy (THOR)** Exponential	**Erdafitinib** Log-logistic **Paclitaxel ± carboplatin** Log-normal	**Erdafitinib** Log-logistic **Paclitaxel ± carboplatin** The ratio of PFS to TTNT per cycle for erdafitinib was used to derive a PFS extrapolation for paclitaxel ± carboplatin **Chemotherapy (THOR)** Log-logistic	**Erdafitinib** Log-logistic **Paclitaxel ± carboplatin** TTD for paclitaxel ± carboplatin equivalent to the generated PFS **Chemotherapy (THOR)** Generalised gamma
Scenario analyses	**Erdafitinib** Gamma and Gompertz (lower and upper limits)	**Erdafitinib** None	**Erdafitinib** None	**Erdafitinib** None

	OS	TTNT	PFS	TTD
	Paclitaxel ± carboplatin Weibull **Chemotherapy (THOR)** None	**Paclitaxel ± carboplatin** None	**Paclitaxel ± carboplatin** Set PFS equal to that of paclitaxel from PLUTO trial **Chemotherapy (THOR)** None	**Paclitaxel ± carboplatin** Derive paclitaxel and paclitaxel ± carboplatin TTD from TTD-to-PFS ratio of chemotherapy (THOR) **Chemotherapy (THOR)** None

AIC = Akaike information criterion; BIC = Bayesian information criterion; KM curve = Kaplan-Meier curve; mUC = metastatic urothelial carcinoma; N/A = not applicable; OS = overall survival; PH = proportional hazards; PFS = progression-free survival; RW = real-world; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; TTD = time to treatment discontinuation; TTNT = time to next treatment; UK = United Kingdom

For paclitaxel (PLUTO), OS and PFS were estimated by applying a HR of 1.55 and 1.06 to the erdafitinib OS and PFS curves, respectively. The methods of estimating these HRs was described in CS Appendix Q2. TTD for paclitaxel (PLUTO) was assumed to be equal to PFS.

The company stated that modelling of waning of the erdafitinib treatment effect was not required, as it was anticipated that the range of survival models considered within the cost effectiveness model (CEM) reflects differences in treatment effects over time.

EAG comment: The main comments of the EAG relate to: a) the lack of PFS data for paclitaxel ± carboplatin in the UK RW mUC study, b) the lack of TTD data for paclitaxel ± carboplatin in the UK RW mUC study, c) issues related to the assessment of the best-fitting parametric survival curves, d) not explicitly modelling waning of the erdafitinib treatment effect, and e) an error in the calculation of TTNT for erdafitinib.

a) Due to the absence of PFS data for paclitaxel ± carboplatin in the UK RW mUC study, the company initially used the ratio of PFS to TTNT per cycle for erdafitinib to derive PFS for paclitaxel ± carboplatin. The company argued that it was deemed inappropriate to use TTNT as a proxy for PFS for paclitaxel ± carboplatin, given that the TTNT curves for both erdafitinib and paclitaxel ± carboplatin were close to the OS curves. Therefore, a simplifying assumption was made to use the ratio of PFS to TTNT risk per cycle for erdafitinib to derive a PFS extrapolation for paclitaxel ± carboplatin. The EAG, however, questions the plausibility of this approach, as it assumes a consistent ratio between PFS and TTNT across different treatments. The EAG's clinical expert noted that chemotherapies are time limited (i.e. paclitaxel is given for a maximum of 6 treatment cycles), whereas erdafitinib is continued until disease progression. Hence the assumption of a consistent ratio between PFS and TTNT across these treatments is likely not valid.
   In response to clarification question B9d, the company provided alternative scenario analyses, including using TTNT of paclitaxel ± carboplatin from the UK RW mUC study,[3] PFS from Vaishampayan et al. 2005[34] and PFS from paclitaxel (PLUTO) as a proxy for the estimation of paclitaxel ± carboplatin PFS. The company concluded that using the PFS for paclitaxel ± carboplatin from Vaishampayan et al. 2005 was more plausible than their initial approach of using the ratio of PFS to TTNT risk per cycle for erdafitinib, because the median PFS from Vaishampayan et al. (4 months) was more in line with the median PFS observed in other trials than the median PFS (1.5 months) of their initial approach. Therefore Vaishampayan et al. 2005, extrapolated using the log-logistic curve, was used in the company's revised base-case to estimate paclitaxel ± carboplatin PFS. The EAG questions the suitability of the company's literature source to inform paclitaxel ± carboplatin PFS in their revised base-case. The study of Vaishampayan et al. 2005 was conducted a relatively long time ago and included only 44 patients, of which none were from the UK. In addition, the company did not provide details of any assessment showing that the log-logistic curve is the most appropriate curve to extrapolate the PFS data from Vaishampayan et al. 2005. Although the EAG appreciates the scenario analyses that were provided by the company in response to clarification to address the uncertainty surrounding the absence of PFS data for paclitaxel ± carboplatin in the UK RW mUC study, additional scenarios using the PFS of taxanes in TA525 and TA692 would be informative.
   The EAG considers the lack of PFS data for paclitaxel ± carboplatin in the UK RW mUC study to inform the economic model a major limitation. Alternative to the company's initial approach (ratio of PFS to TTNT risk per cycle for erdafitinib) and revised approach (PFS from

Vaishampayan et al. 2005), the EAG will use TTNT of paclitaxel ± carboplatin (extrapolated using the log-normal curve) from the UK RW mUC study as a proxy to inform PFS data for paclitaxel ± carboplatin in its base-case. The company argued that this was inappropriate given that the TTNT curve for paclitaxel ± carboplatin was close to its OS curve, but the relatively low number of modelled LYs gained in the PD health state in the paclitaxel ± carboplatin arm of the company's base-case is an indication to the EAG that PFS being close to OS for paclitaxel ± carboplatin is seemingly plausible. The EAG's main argument of selecting this approach for its base-case is that it prefers a proxy derived from UK RW mUC patients. The EAG acknowledges that using TTNT may overestimate PFS for patients that progress before the paclitaxel stopping rule of 24 weeks, and may underestimate PFS for patients progressing thereafter. However, all alternatives considered, the EAG believes this is the most plausible approach of modelling PFS for paclitaxel ± carboplatin in its base-case. Finally, using PFS of paclitaxel monotherapy from PLUTO was explored as an EAG scenario analysis.

b) Due to the absence of TTD data for paclitaxel ± carboplatin in the UK RW mUC study, the company made a simplifying assumption that TTD for paclitaxel ± carboplatin would be equivalent to the generated PFS (i.e. PFS from Vaishampayan et al. 2005 in the company's base-case). In response to clarification, the company justified this assumption by stating that paclitaxel ± carboplatin treatment is continued until disease progression or unacceptable toxicity. However, according to the NHS guidelines[35] and acknowledged by the company in response to clarification question B9h, paclitaxel ± carboplatin should be given for a maximum of 6 treatment cycles (equivalent to 24 weeks/model cycles). According to the company's response to clarification question B9f, this hard stop was also assumed in TA530 and TA692. In addition, a proportion of patients may discontinue due to toxicity and reasons other than disease progression or reaching the maximum number of treatment cycles. Therefore, assuming that paclitaxel ± carboplatin TTD is equivalent to the generated PFS likely overestimates the true TTD, and hence overestimates the total treatment costs of paclitaxel ± carboplatin. In response to clarification, the company provided scenario analyses assuming similar TTD for erdafitinib and paclitaxel ± carboplatin, and using TTD from taxanes of TA525 to inform TTD for paclitaxel ± carboplatin. The EAG considered the scenario analysis assuming similar TTD for erdafitinib and paclitaxel ± carboplatin to be implausible given their different safety profiles and the fact that erdafitinib is treated until disease progression whereas chemotherapies are given for a maximum number of treatment cycles. The scenario using TTD from taxanes of TA525 to inform TTD for paclitaxel ± carboplatin relied on the same assumption of TTD equalling PFS and was explored as an EAG scenario analysis. Due to the absence of better alternatives, the EAG in its base-case remains assuming that TTD for paclitaxel ± carboplatin is equivalent to the generated PFS (which in the EAG base-case equals to TTNT from the UK RW mUC study). Additionally, in line with the NHS guidelines and TA's 530 and 692, a hard stop will be assumed after 24 weeks (i.e. TTD for paclitaxel ± carboplatin in the economic model will be zero from week 25 onwards).

c) The company fitted parametric survival curves to the observed THOR and UK RW mUC study data based on NICE DSU TSD14 for the modelling of OS, TTNT, PFS and TTD over a lifetime horizon. In its clarification letter, the EAG requested additional details regarding the process of selecting the most suitable curves and identified a number of issues.

   Firstly, in the overview of the requested numbers of patients at risk in intervals of 3 months, the EAG noticed low numbers of patients at risk for all outcomes at relatively early timepoints in the observed data, meaning that a substantial part of the total observed data that was used for the extrapolation of outcomes was based on few patients. For example, for erdafitinib OS and TTNT approximately 6% of patients was still at risk after 30 months (in total 51 months of

data), for erdafitinib PFS approximately 4% of patient was still at risk after 15 months (in total 36 months of data), and for erdafitinib TTD approximately 4% of patients was still at risk after 18 months (in total 39 months of data). Similar results were observed for paclitaxel ± carboplatin. The EAG is concerned that fitting parametric curves to observed data including few patients at risk for a substantial period of time adds uncertainty to the long-term extrapolations of the outcomes (i.e. OS, PFS, TTNT and TTD). This seems particularly true for OS, as the company's scenario analyses showed that the ICER difference between the most pessimistic and optimistic erdafitinib OS curves is approximately £7,000 per QALY gained. The EAG would like to see additional scenario analyses also selecting the most pessimistic and optimistic parametric survival curves for the other outcomes (e.g. PFS, TTNT, and TTD). Secondly, the company assumed in their base-case approach for the modelling of OS, TTNT, PFS and TTD that the proportional hazards (PH) assumption failed to hold. In response to clarification question B8, however, the company stated that the scaled Schoenfeld residual plot for OS did not show strong evidence for lack of proportionality between the hazards of erdafitinib and paclitaxel ± carboplatin. For TTNT, there was more evidence to suggest that the PH assumption could be violated. The company further argued that the parametric distributions that can model PH (exponential, Weibull and Gompertz) provide poor fits to the data even when fitted individually to each group, and that it can be expected that placing an additional constraint on them in the form of a shared parameter would only worsen their fit. While acknowledging that AFT joint models could potentially provide good fits, the company stated that models the assumption of a constant treatment effect over time is very strong, and even small violations of that assumption can be meaningful in long-term extrapolations. The company did not add jointly fitted models to their updated economic model due to their reasons above and time limits, but provided the estimated parameters for joint OS and TTNT of erdafitinib in Tables 17 and 18 of the clarification responses. The EAG, however, would like to see these being implemented in an updated economic model to assess the potential impact on the cost effectiveness results.

Thirdly, the EAG noted that for erdafitinib, the standard parametric survival curves for the extrapolation of OS, PFS, TTD and TTNT did not seem to fit very well to the observed THOR data (underestimation of the observed data in the first few months and overestimation thereafter). The EAG therefore requested to explore spline-based models, which were provided by the company in response to clarification. The company's results showed that most of the best fitting spline models predicted implausible long-term estimates, whereas the ones predicting plausible long-term estimates had statistical fit to the observed THOR data that were similar to the best fitting standard parametric models. Hence, the EAG agrees with the company that it remains using the standard parametric models to inform their base-case.

Finally, the company did initially not examine the validity of the extrapolated outcomes based on external data. In response to clarification, the company provided a comparison of their current model predictions for erdafitinib and predictions accepted by the committee from TA692 and TA525 (both 2L immunotherapies for mUC).[36, 37] The results showed higher survival estimates for erdafitinib at 1 year, and lower estimates thereafter. The company argued that the higher survival at 1-year matches with the higher median OS in THOR of 12.1 months. The company further stated that the lower predictions thereafter is in line with clinicians stating that the prolonged survival tail typically observed with immunotherapies may not be present with erdafitinib. Additionally, patients from THOR were likely to have undergone more extensive prior treatments and were situated further along the treatment pathway. The EAG is satisfied with the external data validation provided by the company.

d) Waning of the erdafitinib treatment effect was not explicitly modelled in the company's base-case. Upon request, the company provided the OS and TTNT implied HR plots for erdafitinib versus paclitaxel ± carboplatin in response to the clarification letter. For OS, there is a steep increase of the HR in the first 5 years, whereafter the HR gradually increases towards 1. For TTNT, there is a steep increase of the HR in the first 2 years, whereafter it gradually decreases. The company argued that the time-to-event curves of erdafitinib and paclitaxel ± carboplatin were modelled independently, and the implied treatment effect could, therefore, vary over time according to trends observed in the data that the independent statistical models capture. The company further stated that a constant effect was assumed in their approach using HRs to derive OS and PFS for PLUTO-based paclitaxel scenario analyses. According to the company, however, treatment waning would only have a minimal impact as the PFS HR was close to 1. The EAG noted from the log-cumulative hazard plots provided by the company in Figures 53 and 54 of Appendix P that the OS and TTNT hazards for erdafitinib and paclitaxel ± carboplatin were converging, indicating that waning of the erdafitinib treatment effect was indeed implicitly modelled in the independent survival curves. The EAG is therefore satisfied with the company's justification for not explicitly modelling waning of the erdafitinib treatment effect in their current base-case. Nevertheless, in the scenario analyses using jointly fitted models as requested in comment c) above, exploring the modelling of erdafitinib treatment waning would be necessary.

e) In their clarification responses, the company highlighted that an error was corrected for the calculation of TTNT for erdafitinib.[3] TTNT was initially defined from initiation of erdafitinib to OS, suggesting that those who switched treatment had their TTNT over estimated. This was corrected to make sure it measured the time from initiation of treatment to change of treatment. The EAG agrees with this correction.

4.2.7 Adverse events

The main sources of evidence on treatment associated AEs were the THOR (adjusted to UK RW mUC study) and the PLUTO trial (Table 4.7).[16, 24] The PLUTO trial only considered patients receiving paclitaxel monotherapy. Only Grade 3+ AEs with an incidence of ≥ 5% were included in the economic model and analyses. Duration of AEs was informed by the THOR trial (adjusted to UK RW mUC study).

Table 4.7: Incidence and duration of AEs per treatment arm

Adverse event	Erdafitinib	Paclitaxel ± carboplatin	Paclitaxel monotherapy	Chemotherapy THOR trial	Duration in days
Palmar-plantar erythrodysesthesia syndrome	[redacted]	0.00%	0.00%	[redacted]	[redacted]
Stomatitis	[redacted]	0.00%	0.00%	[redacted]	[redacted]
Anaemia	[redacted]	0.00%	0.00%	[redacted]	[redacted]
Hyponatraemia	[redacted]	0.00%	0.00%	[redacted]	[redacted]
Onycholysis	[redacted]	0.00%	0.00%	[redacted]	[redacted]
Hyperphosphataemia	[redacted]	9.38%*	9.38%	[redacted]	[redacted]
Hypophosphataemia	[redacted]	9.38*	9.38*	*	[redacted]
Neutropenia	[redacted]	9.38%	9.38%	[redacted]	[redacted]

Adverse event	Erdafitinib	Paclitaxel ± carboplatin	Paclitaxel monotherapy	Chemotherapy THOR trial	Duration in days
Leukopenia*	[redacted]	0.00%	0.00%	[redacted]	[redacted]
Febrile neutropenia*	[redacted]	0.00%*	0.00%*	[redacted]	[redacted]
Fatigue	[redacted]	7.81%	7.81%	[redacted]	[redacted]

* Discrepancy between CEM and the CS, the table is according to the CEM

AEs = adverse events; CEM = cost effectiveness model; CS = company submission; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations;

EAG comment: The main concerns of the EAG relate to: a) using disutilities from the literature in various disease areas, b) the modelled incidence of treatment-associated AEs for paclitaxel ± carboplatin being based on paclitaxel monotherapy from PLUTO, c) discrepancies between the CS and the modelled AEs, d) including Grade 3+ AEs with an incidence of ≥ 5%.

a) The company modelled AE disutilities based on various literature sources in its base-case. Another option in their economic model was to use AE disutilities from the THOR trial. The company reported some minor differences in the QALY loss depending on the method for erdafitinib (literature: 0.0018, THOR: 0.0024), paclitaxel ± carboplatin (literature: 0.0027, THOR: 0.0024), which slightly benefited erdafitinib. The EAG noted that the literature-based disutilities were derived from several disease areas (e.g., leukaemia, metastatic breast cancer, non-small cell lung cancer). The EAG questions whether these are representative of the population used in the current appraisal. However, the THOR-based disutilities present some limitations as well, such as that the impact of different safety profiles could not be appropriately taken into account, as paclitaxel ± carboplatin was not a comparator in the THOR trial. The EAG agrees that neither option is ideal, but noted that switching between approaches had a very limited impact on the ICER.
b) The main source of evidence to inform treatment-associated AEs incidences for paclitaxel ± carboplatin was the PLUTO trial. This trial, however, only considered patients receiving paclitaxel monotherapy. According to the clinical expert consulted by the EAG, paclitaxel and carboplatin "*tend to be more toxic than single agent paclitaxel, even though higher cumulative doses are given in weekly paclitaxel regimen*". Although the EAG is unsure whether the paclitaxel monotherapy arm from PLUTO is suitable to inform the treatment-associated AEs incidences for paclitaxel ± carboplatin, it is likely conservative and only has a minor impact on the cost-effectiveness results.
c) The EAG noted some discrepancies between the AEs mentioned in the CS and those included in the economic model (Table 4.7). First, hypophosphatemia was mentioned in CS, Table 43 as one of the AEs used in the model; however, the company did not provide information on its associated disutility and duration (CS, Table 44), and it was not implemented in the economic model. Second, the incidence of hyperphosphatemia for paclitaxel ± carboplatin reported in the CS (i.e., 0.00%) did not match the one implemented in the economic model (i.e., 9.38%). Third, leukopenia and febrile neutropenia were modelled, but not mentioned in the CS. The EAG would like the company to clarify these discrepancies, and, if needed, to provide a corrected economic model and details of the corrections that were made.
d) The company modelled Grade 3+ AEs with an incidence of ≥5% (in the THOR and PLUTO trials). In response to clarification, the company provided a scenario analysis in which all Grade 3+ AEs were modelled, regardless of the percentage of patients that experienced it in the clinical

trials. This resulted in a slight increase of the ICER (from £26,487/QALY to £26,695/QALY). The EAG is satisfied with the company's response, which demonstrated that inputs related to AE incidences are likely not model drivers.

4.2.8 Health-related quality of life

The utility values were estimated for the PF and PD health states based on data from the THOR trial.[24]

4.2.8.1 Health-related quality of life data identified in the literature review

According to the CS, the SLR identified five studies reporting on utility values in patients with mUC treated with at least one line of systemic therapy. However, none of these studies reported UK relevant utility values, therefore, the company did not include any of the five studies in their economic model. Therefore, the company considered only three TAs reporting UK relevant utility values (TA522, TA739, and TA788).[38-40]

4.2.8.2 Health state utility values

The HRQoL data used in the model were based on the EQ-5D-5L data collected in the THOR clinical trial[24]. No data imputation was performed for missing evaluations. In line with NICE guidelines, the EQ-5D-5L were mapped to EQ-5D-3L using the UK value set. Health state utilities were also adjusted within the model to account for the age-matched general population, using the utility multiplier derived from Hernández Alava et al[41].

The company tested two approaches to derive health state utility values (HSUVs) from the trial data: linear MMRMs and multivariable regression modelling. In the MMRMs approach, which is used in the CS base-case, utility estimates were derived separately for the PF and PD health states. Both arms of the THOR trial were used (erdafitinib and comparator, i.e. docetaxel or vinflunine). The PF health state utility was based on the AUC of the mean utility estimates for each treatment cycle among patients remaining progression free (PF) in that cycle. PD health state utility was estimated from questionnaires of patients who were known to have progressed using a single MMRM that accounted for correlations between EQ-5D measurements within the same patient. Compound symmetry covariance structure was selected as it resulted in the lowest AIC.

Alternatively, the company estimated utility values using a multivariable regression model. Several mixed-effects regression models were considered, each with a different combination of the following variables:

- Health state (PF, PD)
- Treatment (erdafitinib, docetaxel or vinflunine)
- Grade 3–5 AE occurrence (Yes, No)
- Age, sex, race, body mass index, PD-(L)1 status (CPS 10% cut-off), metastasis status as initial diagnosis, baseline ECOG PS, and number of prior lines of therapy.

Single univariable models were fitted for each covariate identified as being potentially relevant. Three univariable models with improved fit to the data compared to a model with random intercept alone were identified: health state, Grade 3–5 AE occurrence, and baseline ECOG PS. These were carried forward to a backward stepwise model selection, which considered models with multiple covariates. The model that considered progression and AEs was considered the best-fitting model and was used in a scenario analysis (Table 4.8).

The company also explored time-to-death utilities and utility values based on TA522, TA739 and TA788 in scenario analyses.[38-40]

Table 4.8: Health state utility values

Health state	MMRM approach (SE)	Multivariable regression model approach
Progression free	[redacted]	[redacted]
Progressed disease	[redacted]	[redacted]

*Weighted average of ECOG 1–2 coefficients applied to the intercept.
ECOG = Eastern Cooperative Oncology Group; MMRM = mixed models for repeated measures; SE = standard error

4.2.8.3 Disutility values

In their base-case, the company used disutility values to reflect the impact of AE on quality of life (QoL). The decrement associated with each AE is based on values from the literature (Table 4.9). The QALY loss associated with each AE was calculated by multiplying the utility decrement by the duration of the AE (Table 4.7) and the proportion of patients experiencing the AE for each treatment.

Table 4.9: disutility values associated with AEs

Adverse event	Disutility	Source
Palmar-plantar erythrodysesthesia syndrome	-0.040	Assumed equal to stomatitis (following TA780)[42]
Stomatitis	-0.040	TA498[43]
Anaemia	-0.090 (0.02)	Beusterien et al. 2010[44]
Hyponatraemia	-0.115	Lloyd et al. 2006[45] - assumed equivalent to fatigue
Onycholysis	-0.032 (0.012)	Nafees et al. 2017[46] - assumed equivalent to skin reactions
Hyperphosphataemia	-0.115	Nafees et al. 2017[46] - assumed equivalent to fatigue
Neutropenia	-0.090 (0.015)	Nafees et al. 2017[46]
Fatigue	-0.073 (0.018)	Nafees et al. 2017[46]

*Weighted average of ECOG 1–2 coefficients applied to the intercept.
AEs = adverse events; ECOG = Eastern Cooperative Oncology Group

EAG comment: The main concerns from the EAG relate to: a) the approach used for the estimation of health utility values in the economic model, b) handling of missing HRQoL data, and c) using HRQoL data from chemotherapy regimens in THOR that were not considered relevant comparators for the UK.

a) In its base-case, the company estimated the PF and PD HSUVs separately using linear MMRMs without including any additional covariates. The PF health state utility was based on the AUC of mean utility estimates for each treatment cycle among patients remaining PF in that cycle. PD state utility was estimated from questionnaires of patients who were known to have progressed (i.e., excluding questionnaires after censoring) using a single MMRM that accounted for correlations between EQ-5D measurements from the same patient. Alternatively, in a scenario analysis, the company explored multivariable regression models with additional covariates for the estimation of the PF and PD health state utilities. In its clarification letter, the

EAG asked the company to elaborate on why their base-case approach was preferred over the multivariable regression models. The company responded that using multivariable models including baseline characteristics may not be valid unless the distribution of those characteristics is tracked over time, given that baseline characteristics may change over time and may therefore bias the results. Although the EAG acknowledges this potential limitation, the company's best fitting multivariable regression model included progression status and AEs, which are covariates that were tracked over time. Next to that, potential confounding effects may be missed by not considering additional covariates, which may result in potentially biased HSUVs. Additionally, the company argues that fitting a joint MMRM for the PF and PD health states would mean that a patient's HRQoL prior to progression would influence their estimated utility after progression. This was deemed undesirable by the company as patients spent much more time in pre-progression than in post-progression. The EAG, however, considers it reasonable to assume that there is a relationship between patients HRQoL in the PF and PD health states and hence considers it reasonable to estimate PF and PD utility values within a single model. Finally, the company preferred using their base-case approach by stating that it produced utilities values that were close to those estimated in TA522[38]. The EAG agrees on this, although the PF utility from the multivariable regression model ([redacted]) was even closer to the PF utility estimated in TA522. Based on its arguments as stated above, the EAG prefers estimating the PF and PD HSUVs within a single model, including additional relevant covariates. Therefore, the EAG used the company's best fitting multivariable regression model (i.e. model 1, including progression status and AEs) in its base-case.

b) In response to clarification question B15, the company provided an overview of the number of expected and received EQ-5D-5L questionnaires up to cycle 21 for erdafitinib and the chemotherapy arm of the THOR trial.[3, 27] The company stated that the proportions of missing data were similar between both trial arms, and that there was no clear pattern over time even though the absolute number of completed questionnaires decreased more rapidly in the chemotherapy arm. The EAG noted that the average percentages of missingness over time were approximately 15% and 26% for the erdafitinib arm and the chemotherapy arm respectively. The company further stated that missing data were not explicitly imputed, as MMRM impute missing observations implicitly. These models, however, assume that data is missing completely at random, and it is unclear to the EAG whether this is true. Scenario analyses using imputation methods to impute HRQoL data where missing values were observed could provide further insight into the potential impact of this on the cost-effectiveness results.
c) The company used pooled data from both treatment arms of THOR for their estimation of HSUVs, despite that the chemotherapy regimens in THOR (i.e. docetaxel and vinflunine) were not considered relevant comparators for the UK. It was therefore unclear to the EAG whether it is appropriate to include data from this comparator arm from THOR to estimate the HSUVs. However, in response to clarification question B15, the company explained that the mixed effects models demonstrated that the treatment covariate did not have a statistically significant impact on the estimated utility values. The EAG agrees that this is unlikely to be impactful.

4.2.9 Resource use and costs

The cost categories included in the model were treatment drug acquisition and administration costs, health state resource use costs, AE costs, subsequent treatment costs, end-of-life-care costs, and the cost of FGFR testing and ophthalmology assessments.

Unit prices were based on the NHS reference prices, Drugs and pharmaceutical electronic market information tool (eMIT), Personal Social Services Research Unit (PSSRU), and previous TAs.

4.2.9.1 Resource use and costs data identified in the literature review

According to the CS, the SLRs identified 22 studies reporting on relevant resource use and cost information in patients with locally advanced, surgically unresectable or metastatic urothelial cancer beyond the first line of systemic therapy. However, none of these studies reported UK relevant resource use and costs. It is unclear whether the company did include any of the 22 studies in their economic model. The company considered three TAs reporting UK relevant resource use and costs.

4.2.9.2 Treatment costs (with PAS)

Treatment costs were calculated based on dosage, unit costs, relative dose intensity (RDI), dosing schedules and stopping rules. The unit cost for erdafitinib was provided by the company, which included a Patient Access Scheme (PAS) with a discount of [redacted]% (Table 4.10), and the unit costs of other drugs were retrieved from the drugs and pharmaceutical eMIT.

Table 4.10: Drug acquisition unit costs

Drug name	Drug form	Quantity per unit (mg)	Units in packet	Price per pack
Erdafitinib	Tablet	Per physician prescription	28, 56 or 84 units per pack, dependent on physician prescription. Dose per patient varies per patient as this is based on the amount of erdafitinib prescribed per 28 days.	£12,750.00 (including PAS: £[redacted])
Paclitaxel	6 mg/ml (vial)	30 mg	1	£3.88
Paclitaxel	6 mg/ml (vial)	100 mg	1	£9.13
Paclitaxel	6 mg/ml (vial)	150 mg	1	£16.92
Paclitaxel	6 mg/ml (vial)	300 mg	1	£24.43
Carboplatin	10 mg/ml (vial)	15 ml	1	£20.22
Carboplatin	10 mg/ml (vial)	45 ml	1	£48.09
Carboplatin	10 mg/ml (vial)	5 ml	1	£9.28
Carboplatin	10 mg/ml (vial)	60 ml	1	£71.44

Based on Table 46 of the CS
CS = company submission; PAS = Patient Access Scheme

4.2.9.3 Dosage + vial sharing

Contrary to the THOR trial (8 mg daily for 21 days), the company in their revised base-case modelled erdafitinib at a dose of 8 mg daily for 28 days (prescribed as a 28-day pack of tablets). The CS states that treatment may be up titrated to 9 mg, maintained at 8 mg, or withheld, based on phosphate levels as measured on cycle 1, day 14. Paclitaxel monotherapy is dosed at 80 mg/kg as a 1-hour IV infusion in 250 ml sodium chloride on days 1, 8 and 15 every 28 days. In the paclitaxel ± carboplatin regimen, paclitaxel is dosed 175 mg/m² administered over a period of 3 hours every 3 weeks and carboplatin is dosed to a targeted area under the concentration-time curve = 6 mg/mL/minute over 30 minutes. The dose of carboplatin is calculated by the Calvert formula: mg = targeted AUC × (GFR + 25). Glomerular filtration rate (GFR) assumed to be the estimated creatinine clearance (CS, Table 47).

In the economic model, the cost of erdafitinib was applied per treatment cycle (28 days) until progression, withdrawal, or intolerable toxicity. A full drug packet was costed upfront to all patients on treatment regardless of whether it is fully used.

Paclitaxel and carboplatin are stored in treatment vials and administered IV. The distribution of patients receiving monotherapy or combination therapy is costed directly based on data from the National Cancer Registration and Analysis Service (NCRAS) paclitaxel ± carboplatin cohort[47]: 75% paclitaxel monotherapy and 25% paclitaxel ± carboplatin.

In the base-case analysis, the model included the cost of any wastage in the erdafitinib arm by costing erdafitinib every 28 days, regardless of whether all the of tablets are utilised within the cycle or not. The company assumed no vial sharing in the chemotherapy arm.

4.2.9.4 Dose intensity

The dose intensity for erdafitinib was determined based on the proportion of doses that were skipped in the THOR safety population (17.07%, based on a mean duration of exposure of 206.8 days and a sample size of N=135).

The RDI for paclitaxel monotherapy and paclitaxel ± carboplatin was based on the RDI of chemotherapy observed in the THOR trial ([redacted]%).

4.2.9.5 Treatment duration

The SmPC of erdafitinib states that treatment should continue until disease progression or unacceptable toxicity occurs. Paclitaxel ± carboplatin is continued until progression, withdrawal, or intolerable toxicity.[48]

4.2.9.6 Treatment administration costs

The unit administration costs were obtained from the National Cost Collection based on route of administration (CS, Table 48). A one-time oral administration cost of £232 was applied for erdafitinib. For both paclitaxel and carboplatin, which are administered IV, it was assumed that patients would receive each administration in a hospital setting. For paclitaxel monotherapy simple chemotherapy administration costs were assumed, while for paclitaxel ± carboplatin complex chemotherapy administration costs were assumed. Average drug acquisition and administration costs per model cycle are shown in Table 4.11.

Table 4.11: Average drug acquisition and administration costs per model cycle

Strategy	Average drug cost per model cycle	Average administration cost per model cycle
Erdafitinib	£[redacted]	£0
Paclitaxel ± carboplatin (NCRAS)	£16	£262
Paclitaxel (PLUTO)	£12	£307
Chemotherapy (THOR)	£309	£102

Based on data from the CEM, drug costs sheet.
CEM = cost effectiveness model; NCRAS = National Cancer Registration and Analysis Service; THOR = Trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations

4.2.9.7 Health state unit costs and resource use

Costs related to disease management, monitoring and patient follow-up are included in the economic model. Pre- and post-progression costs were calculated separately for each treatment arm. Healthcare use frequencies were based on clinician's estimates,[14] previous TAs and the UK RW mUC study (CS, Table 51).[6] Costs were applied to each resource (CS, Table 50) and accrued according to the time spent in each health state (Table 4.12).

Table 4.12: Health state costs per cycle

Health state	Treatment	Cost per cycle
Progression-free	Erdafitinib	[redacted]
	Paclitaxel ± carboplatin	[redacted]
Progressed	Erdafitinib	[redacted]
	Paclitaxel ± carboplatin	[redacted]
Based on revised CEM, HCRU costs sheet CEM = cost effectiveness model; HCRU= healthcare resource use		

4.2.9.8 Adverse event costs

Adverse event costs informed by previous TAs and NHS reference costs (Table 4.13).[49] AE unit costs were multiplied by the per cycle probability of each AE occurring to calculate the total per-cycle cost.

Table 4.13: Adverse event costs

Adverse event	Unit cost (inflated to 2022/2023 prices)	Cost per cycle
Palmar-plantar erythrodysesthesia syndrome	£642.05	NHS reference costs 2021/22 – Non-elective inpatient – short stay[49]
Stomatitis	£1,025.75	NHS reference costs 2021/22 – Non-elective inpatient – short stay[49]
Anaemia	£864.82	NHS reference costs 2021/22 – SA01G-K – Total HRG's – Weighted average of Acquired Pure Red Cell Aplasia or Other Aplastic Anaemia – NES[49]
Hyponatraemia	£3.17	NHS reference costs 2021/22 – DAPS05 – DAPS – Haematology[50]
Onycholysis	£534.70	NHS reference costs 2021/22 – JD07E-K – Total HRGs – Weighted average of Skin Disorders without Interventions – NES[50]
Hyperphosphataemia	£3.17	NHS reference costs 2021/22 - DAPS05 - DAPS – Haematology. Assumed to be the cost of a blood test[50]
Neutropenia	£892.31	NHS reference costs 2021/22 – WJ11Z – Other Disorders of Immunity – HRGs – NES[50]
Leukopenia	£428.18	TA522[38]
Febrile neutropenia	£3,188.10	TA522[38]
Fatigue	£1,081.41	NHS reference costs 2021/22 – WH52A – NELS (Follow TA788)[40]

Adverse event	Unit cost (inflated to 2022/2023 prices)	Cost per cycle
Based on CS Table 53[1] DAPS = Directly Accessed Pathology Services; DSU = Decision Support Unit; HRG = Healthcare Resource Group; NES = non-elective short stay; NEL = non-elective long stay; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; TA = Technology Appraisal		

4.2.9.9 Miscellaneous unit costs and resource use

4.2.9.9.1 Subsequent treatment costs

According to the CS, most patients who progress to advanced disease were not expected to receive subsequent treatment. The company assumed similar distributions of subsequent therapies among erdafitinib and paclitaxel ± carboplatin in the economic, except that patients who progress on paclitaxel ± carboplatin were not expected be retreated with a paclitaxel or docetaxel regimen. The subsequent treatment distribution for both arms was based on the chemotherapy distribution of treatments after exposure to PD-(L)1 inhibitors in the UK RW mUC study, then adjusted for the attrition rate from THOR (CS, Table 55).

Subsequent treatments were modelled once in the model after disease progression. The proportion of patients incurring subsequent treatment costs per model cycle was calculated as the percentage of patients who transition from pre-progression post-progression, excluding deaths. This approach likely overestimates subsequent treatment costs, as these were applied at the point of progression, which may be earlier than it would be incurred in practice if the initial treatment was allowed to continue beyond progression. The company, however, stated that the impact of this overestimation is likely minimal due to the short treatment beyond progression.

4.2.9.9.2 FGFR and ophthalmology testing costs

A one-off *FGFR* testing cost of £224.85 was included in the base-case analyses of the model, assuming that all patients who receive erdafitinib are tested for *FGFR.*

As erdafitinib was associated with potential ophthalmological complications, the company assumed that patients in the erdafitinib arm would require monthly ophthalmological examinations during the first four months of treatment and every three months thereafter, at a cost of £178.35, based on the NHS reference costs adjusted for 2022/2023.

4.2.9.9.3 End of life costs

An average one-off end-of-life cost of £8,769.55 was applied to patients at the point of dying to reflect the cost of terminal care. The cost was calculated by multiplying the costs of relevant care received at the end-of-life, by the frequency of getting each type of care, as informed by Bardsley and Georghiou 2014 and PSSRU costs (CS, Tables 57 and 58).

EAG comment: The main EAG comments relate to: a) modelling different HCRU for erdafitinib and paclitaxel ± carboplatin based on expert opinion b) upfront costing of a full erdafitinib pack in the economic model, c) assuming the RDI for paclitaxel ± carboplatin to be equal to the chemotherapy arm of THOR, d) the modelling of paclitaxel ± carboplatin administration costs, and e) the modelling of wastage costs.

a) In CS, Tables 51 and 52, the company provided a summary of the HCRU by health state and the HCRU costs per cycle per health state for both erdafitinib and paclitaxel ± carboplatin respectively. The EAG noted differences in modelled resource use between erdafitinib and paclitaxel ± carboplatin, both pre-and post-progression, and requested justification for this in its clarification letter. The company responded that it corrected an error in the frequency of inpatient hospitalisations and added a one-off cost for a blood test to determine phosphate levels for patients on erdafitinib. The company further argued that the difference in pre-progression resource use could be attributed to a lower number of outpatient visits for patients receiving erdafitinib compared to those receiving paclitaxel ± carboplatin. This assumption was based on a single clinical expert comment during the advisory board stating that "[redacted]".[28] Post progression, the company assumed equivalent resource use per treatment cycle for erdafitinib and paclitaxel ± carboplatin in their revised economic model, stating that this would be conservative as patients receiving erdafitinib are expected to have a prolonged survival and improvements in overall health in comparison to patients who are not on erdafitinib. The EAG considers the company's evidence (a single expert opinion) insufficient to justify modelling different resource use for erdafitinib and paclitaxel ± carboplatin, and therefore adopted the company's scenario analysis (provided in response to clarification) assuming equal resource use for erdafitinib and paclitaxel ± carboplatin in its base-case.

b) In the CS, it is stated that erdafitinib is prescribed and distributed in packs of tablets of 28 days, and that if a new drug pack is required, the full pack is costed upfront. The EAG asked for more clarification on how the company applied erdafitinib costs in the economic model in clarification question B23. In their response, the company stated that they have changed the treatment cycle length from 21 days to 28 days in the updated economic model. However, they did not address the EAG's specific inquiry how a new drug pack of erdafitinib was costed upfront. Based on its own assessment, the EAG concluded that the application of erdafitinib costs in the economic model seems correct.

c) A RDI modifier was included in the economic model for erdafitinib (17.07%) based on the proportion of doses that were skipped in the THOR safety population. In its clarification letter, the EAG asked for an explanation of how RDI was incorporated in the economic model for the comparators. The company responded that for paclitaxel ± carboplatin an RDI equal to the THOR chemotherapy arm was assumed. The EAG questions the plausibility of this assumption, given that the chemotherapy arm of the THOR trial included different chemotherapy regimens (i.e. docetaxel and vinflunine). The company, however, also provided a scenario analysis assuming the same RDI (17.07%) to be applied to both treatment arms, which had a negligible impact on the cost-effectiveness results. The EAG therefore considers RDI likely not to be a model driver.

d) In the economic model, the company applied an administration cost in every model cycle for paclitaxel ± carboplatin. The company justified this by stating that chemotherapy treatment is given IV, which requires administration at a hospital every time. In question B21 of the clarification letter, the EAG questioned whether applying first attendance costs (SB12Z and SB13Z) in every treatment cycle for paclitaxel ± carboplatin is reasonable, especially given that a chemotherapy subsequent cycle cost (SB15Z) was also available. In their response, the company clarified that the subsequent cycle cost (SB15Z) was applied to any administrations within a treatment cycle that take place after day 1. Therefore, it was only applied for carboplatin plus gemcitabine (as subsequent treatment) in the economic model and was not

used for paclitaxel, carboplatin and docetaxel as these treatments were administered only on day 1 of each cycle. The EAG considers the company's clarification regarding the differences in administration costs for paclitaxel ± carboplatin that were applied in the economic model to be reasonable.

e) According to the CS, it was assumed that in the base-case there will be no wastage of erdafitinib in clinical practice. However, the company stated in the same sentence that "there is no tablet splitting or vial sharing", which seems to contradict their statement of no wastage. The EAG inquired about which assumption has been used eventually in the economic model in its clarification letter. In their response, the company acknowledges the confusion implied by the different wording in their submission and further clarified that the full pack costs of erdafitinib were applied every modelled treatment cycle (28 days), regardless of whether all the tablets were used or not. The company further stated that it did not account for vial sharing in the paclitaxel ± carboplatin arm, despite indicating that it might be done in clinical practice. A scenario analysis including wastage for paclitaxel ± carboplatin resulted in a minor decrease in the ICER, indicating that wastage is likely not a model driver.

4.2.10 Disease severity

The following features were used to inform QALY shortfall calculations for paclitaxel ± carboplatin, paclitaxel (PLUTO), and chemotherapy (THOR) in the company's revised base-case:

- Starting age of the patient population: 66.5 (THOR-ATC adjusted data)
- Percentage female in the patient population: 26.5% (THOR-ATC adjusted data)
- Expected (discounted) QALYs for paclitaxel ± carboplatin: [redacted]
- Expected (discounted) QALYs for paclitaxel monotherapy (PLUTO): [redacted]
- Expected (discounted) QALYs for chemotherapy (THOR): [redacted]

Table 4.14 summarises the QALY shortfall analysis for paclitaxel ± carboplatin, paclitaxel (PLUTO) and chemotherapy (THOR).

Table 4.14: Summary of company QALY shortfall analysis depending on the selected comparator arm

	Paclitaxel ± carboplatin (NCRAS)	Paclitaxel (PLUTO)	Chemotherapy (THOR)
Total expected QALYs for people with metastatic urothelial cancer with the current treatment	[redacted]	[redacted]	[redacted]
Absolute QALY shortfall	[redacted]	[redacted]	[redacted]
Proportional QALY shortfall	95.05%	93.18%	93.26%
QALY weight	1.7	1.2	1.2

Based on the revised CEM.
CEM = cost effectiveness model; NCRAS = National Cancer Registration and Analysis Service; QALY= quality-adjusted life-year; THOR = Trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations

For the paclitaxel ± carboplatin arm, the company also performed scenario analysis assuming different parametric survival curves. For each curve, the severity weight has been calculated using different

scoring algorithms (EQ-5D-3L value set from the 1993 MVH study, EQ-5D-5L to 3L mapping by Hernandez Alava, et al. 2020, and EQ-5D-5L to 3L mapping by van Hout et al. 2012), health state profiles (EQ-5D-3L from the Health Survey for England 2014, Health Survey for England 2017 and 2018 (pooled), EQ-5D-3L from the 1993 MVH study by Kind et al., 1999, and Health Survey for England 2012 + 2014 (pooled)), and model (empirical means / no interpolation) as provided by the https://shiny.york.ac.uk/shortfall/ tool.[51] According to the CS, in all these 35 different scenarios, the criteria for the x1.7 severity modifier were met. The QALYs shortfall analyses for these 35 scenarios are summarised in Table 61 in the CS.

EAG comment: The main EAG comment relates to uncertainty regarding which severity weight should be applied in the economic model.

In the company's initial economic model, the severity weight was calculated for erdafitinib versus the different comparators (paclitaxel ± carboplatin: 1.7x, paclitaxel monotherapy [PLUTO]: 1.2x and chemotherapy [THOR]: 1.2x). The EAG is concerned about uncertainty in the modelled patient characteristics and treatment effectiveness of the comparators, which impact the estimated severity weight. The company calculated the severity weight for erdafitinib versus paclitaxel ± carboplatin based on the adjusted THOR trial population characteristics (mean age of 66.5 years and a 26% females). However, and as discussed in Section 4.2.3 of the EAG report, the adjusted THOR trial population characteristics deviate from the UK patient characteristics (n=12) in THOR. In addition, a clinical expert during the advisory board stated that patients in clinical practice were expected to be older (i.e. mean starting age of 76 years). Furthermore, there is substantial uncertainty regarding the estimation of PFS for paclitaxel ± carboplatin, as extensively discussed in Section 4.2.6 of the EAG report. The EAG therefore requested 1) to calculate the severity weight for each PSA iteration and report on the percentage of simulations with a 1.0x, 1.2x and 1.7x severity weight for all comparators, and 2) to calculate the severity weight based on UK patient characteristics. The company responded that assessing the modifier using the PSA methodology is not appropriate, as it includes parameters that might not be relevant for the remaining QALYs in the patient population (e.g. costs). The EAG disagrees with this statement and considers using the PSA to quantify uncertainty in the selected severity weight an informative approach. The company provided the requested analysis, in which 51% of PSA simulations the 1.7x severity modifier was met and 49% of simulations met the 1.2x severity modifier. Regarding the modelled patient characteristics, the company further argued that the proposed ages based the UK patients from THOR were informed by a very small patient sample (n=12) which was not regarded representative of the UK population. The company additionally stated that, according to the THOR trial and the UK RW world mUC study, the targeted patient population would be younger than 69 years (THOR ITT analysis: mean age of 66.3 years, UK RW mUC study: mean age of 68.8 years for all patients who received prior PD-(L)1 therapy). However, although the EAG acknowledges that the patient numbers are low, the mean age and percentage females of the UK patients in THOR were higher ([redacted]), which is also true for the mean starting age (76 years) suggested by the clinical expert during the advisory board. The EAG calculated the severity weight conditional on the EAG base-case assumptions, which in line with the company resulted in a severity weight of x1.7. However, calculating the severity weight based on UK population characteristics from THOR ([redacted]) and the clinical expert input (age 76 years) both resulted in a severity weight of x1.2. Based on these results and the PSA results (x1.7 and x1.2 severity weight in 51% and 49% of simulations respectively), the EAG considers it uncertain whether the x1.2 or x1.7 severity weight should be applied in the economic model.

4.2.11 Uncertainty

According to the company, the key areas of uncertainty are:

- The THOR trial included comparators that do not align with UK clinical practice. To address this, the company conducted a UK RW mUC study, where paclitaxel ± carboplatin was identified as the most relevant comparator for this appraisal.
- Uncertainty associated with the ITC that was conducted to inform the relative efficacy of paclitaxel ± carboplatin, such as losing the power of randomisation in the THOR trial and population differences which are accounted for through the ATC-adjusted matching exercise. To assess the validity of the efficacy results produced by the ITC, an alternative secondary approach was considered using PLUTO data.
- The UK RW mUC study population had unknown FGFR status. To address this uncertainty, the company conducted a MAIC analysis that revealed no differences between the OS, PFS and responses between the chemotherapy arms of the THOR trial (vinflunine or docetaxel) and the EV301 trial (vinflunine, docetaxel, or paclitaxel).

EAG comment: The EAG broadly agrees with the company's assessment of the key areas of uncertainty. In addition to the uncertainty related to the relevant comparator for this appraisal, the EAG considers the choice of modelling paclitaxel ± carboplatin as a basket as a key area of uncertainty, as discussed in Section 4.2.4. Next to that, the EAG also considers the lack of PFS and TTD data for paclitaxel ± carboplatin from the UK RW mUC study (and the modelling assumptions related to that) to be a key area of uncertainty.

5. Cost effectiveness results

5.1 Company's cost effectiveness results

The revised economic model submitted by the company included the results (probabilistic [95% CI]) for erdafitinib compared to paclitaxel ± carboplatin, paclitaxel (PLUTO) and chemotherapy (THOR) as summarised in Table 5.1. Erdafitinib was more effective with incremental QALYs of 0.99 [0.52 to 1.54] compared to paclitaxel ± carboplatin, 0.63 [-0.02 to 1.24] compared to paclitaxel (PLUTO), and 0.68 [0.17 to 1.23] compared to chemotherapy (THOR). Erdafitinib was also more costly with additional costs of [redacted] compared to paclitaxel ± carboplatin, [redacted] compared to paclitaxel (PLUTO), and [redacted] compared to chemotherapy (THOR). This amounted to ICERs of £26,870, £36,854, and £37,826 compared to paclitaxel ± carboplatin, paclitaxel (PLUTO) and chemotherapy (THOR) respectively. With the applied 1.7x severity weight, the probability of erdafitinib being cost effective at a willingness-to-pay threshold of £30,000 per QALY gained was 67% versus paclitaxel ± carboplatin, 28% versus paclitaxel (PLUTO) and 23.1% versus chemotherapy (THOR). A summary of the company's fully incremental probabilistic results is reported in Table 5.2.

Table 5.1: Summary of the company pairwise probabilistic results

Treatment	Total costs	Total LYs	Total QALYs	Incr. cost	Incr. LYs	Incr. QALYs	ICER
Erdafitinib	[redacted]	1.67	[redacted]	-	-	-	-
Paclitaxel ± carboplatin (NCRAS)	[redacted]	0.74	0.87	[redacted]	0.93	[redacted]	£26,870
Paclitaxel (PLUTO)	[redacted]	1.07	1.22	[redacted]	0.60	[redacted]	£36,854
Chemotherapy (THOR)	[redacted]	1.05	1.18	[redacted]	0.62	[redacted]	£37,826

Based on the PSA tab in the updated CEM
CEM = cost effectiveness model; ICER = incremental cost-effectiveness ratio; LY = life year; NCRAS = National Cancer Registration and Analysis Service; NMB = net monetary benefit; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations

Table 5.2: Summary of the company fully incremental probabilistic results

Treatment	Total costs	Total LYs	Total QALYs	Incr. cost	Incr. LYs	Incr. QALYs	ICER
Paclitaxel ± carboplatin (NCRAS)	[redacted]	0.74	[redacted]	-	-	-	-
Paclitaxel (PLUTO)	[redacted]	1.05	1.18	[redacted]	0.31	[redacted]	£2,960
Chemotherapy (THOR)	[redacted]	1.07	1.22	-	-	-	Extendedly Dominated
Erdafitinib	[redacted]	1.67	[redacted]	[redacted]	0.62	[redacted]	£37,826

Based on the PSA tab in the updated CEM.
CEM = cost effectiveness model; ICER = incremental cost-effectiveness ratio; LY = life year; NCRAS = National Cancer Registration and Analysis Service; NMB = net monetary benefit; PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life year; THOR = trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations

Overall, erdafitinib is modelled in the company's revised economic model to affect QALYs by:

- Increased OS. Incremental QALYs in the PD health state were [redacted] compared to paclitaxel ± carboplatin (98% of total incremental QALYs, including 1.7x severity weight).

Overall, erdafitinib is modelled the company's revised economic model to affect costs by:

- Increased treatment costs (additional cost of [redacted] compared to paclitaxel ± carboplatin, 67% of the total incremental costs).
- Reduced administration costs (reduction of [redacted] compared to paclitaxel ± carboplatin, 19% of the total incremental costs).
- Increased resource-use costs (additional cost of [redacted] compared to paclitaxel ± carboplatin, 13% of the total incremental costs).

EAG comment: The main comments of the EAG relate to: a) the majority of LYs and QALYs for erdafitinib being gained in the PD health state, and b) the company's changes in their revised base-case analysis.

a) The EAG noted in the results breakdown of the company's revised base-case results that, contrary to what was observed in the LY and QALY gains for paclitaxel ± carboplatin, the majority of the LY gains (65% of the total LY gains) and QALY gains (62% of the total QALY gains) for erdafitinib were modelled to occur in the PD health state. The EAG, however, expected the majority of treatment benefits to occur in the PF health state, as patients on erdafitinib were treated until disease progression (or unacceptable toxicity). This could partially be explained by uncertainty in the extrapolated long-term OS as discussed by the EAG in comment c) of Section 4.2.6. However, the EAG noted in the company's response to clarification question B29 that the majority of LYs (58% of the total LY gains) and QALYs (54% of the total QALY gains) in the observed erdafitinib trial data were also gained in the PD health state (although the difference being smaller between the PF and PD health states). The EAG would like to see an explanation by the company of the mechanism by which the economic model generated these results for erdafitinib.
b) In response to the clarification letter, the company made changes to their initial base-case analysis and provided a revised base-case and updated economic model. These changes included corrections to the frequency of inpatient hospitalisations, inclusion of a blood test to determine phosphate levels, changing the drug cost interval of erdafitinib from 21 to 28 days and using a different approach to estimate PFS for paclitaxel ± carboplatin (Table 5.3).

Table 5.3: Summary of changes from the CS original base-case and the justification

Original base-case	Revised base-case	Justification
Frequency of inpatient hospitalisations was incorrectly given as two visits every month	Corrected to two every year to match the input table in the CS.	This was an error in the model that was fixed.
No blood tests to determine phosphate levels were included for patients receiving erdafitinib	A one-off blood test cost has been included in the model.	A single blood test is required on day 14 to determine serum phosphate concentration. Clarification questions B22 (b) and B25.
Erdafitinib drug cost was applied once every "treatment cycle", which was defined as 21 days based on the trial.	Erdafitinib drug cost is now applied once every "treatment cycle", which is defined as 28 days.	Clarification question B24.

Original base-case	Revised base-case	Justification
The ratio of the PFS to TTNT for erdafitinib was applied to the paclitaxel ± carboplatin TTNT extrapolation to derive a PFS extrapolation for paclitaxel ± carboplatin.	The PFS curve from Vaishampayan et al 2005[34] or paclitaxel ± carboplatin	Data from literature derived from patients with prior platinum treatment is plausible. Generalized gamma fit gave the best AIC/BIC, but it predicted a very long-tail. Log-logistic and log-normal fit well and are more reasonable, so a log-logistic was preferred to match the choice for erdafitinib.
AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; PFS = progression-free survival; TTNT = time to next treatment		

5.2 Company's sensitivity analyses

The company performed and presented the results of a deterministic sensitivity analyses (DSAs) as well as scenario analyses.

The DSA showed that the parameters that had the greatest effect on the ICER compared to paclitaxel ± carboplatin, were:

- The OS extrapolation of erdafitinib
- The TTD extrapolation of erdafitinib

Scenario analyses showed that the three most influential scenarios were:

- Assuming the THOR ITT arm as a comparator.
- The OS extrapolation of erdafitinib using the Gamma curve.
- The OS extrapolation of erdafitinib using the Gompertz curve.

EAG comment: The main concern of the EAG relates to excluding input parameters to inform the proportion of patients receiving subsequent treatments from the one-way DSAs.

The EAG noted from Table 44 in Appendix R of the CS that the input parameters to inform proportions of patients receiving various subsequent treatments were excluded from the one-way DSAs, and therefore requested justification and a scenario analysis for this in their clarification letter.[7] In their response, the company clarified that they omitted the proportions of patients receiving various subsequent treatments from the one-way DSAs as these were deemed not to be impactful due to the few patients that were expected to receive 3L or fourth line (4L) therapy (only 19 patients were on 4L treatment in the UK RWE study).[3, 27] In their revised economic model, the company updated the one-way DSAs to include input parameters that inform the proportion of patients receiving subsequent treatments. The updated results showed that he proportions of patients receiving atezolizumab after either erdafitinib or paclitaxel ± carboplatin were among the top 10 most influential parameters. Based on the updated results of the one-way DSAs, despite the relatively low percentage of patients receiving subsequent lines of treatment, the EAG considers the proportion of patients receiving subsequent atezolizumab to have a moderate impact on the cost effectiveness results. However, if these proportions are indeed similar between erdafitinib and paclitaxel ± carboplatin in line with how it was currently modelled by the company, the impact on the cost effectiveness results is negligible.

5.3 Model validation and face validity check

Model validation efforts reported by the company in the CS included internal and external validation, and validation based on UK clinician input. In the remaining part of this Section, the validation efforts performed on the model, as presented by the company, are categorised according to the types of validation used in the Assessment of the Validation Status of Health-Economic (AdViSHE) decision models tool[52].

5.3.1 Validation of the conceptual model

5.3.1.1 Face validity testing (conceptual model)

An advisory board was held to seek for clinical expert opinion during the development of the CEM. Objectives of the advisory board were:

- To perform a critical analysis of the company's UK RW mUC study to identify relevant compactors to be used in the CEM
- Review healthcare resource utilisation cost components of the model
- Record consensus estimates of long-term OS projections for patients with mUC on erdafitinib, BSC, and chemotherapy in mUC

5.3.1.2 Cross-validity testing (conceptual model)

The company's economic model was compared to the economic models of TA's 525, 530, 692, 739 and 788 in response to clarification question B33, including comparisons of the model structure and assumptions, input parameters (clinical effectiveness, health state utilities and resource use and costs inputs), and outcomes (costs, LYs and QALYs).[36, 37, 39, 40, 53]

5.3.2 Input data validation

5.3.2.1 Face validity testing (input data)

The face validity of the economic model's input data was assessed by clinical experts in an advisory board, including validation of modelled patient baseline characteristics, relevant comparators, healthcare resource use (HCRU) utilisation, and genome testing.

5.3.2.2 Model fit testing

The statistical fits of the multivariable regression models that were used to estimate HSUVs in a company scenario analysis were assessed and reported in Table 38 of the CS.

5.3.3 Validation of the computerised model (technical verification)

5.3.3.1 External review

An economist not involved in developing the CEM reviewed the technical implementation of calculations and coding for correctness, reviewing and testing inputs and checking for implementation and/or logical inconsistencies. The validation process was documented via a checklist of modelling errors and corrections applied. The model's Visual Basic user defined functions were verified through double programming. For transparency, comments detailing the functions' internal processes were provided throughout the code.

5.3.3.2 Extreme value testing

Extreme value testing was performed in the economic model for mortality rates, discount rates, AE rates and discontinuation rates as reported in the TECH-VER checklist provided by the company in response to the clarification letter.

5.3.3.3 Testing of traces

Patient traces in the economic model were checked as reported in the TECH-VER checklist provided by the company in response to the clarification letter.

5.3.3.4 Unit testing

Not explicitly mentioned.

5.3.4 Operational validation (validation of model outcomes)

5.3.4.1 Face validity testing (model outcomes)

The face validity of the long-term OS extrapolations was assessed by the clinical experts in the advisory board.

5.3.4.2 Cross validation testing (model outcomes)

The company identified studies to which the economic model outcomes could be compared to from a review of previous cost effectiveness studies. TA525 (atezolizumab) was identified as the most appropriate appraisal.

5.3.4.2.1 Comparisons with other technology appraisals

The base-case results of TA525 reported 0.57 remaining QALYs in a population treated with taxanes (docetaxel and paclitaxel), compared to 0.47 remaining QALYs in the company's current model before weighting. The company explained that the estimated QALY difference can be attributed to several factors, including 1) patients in the current model had already received immunotherapy and were later in the treatment pathway, whereas the population in TA525 had only received chemotherapy without immunotherapy, and 2) the trial population in TA525 tends to be generally fitter and younger compared to patients in standard clinical practice.

5.3.4.2.2 Comparisons with other models (not necessarily technology appraisals)

Model outcomes (LYs, QALYs and costs) were compared to the economic models of TA's 525, 530, 692, 739 and 788 in response to clarification question B33.

5.3.4.3 Validation against outcomes using alternative input data

The company conducted various analyses to compare the modelled outcomes to the outcomes obtained when using alternative input data (e.g. using the PFS curve of the paclitaxel monotherapy arm of the PLUTO trial and the chemotherapy arm of the THOR trial to inform the paclitaxel ± carboplatin PFS curve.

5.3.4.4 Validation against empirical data

5.3.4.4.1 Comparison with empirical data used to develop the economic model (dependent validation)

In response to clarification question B34, the company stated that for the selection of the most suitable survival curves, survival probabilities derived from the parametric models were assessed by comparing them to the observed probabilities for OS, PFS, and TTD.[3, 27]

5.3.4.4.2 Comparison with empirical data not used to develop the economic model (independent validation)

In response to clarification question B34, the company stated that it was not feasible to validate the predictions of their economic model using an appropriate patient cohort due to the limited availability of data regarding clinical outcomes in patients with mUC who have undergone prior immunotherapy.[3,27] However, a comparative analysis with similar appraisals (TA525 and TA692) was conducted to provide valuable insights for comparison.[36, 37]

EAG comment: The main concerns of the EAG relate to: a) the validation of the computerised model, and b) cross validation of the economic model structure, input parameters and outcomes.

a) An economist not involved in developing the CEM reviewed the technical implementation of calculations and coding for correctness, reviewing and testing inputs and checking for implementation and/or logical inconsistencies. In response to clarification, the company provided the checklist of this. The EAG noted that not all components of the checklist were completed by the economist and the technical verification of the economic model therefore seems incomplete.
b) In response to clarification question B33, the company provided a cross validation of the economic model structure, input parameters, and outcomes against other relevant TAs. The EAG noted a substantial amount of missing information related to input parameters and outcomes in Tables 8, 9 and 10 of the clarification responses. However, the EAG understands that this is likely due to data unavailability and/or confidentiality.

6. Evidence Assessment Group's Additional Analyses

6.1 Exploratory and sensitivity analyses undertaken by the EAG

Table 6.1 summarises the key issues related to the cost effectiveness categorised according to the sources of uncertainty as defined by Grimm et al. 2020[54]:

- Transparency (e.g. lack of clarity in presentation, description, or justification)
- Methods (e.g. violation of best research practices, existing guidelines, or the reference case)
- Imprecision (e.g. particularly wide CIs, small sample sizes, or immaturity of data)
- Bias & indirectness (e.g. there is a mismatch between the decision problem and evidence used to inform it in terms of population, intervention/comparator and/or outcomes considered)
- Unavailability (e.g. lack of data or insight)

Identifying the source of uncertainty can help determine what course of action can be taken (i.e. whether additional clarifications, evidence and/or analyses might help to resolve the key issue). Moreover, Table 6.1 lists suggested alternative approaches, expected effects on the cost effectiveness, whether it is reflected in the EAG base-case as well as additional evidence or analyses that might help to resolve the key issues.

Based on all considerations in the preceding Sections of this EAG report, the EAG defined a new base-case. This base-case included multiple adjustments to the original base-case presented in the previous Sections. These adjustments made by the EAG form the EAG base-case and were subdivided into three categories (derived from Kaltenthaler et al 2016):

- Fixing errors (FE) (correcting the model where the company's submitted model was unequivocally wrong)
- Fixing violations (FV) (correcting the model where the EAG considered that the NICE reference case, scope or best practice had not been adhered to)
- Matters of judgement (MJ) (amending the model where the EAG considers that reasonable alternative assumptions are preferred)

6.1.1 EAG base-case

Adjustments made by the EAG, to derive the EAG base-case (using the CS base-case as starting point) are listed below. Tables 6.2, 6.3 and 6.4 show how individual changes impact the results plus the combined effect of all changes simultaneously for erdafitinib versus the basket of paclitaxel ± carboplatin, paclitaxel monotherapy and paclitaxel + carboplatin respectively

6.1.1.1 Fixing errors

There were no errors identified by the EAG.

6.1.1.2 Fixing violations

1. Applying a stopping rule to paclitaxel monotherapy and paclitaxel ± carboplatin at 24 weeks (Section 4.2.4)
   The EAG, in line with the existing guidelines and other relevant TA's (i.e. TA530 and TA692), applied a stopping rule to paclitaxel monotherapy and paclitaxel ± carboplatin at 24 weeks.

6.1.1.3 Matters of judgement

2. Using TTNT of paclitaxel ± carboplatin from the UK RW mUC study as a proxy to inform PFS data for paclitaxel ± carboplatin (Section 4.2.6)
   Instead of the study of Vaishampayan et al. 2005, the EAG modelled paclitaxel ± carboplatin PFS based on the TTNT of paclitaxel ± carboplatin from the UK RW mUC study.
3. Estimating the PF and PD HSUVs based on a multivariable regression model (Section 4.2.8).
   Instead of estimating the PF and PD HSUVs separately without including additional covariates, the EAG estimated the PF and PD HSUVs covariates based on the company's best fitting multivariable regression model (i.e. model 1, including progression status and AEs).
4. Assuming equal HCRU between erdafitinib and paclitaxel ± carboplatin (Section 4.2.9)
   The EAG assumed HCRU pre and post progression to be equal between erdafitinib and paclitaxel ± carboplatin.

6.1.2 EAG exploratory scenario analyses

The EAG performed the following exploratory scenario analyses to explore the impact of alternative assumptions conditional on the EAG base-case.

6.1.2.1 Exploratory scenario analyses

5. Using the adjusted population where patients with missing ECOG PS and/or disease stage were omitted (Section 4.2.3).
   Instead of the worst-case approach assuming the worst possible value for missing disease stage and ECOG PS, the EAG explored using the adjusted population where patients with missing ECOG PS and/or disease stage were omitted.
6. Using PFS of paclitaxel monotherapy from PLUTO as a proxy to inform PFS data for paclitaxel ± carboplatin (Section 4.2.6).
   Instead of using TTNT of paclitaxel ± carboplatin from the UK RW mUC study, the EAG explored modelling paclitaxel ± carboplatin PFS based on the PFS of the paclitaxel monotherapy arm from PLUTO.
7. Using TTD of taxanes from TA525 as a proxy to inform TTD for paclitaxel ± carboplatin (Section 4.2.6).
   Instead of assuming TTD to be equal to PFS, the EAG explored informing TTD for paclitaxel ± carboplatin based on TTD of taxanes from TA525.

6.1.3 EAG subgroup analyses

No subgroup analyses were performed by the EAG.

Table 6.1: Overview of key issues related to the cost effectiveness (conditional on fixing errors highlighted in Section 5.1)

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
A worst-case scenario approach was used for dealing with missing data in the population adjustment, rather than using data imputation methods.	4.2.3	Methods	Alternative data imputation methods and a best-case scenario analysis for dealing with missing data in the ATC.	+/-	No	Alternative data imputation methods and a best-case scenario analysis for dealing with missing data in the ATC.
Paclitaxel ± carboplatin was implemented as a basket of paclitaxel monotherapy and paclitaxel + carboplatin, which may bias the overall effectiveness of the comparator and may not be aligned with UK clinical practice.	4.2.4	Methods, bias & indirectness	Results also presented for erdafitinib versus the individual comparators (i.e. paclitaxel monotherapy and paclitaxel + carboplatin).	+	Partly	A fully incremental analysis including all relevant comparators.
Paclitaxel monotherapy and paclitaxel + carboplatin are recommended to be given for a maximum of six treatment cycles for mUC in the UK. However, this stopping rule was not applied in the company's economic model.	4.2.4	Methods	An updated economic model and scenario analysis in which patients on paclitaxel ± carboplatin are treated up to a maximum of 6 cycles.	+	Yes	N/A
Lack of PFS and TTD data for paclitaxel ± carboplatin in the UK RW mUC study.	4.2.6	Unavailability, bias & indirectness	Use TTNT as a proxy to inform PFS for paclitaxel ± carboplatin and apply a hard stop for paclitaxel ± carboplatin after 24 weeks (i.e. TTD is zero from week 25 onwards).	+	No	Scenario analyses using the PFS of taxanes in TA525 and TA692 as a proxy for paclitaxel ± carboplatin PFS.

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
Issues related to the assessment of the best-fitting parametric survival curves.	4.2.6	Methods, bias & indirectness	Scenario analyses including the most pessimistic and optimistic parametric curves, jointly fitted parametric models, and spline-based models. Examine the validity of extrapolated outcomes based on external data.	+/-	Partly	Scenario analyses including the most pessimistic and optimistic parametric curves, and jointly fitted parametric models.
PF and PD HSUVs were estimated separately without including additional covariates, which may result in potentially biased HSUVs.	4.2.8	Methods	Estimating the PF and PD HSUVs within a single model, including additional relevant covariates.	+	Yes	N/A
Modelling different HCRU for erdafitinib and paclitaxel ± carboplatin based on expert opinion.	4.2.9	Bias & indirectness	Assuming equal HCRU for erdafitinib and paclitaxel ± carboplatin.	+	No	Providing additional evidence based on relevant data to justify differences in HCRU between erdafitinib and paclitaxel ± carboplatin.
Uncertainty in the modelled patient characteristics and treatment effectiveness of the comparators, which impact the estimated severity weight.	4.2.10	Bias & indirectness	Calculate the severity weight for each PSA iteration, and calculate the severity weight based on UK patient characteristics.	+ (based on UK patients from THOR).	No	Additional evidence and justification on which patient characteristics are reflective of UK clinical practice.
The majority of the LY and QALY gains for erdafitinib, which was given until disease progression, were acquired in the PD health state.	5.1	Transparency	Explanation of the mechanism by which the economic model generated these results for erdafitinib.	+/-	No	Explanation of the mechanism by which the economic model.generated these results for erdafitinib.

Key issue	Section	Source of uncertainty	Alternative approaches	Expected impact on ICER[a]	Resolved in EAG base-case[b]	Required additional evidence or analyses
[a] Likely conservative assumptions (of the intervention versus all comparators) are indicated by '-'; while '+/-' indicates that the bias introduced by the issue is unclear to the EAG and '+' indicates that the EAG believes this issue likely induces bias in favour of the intervention versus at least one comparator [b] Explored ATC = average treatment effect for the control; EAG = Evidence Assessment Group; FE = fixing errors; FV = fixing violations; HCRU = healthcare resource use; HSUVs = health state utility values; ICER = incremental cost-effectiveness ratio; LY = life year; MJ = matters of judgement; mUC = metastatic urothelial carcinoma; N/A = not applicable; PD = progressed disease; PF = progression free; PFS = progression-free survival; PSA = Patient Access Scheme; QALY = quality-adjusted life year; RW = real-world; THOR = Trial to investigate the efficacy of erdafitinib compared with chemotherapy in advanced urothelial cancer and selected FGFR gene aberrations; TA = Technology Appraisal; TTD = time to treatment discontinuation; TTNT = time to next treatment; UK = United Kingdom						

6.2 Impact on the ICER of additional clinical and economic analyses undertaken by the EAG

In Section 6.1 the EAG base-case was presented, which was based on various changes compared to the company base-case. Tables 6.2, 6.3 and 6.4 show how individual changes impact the results plus the combined effect of all changes simultaneously for erdafitinib versus the basket of paclitaxel ± carboplatin, paclitaxel monotherapy and paclitaxel + carboplatin respectively. The exploratory scenario analyses for erdafitinib versus the basket of paclitaxel ± carboplatin, paclitaxel monotherapy and paclitaxel + carboplatin are presented in Tables 6.5, 6.6 and 6.7 respectively. These are all conditional on the EAG base-case. The submitted model file contains technical details on the analyses performed by the EAG (e.g. the "EAG" sheet provides an overview of the cells that were altered for each adjustment).

Table 6.2: 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)
CS base-case							
Erdafitinib	[redacted]	1.660	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.856	[redacted]	0.927	[redacted]	26,487
Fixing violations (1- Stopping rule of 6 cycles (i.e. 24 weeks) to paclitaxel monotherapy and paclitaxel + carboplatin)							
Erdafitinib	[redacted]	1.660	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.856	[redacted]	0.927	[redacted]	30,657
Matter of judgment (2- TTNT of paclitaxel +carboplatin RW data for modelling of paclitaxel +carboplatin PFS)							
Erdafitinib	[redacted]	1.660	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.851	[redacted]	0.927	[redacted]	27,153
Matter of judgment (3- Multivariable regression model for estimation of health state utilities)							
Erdafitinib	[redacted]	1.660	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.829	[redacted]	0.927	[redacted]	28,683
Matter of judgment (4- Assuming equal HCRU between erdafitinib and comparators)							
Erdafitinib	[redacted]	1.660	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.856	[redacted]	0.927	[redacted]	29,255
Deterministic EAG base-case							
Erdafitinib	[redacted]	1.660	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.822	[redacted]	0.927	[redacted]	36,034
Probabilistic EAG base-case							
Erdafitinib	[redacted]	1.671	[redacted]				

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
Paclitaxel ± carboplatin	[redacted]	0.743	0.833	[redacted]	0.928	[redacted]	36,249

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; PAS = Patient Access Scheme; RW = real-world; TTNT = time to next treatment

Table 6.3: EAG base-case – erdafitinib versus paclitaxel monotherapy (PAS price, 1.7x severity modifier applied)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
CS base-case							
Erdafitinib	[redacted]	1.683	[redacted]				
Paclitaxel monotherapy	[redacted]	0.773	0.634	[redacted]	0.910	[redacted]	36,034
Fixing violations (1- Stopping rule of 6 cycles (i.e. 24 weeks) to paclitaxel monotherapy and paclitaxel + carboplatin)							
Erdafitinib	[redacted]	1.683	[redacted]				
Paclitaxel monotherapy	[redacted]	0.773	0.634	[redacted]	0.910	[redacted]	42,970
Matter of judgment (2- TTNT of paclitaxel +carboplatin RW data for modelling of paclitaxel +carboplatin PFS)							
Erdafitinib	[redacted]	1.683	[redacted]				
Paclitaxel monotherapy	[redacted]	0.773	0.634	[redacted]	1	[redacted]	35,912
Matter of judgment (3- Multivariable regression model for estimation of health state utilities)							
Erdafitinib	[redacted]	1.683	[redacted]				
Paclitaxel monotherapy	[redacted]	0.773	0.613	[redacted]	1	[redacted]	39,030
Matter of judgment (4- Assuming equal HCRU between erdafitinib and comparators)							
Erdafitinib	[redacted]	1.683	[redacted]				
Paclitaxel monotherapy	[redacted]	0.773	0.634	[redacted]	0.910	[redacted]	40,017
Deterministic EAG base-case							
Erdafitinib	[redacted]	1.683	[redacted]				
Paclitaxel monotherapy	[redacted]	0.773	0.613	[redacted]	0.910	[redacted]	50,221
Probabilistic EAG base-case							
Erdafitinib	[redacted]	1.694	[redacted]				
Paclitaxel monotherapy	[redacted]	0.786	0.624	[redacted]	0.908	[redacted]	50,581

CS = company submission; EAG = Evidence Assessment Group; HCRU = healthcare resource use; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; PAS = Patient Access Scheme; PFS = progression-free survival; QALY = quality-adjusted life year; RW = real-world; TTNT = time to next treatment

Table 6.4: EAG base-case – erdafitinib versus paclitaxel + carboplatin (PAS price, 1.7x severity modifier applied)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
CS base-case							
Erdafitinib	[redacted]	1.535	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.528	0.625	[redacted]	1.007	[redacted]	29,454
Fixing violations (1- Stopping rule of 6 cycles (i.e. 24 weeks) to paclitaxel monotherapy and paclitaxel + carboplatin)							
Erdafitinib	[redacted]	1.535	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.528	0.625	[redacted]	1.007	[redacted]	31,454
Matter of judgment (2- TTNT of paclitaxel +carboplatin RW data for modelling of paclitaxel +carboplatin PFS)							
Erdafitinib	[redacted]	1.535	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.528	0.611	[redacted]	1.007	[redacted]	30,864
Matter of judgment (3- Multivariable regression model for estimation of health state utilities)							
Erdafitinib	[redacted]	1.535	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.528	0.611	[redacted]	1.007	[redacted]	31,715
Matter of judgment (4- Assuming equal HCRU between erdafitinib and comparators)							
Erdafitinib	[redacted]	1.535	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.528	0.625	[redacted]	1.007	[redacted]	32,011
Deterministic EAG base-case							
Erdafitinib	[redacted]	1.535	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.528	0.591	[redacted]	1.007	[redacted]	36,771
Probabilistic EAG base-case							
Erdafitinib	[redacted]	1.547	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.570	0.630	[redacted]	0.976	[redacted]	37,765

CS = company submission; EAG = Evidence Assessment Group; HCRU = healthcare resource use; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; PAS = Patient Access Scheme; PFS = progression-free survival; QALY = quality-adjusted life year; RW = real-world; TTNT = time to next treatment

Table 6.5: Probabilistic scenario analyses - 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)
EAG base-case							
Erdafitinib	[redacted]	1.671	[redacted]				

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
Paclitaxel ± carboplatin	[redacted]	0.743	0.833	[redacted]	0.928	[redacted]	36,249
Scenario 1 (Adjusted population where patients with missing ECOG PS PF and/or stage were omitted)							
Erdafitinib	[redacted]	1.482	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.677	0.754	[redacted]	0.805	[redacted]	51,454
Scenario 2 (PFS of paclitaxel monotherapy from PLUTO to inform comparator PFS)							
Erdafitinib	[redacted]	1.671	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.743	0.830	[redacted]	0.928	[redacted]	35,946
Scenario 3 (TTD of paclitaxel + carboplatin modelled using TTD of taxanes from TA525)							
Erdafitinib	[redacted]	1.671	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.743	0.833	[redacted]	0.928	[redacted]	37,444

EAG = Evidence Assessment Group; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; PAS = Patient Access Scheme; PF = progression free; PFS = progression-free survival; QALY = quality-adjusted life year; TA = Technology Appraisal; TTD = time to treatment discontinuation

Table 6.6: Probabilistic scenario analyses – erdafitinib versus paclitaxel monotherapy (PAS price, 1.7x severity modifier applied).

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
EAG base-case							
Erdafitinib	[redacted]	1.694	[redacted]				
Paclitaxel monotherapy	[redacted]	0.786	0.624	[redacted]	0.908	[redacted]	50,581
Scenario 1 (Adjusted population where patients with missing ECOG PS PF and/or stage were omitted)							
Erdafitinib	[redacted]	1.490	[redacted]				
Paclitaxel monotherapy	[redacted]	0.754	0.594	[redacted]	0.736	[redacted]	73,615
Scenario 2 (PFS of paclitaxel monotherapy from PLUTO to inform comparator PFS)							
Erdafitinib	[redacted]	1.694	[redacted]				
Paclitaxel monotherapy	[redacted]	0.786	0.875	[redacted]	0.908	[redacted]	35,507
Scenario 3 (TTD of paclitaxel + carboplatin modelled using TTD of taxanes from TA525)							
Erdafitinib	[redacted]	1.694	[redacted]				
Paclitaxel monotherapy	[redacted]	0.786	0.624	[redacted]	0.908	[redacted]	53,090

EAG = Evidence Assessment Group; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; PAS = Patient Access

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
Scheme; PF = progression free; PFS = progression-free survival; QALY = quality-adjusted life year; TA = Technology Appraisal; TTD = time to treatment discontinuation							

Table 6.7: Probabilistic scenario analyses – erdafitinib versus paclitaxel + carboplatin (PAS price, 1.7x severity modifier applied).

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
EAG base-case							
Erdafitinib	[redacted]	1.547	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.570	0.630	[redacted]	0.976	[redacted]	37,765
Scenario 1 (Adjusted population where patients with missing ECOG PS PF and/or stage were omitted)							
Erdafitinib	This scenario could not be run probabilistic due to excel error occurring.						
Paclitaxel + carboplatin							
Scenario 2 (PFS of paclitaxel monotherapy from PLUTO to inform comparator PFS)							
Erdafitinib	[redacted]	1.547	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.570	0.640	[redacted]	0.976	[redacted]	£37,284
Scenario 3 (TTD of paclitaxel + carboplatin modelled using TTD of taxanes from TA525)							
Erdafitinib	[redacted]	1.547	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.570	0.630	[redacted]	0.976	[redacted]	£37,916
EAG = Evidence Assessment Group; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; PAS = Patient Access Scheme; PF = progression free; PFS = progression-free survival; QALY = quality-adjusted life year; TA = technology appraisal; TTD = time to treatment discontinuation							

6.3 EAG's preferred assumptions

The estimated EAG base-case ICERs (probabilistic), based on the EAG preferred assumptions highlighted in Section 5.1, were £35,249, £50,581, and £37,765 per QALY gained for erdafitinib versus the basket of paclitaxel ± carboplatin, paclitaxel monotherapy and paclitaxel + carboplatin respectively. For erdafitinib versus paclitaxel ± carboplatin, the probabilistic EAG base-case analyses indicated a cost effectiveness probability of 17% at a willingness-to-pay threshold of £30,000 per QALY gained. The most influential adjustments were applying the stopping rule of 6 cycles (i.e. 24 weeks) to paclitaxel monotherapy and paclitaxel + carboplatin, and assuming equal HRCU between erdafitinib and the comparators. The ICER increased most in the scenario analysis where patients with missing ECOG PS and/or stage were omitted from the population adjustment.

6.4 Conclusions of the cost effectiveness section

A single set of searches was run in January 2018 to identify relevant studies on cost effectiveness and cost/health care resource and subsequently updated in November 2021, March 2023 and April 2024.

The initial reporting of search methods in the CS and accompanying documents was unclear and contained conflicting, missing and inconsistent information. Whilst an amended appendix was provided, some confusion remained which may affect the reproducibility of the searches, however, those searches that were provided appear appropriate. A second set of searches to identify HRQoL data conducted in 2024 was reported in the CS, and while the strategies appeared appropriate, they only covered a limited time period from May 2023 to April 2024. The PRISMA flowcharts provided at clarification suggest that other searches were performed, but no additional strategies were provided. The EAG therefore remains unsure about how these were sourced and cannot provide a full critique of the appropriateness of the searches for this element of the submission.

The company's CEM complied with the NICE reference case. The most prominent issues highlighted by the EAG were: 1) the approach for dealing with missing data in the population adjustment, 2) modelling of a comparator basket, 3) the lack of a stopping rule for paclitaxel ± carboplatin, 4) lack of PFS and TTD data for paclitaxel ± carboplatin in the UK RW mUC study, 5) issues related to the assessment of the best-fitting parametric survival curves, 6) the approach for estimating HSUVs, 7) assumptions related to the modelling of HCRU, 8) uncertainty regarding which severity weight should be applied in the economic model, and 9) erdafitinib LYs and QALYs mainly gained in the PD health state.

Firstly, a worst-case approach was used to handle patients with missing disease stage or ECOG PS (i.e. assigning values 3-4 for stage and 1-2 for ECOG PS) in the population adjustment. This may lead to bias as it assumes missingness not at random. It is unclear to the EAG why data was deemed not missing at random and scenario analyses using data imputation methods (e.g., multiple imputation) should therefore be explored. Secondly, paclitaxel ± carboplatin was implemented as a basket of paclitaxel monotherapy and paclitaxel + carboplatin (3:1 ratio), which may bias the overall effectiveness of the comparator and may not be aligned with UK clinical practice. Thirdly, the recommended hard stop after a maximum of 6 treatment cycles for paclitaxel ± carboplatin was not applied in the economic model. Fourthly, there was no PFS and TTD data available for paclitaxel ± carboplatin in the UK RW mUC study. The company's alternative assumptions using the PFS from Vaishampayan et al. 2005 to estimate paclitaxel ± carboplatin PFS and assuming that paclitaxel ± carboplatin TTD is equal to PFS seem questionable by the EAG. Fifthly, there were issues regarding the process of selecting the most suitable parametric survival curves, including uncertainty regarding the long-term extrapolated outcomes due to low patient numbers in a substantial part of the observed data, the lack of exploring jointly fitted parametric survival models despite the lack of evidence that the PH assumption was violated, the poor fit of standard parametric models to the observed erdafitinib data, and the lack of assessing the validity of the extrapolated outcomes based on external data. Sixthly, the PF and PD HSUVs were estimated independently without including additional covariates, which may result in potentially biased HSUVs. Seventhly, different HCRU was modelled for erdafitinib and paclitaxel ± carboplatin (mainly outpatient visits). This was based on a single clinical expert comment during the advisory board, which the EAG deemed insufficient evidence to justify this assumption. Eighthly, there is uncertainty regarding which severity weight should be applied in the economic model. The company calculated the severity weight based on the adjusted THOR trial population characteristics, which deviate from the UK patient characteristics in THOR and clinical expert input during the advisory board. Additionally, the calculated severity weight is based on the total modelled QALYs of the comparator, which is particularly uncertain due to the lack of PFS data for paclitaxel ± carboplatin in the UK RW mUC study. Finally, the majority of the LY and QALY gains for erdafitinib were acquired in the PD health state. The EAG is unsure whether this is plausible, as patients on erdafitinib were treated until disease progression (or unacceptable toxicity).

The estimated EAG base-case ICERs (probabilistic), based on the EAG preferred assumptions highlighted in Section 5.1, were £35,249, £50,581, and £37,765per QALY gained for erdafitinib versus the basket of paclitaxel ± carboplatin, paclitaxel monotherapy and paclitaxel + carboplatin respectively. For erdafitinib versus paclitaxel ± carboplatin, the probabilistic EAG base-case analyses indicated a cost effectiveness probability of 17% at a willingness-to-pay threshold of £30,000 per QALY gained. The most influential adjustments were applying the stopping rule of 6 cycles (i.e. 24 weeks) to paclitaxel monotherapy and paclitaxel + carboplatin, and assuming equal HRCU between erdafitinib and the comparators. The ICER increased most in the scenario analysis where patients with missing ECOG PS and/or stage were omitted from the population adjustment.

There is large remaining uncertainty about the effectiveness and cost effectiveness of erdafitinib, of which the impact can be explored by conducting further analyses. This includes providing analyses using data imputation methods (e.g., multiple imputation) for dealing with missing data in the ATC, a fully incremental analysis including all relevant comparators, analyses using the PFS of taxanes in TA525 and TA692 as a proxy for paclitaxel ± carboplatin PFS, analyses selecting the most pessimistic and optimistic parametric survival curves for PFS, TTNT, and TTD, and analyses including jointly fitted parametric survival models. In addition, further evidence and justification could be provided regarding differences in HCRU between erdafitinib and paclitaxel ± carboplatin, regarding which patient characteristics are reflective of UK clinical practice, and regarding the mechanism by which the economic model generated the LY and QALY gains for erdafitinib. Therefore, it is unclear to the EAG whether the CS and the EAG report contain an unbiased ICER of erdafitinib compared with all relevant comparators.

7. References

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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)
CS base-case							
Erdafitinib	[redacted]	1.660	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.856	[redacted]	0.927	[redacted]	21,052
CS base-case probabilistic							
Erdafitinib	[redacted]	1.671	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.743	0.865	[redacted]	0.928	[redacted]	21,406
Deterministic EAG base-case							
Erdafitinib	[redacted]	1.660	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.733	0.822	[redacted]	0.927	[redacted]	30,194
Probabilistic EAG base-case							
Erdafitinib	[redacted]	1.671	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.743	0.833	[redacted]	0.928	[redacted]	£30,386

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; PAS = Patient Access Scheme; RW = real-world; TTNT = time to next treatment

Table 2. EAG base-case – erdafitinib versus paclitaxel monotherapy (PAS price, 1.2x severity modifier applied)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
CS base-case							
Erdafitinib	[redacted]	1.683	[redacted]				
Paclitaxel monotherapy	[redacted]	0.773	0.634	[redacted]	0.910	[redacted]	28,214
CS base-case probabilistic							
Erdafitinib	[redacted]	1.694	[redacted]				
Paclitaxel monotherapy	[redacted]	0.786	0.643	[redacted]	0.908	[redacted]	28,876
Deterministic EAG base-case							
Erdafitinib	[redacted]	1.683	[redacted]				
Paclitaxel monotherapy	[redacted]	0.773	0.613	[redacted]	0.910	[redacted]	41,740
Probabilistic EAG base-case							
Erdafitinib	[redacted]	1.694	[redacted]				
Paclitaxel monotherapy	[redacted]	0.786	0.624	[redacted]	0.908	[redacted]	42,061

CS = company submission; EAG = Evidence Assessment Group; HCRU = healthcare resource use; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; PAS = Patient Access Scheme; PFS = progression-free survival; QALY = quality-adjusted life year; RW = real-world; TTNT = time to next treatment

Table 3. EAG base-case – erdafitinib versus paclitaxel + carboplatin (PAS price, 1.7x severity modifier applied)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
CS base-case							
Erdafitinib	[redacted]	1.535	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.528	0.625	[redacted]	1.007	[redacted]	24,367
CS base-case probabilistic							
Erdafitinib	[redacted]	1.547	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.570	0.666	[redacted]	0.976	[redacted]	25,177
Deterministic EAG base-case							
Erdafitinib	[redacted]	1.535	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.528	0.591	[redacted]	1.007	[redacted]	31,398
Probabilistic EAG base-case							
Erdafitinib	[redacted]	1.547	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.570	0.630	[redacted]	0.976	[redacted]	32,233

CS = company submission; EAG = Evidence Assessment Group; HCRU = healthcare resource use; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; PAS = Patient Access Scheme; PFS = progression-free survival; QALY = quality-adjusted life year; RW = real-world; TTNT = time to next treatment

Table 4. Probabilistic scenario analyses - 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)
EAG base-case							
Erdafitinib	[redacted]	1.671	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.743	0.833	[redacted]	0.928	[redacted]	£30,386
Scenario 1 (Adjusted population where patients with missing ECOG PS PF and/or stage were omitted)							
Erdafitinib	[redacted]	1.482	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.677	0.754	[redacted]	0.805	[redacted]	43,032
Scenario 2 (PFS of paclitaxel monotherapy from PLUTO to inform comparator PFS)							
Erdafitinib	[redacted]	1.671	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.743	0.830	[redacted]	0.928	[redacted]	30,099
Scenario 3 (TTD of paclitaxel + carboplatin modelled using TTD of taxanes from TA525)							
Erdafitinib	[redacted]	1.671	[redacted]				
Paclitaxel ± carboplatin	[redacted]	0.743	0.833	[redacted]	0.928	[redacted]	31,581

EAG = Evidence Assessment Group; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; PAS = Patient Access Scheme; PF = progression free; PFS = progression-free survival; QALY = quality-adjusted life year; TA = Technology Appraisal; TTD = time to treatment discontinuation

Table 5. Probabilistic scenario analyses – erdafitinib versus paclitaxel monotherapy (PAS price, 1.2x severity modifier applied).

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
EAG base-case							
Erdafitinib	[redacted]	1.694	[redacted]				
Paclitaxel monotherapy	[redacted]	0.786	0.624	[redacted]	0.908	[redacted]	42,061
Scenario 1 (Adjusted population where patients with missing ECOG PS PF and/or stage were omitted)							
Erdafitinib	[redacted]	1.490	[redacted]				
Paclitaxel monotherapy	[redacted]	0.754	0.594	[redacted]	0.736	[redacted]	61,024
Scenario 2 (PFS of paclitaxel monotherapy from PLUTO to inform comparator PFS)							
Erdafitinib	[redacted]	1.694	[redacted]				
Paclitaxel monotherapy	[redacted]	0.786	0.875	[redacted]	0.908	[redacted]	29,551
Scenario 3 (TTD of paclitaxel + carboplatin modelled using TTD of taxanes from TA525)							
Erdafitinib	[redacted]	1.694	[redacted]				
Paclitaxel monotherapy	[redacted]	0.786	0.624	[redacted]	0.908	[redacted]	44,570

EAG = Evidence Assessment Group; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; PAS = Patient Access Scheme; PF = progression free; PFS = progression-free survival; QALY = quality-adjusted life year; TA = Technology Appraisal; TTD = time to treatment discontinuation

Table 6. Probabilistic scenario analyses – erdafitinib versus paclitaxel + carboplatin (PAS price, 1.7x severity modifier applied).

Technologies	Total costs (£)	Total LYs	Total QALYs	Incr. costs (£)	Incr. LYs	Incr. QALYs	ICER (£/QALY)
EAG base-case							
Erdafitinib	[redacted]	1.547	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.570	0.630	[redacted]	0.976	[redacted]	32,233
Scenario 1 (Adjusted population where patients with missing ECOG PS PF and/or stage were omitted)							
Erdafitinib	This scenario could not be run probabilistic due to excel error occurring.						
Paclitaxel + carboplatin							
Scenario 2 (PFS of paclitaxel monotherapy from PLUTO to inform comparator PFS)							
Erdafitinib	[redacted]	1.547	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.570	0.640	[redacted]	0.976	[redacted]	31,696
Scenario 3 (TTD of paclitaxel + carboplatin modelled using TTD of taxanes from TA525)							
Erdafitinib	[redacted]	1.547	[redacted]				
Paclitaxel + carboplatin	[redacted]	0.570	0.630	[redacted]	0.976	[redacted]	32,384

EAG = Evidence Assessment Group; ECOG PS = Eastern Cooperative Oncology Group Performance Status; ICER = incremental cost-effectiveness ratio; Incr. = incremental; LY = life year; PAS = Patient Access Scheme; PF = progression free; PFS = progression-free survival; QALY = quality-adjusted life year; TA = technology appraisal; TTD = time to treatment discontinuation

ID1333 erdafitinib EAG report factual accuracy response by Johnson and Johnson

#	Page(s)	Section	Factual inaccuracy	Johnson & Johnson response	EAG response
1	11 and 28	1.1 and 2.3	Comparator selection: The company's focus on paclitaxel ± carboplatin omits other relevant comparators specified in the NICE final scope, potentially leading to an incomplete understanding of erdafitinib's relative efficacy and cost effectiveness within the full treatment landscape.	The statement by the EAG "The company's focus on paclitaxel ± carboplatin omits other relevant comparators specified in the NICE final scope, potentially leading to an incomplete understanding of erdafitinib's relative efficacy…" is not accurate as Johnson & Johnson included the comparators that are relevant for this population. The final scope from NICE is notably broad and included comparators that are inappropriate. In the absence of clear standard of care after PD-(L)1 treatment, Johnson & Johnson utilised clinical validation, NICE guidelines and UK RWE to identify the most suitable comparator. As outlined on pages 27 and 28 in the EAR report, the clinical expert consulted by the EAG supports the appropriate comparator established in the CS. The term "full treatment landscape" is vague and insufficiently defined. Johnson & Johnson believes that, through our CS and the justification we have provided, we have appropriately positioned erdafitinib against the most appropriate comparator, being paclitaxel ± carboplatin. Consequently, we maintain that this approach does not contribute to an incomplete understanding of relative effectiveness. In essence, Johnson & Johnson believes it is not informative to compare an intervention with treatments that are either not in use or deemed irrelevant.	Not a factual inaccuracy. The EAG report highlighted that the CS did not focus on all comparators in the NICE final scope but, as outlined on the left, presented the reasons provided by the company for these omissions.
2	11, 14, 43, 48 and 76	1.1, 2.1 and 3.2	Generalisability of trial population: The THOR trial population may not fully represent the UK patient population, with underrepresentation	Johnson & Johnson would like to split the key issue from the EAG into two topics, both of which we think are factually inaccurate. **Underrepresentation of certain ethnic groups** The lower incidence of advanced urothelial carcinoma with FGFR alterations in minority racial and ethnic populations significantly contributed to the observed underrepresentation of these groups in THOR (CSR, Table 63, page 128). The underrepresentation of certain ethnic groups is also an accurate reflection of the	The information provided helps addressing this issue to some degree, i.e., the EAG considers these aspects to be

#	Page(s)	Section	Factual inaccuracy	Johnson & Johnson response	EAG response
			of certain ethnic groups and patients with poorer PS. This could raise concerns about the applicability of the trial results to the NHS population.	real UK population. The low incidence rate of mUC in non-White minority ethnic populations compared with the corresponding White group has been confirmed by age-standardised incidence rates in England. The majority of bladder cancer cases occur in white patients with only 0.7% of bladder cancer cases occurring in black patients. The THOR trial included 0% and 0.8% of black patients in the erdafitinib and chemotherapy arms respectively, an accurate representation (https://www.nature.com/articles/s41416-022-01718-5). **Underrepresentation of patients with poorer PS** Johnson & Johnson believe the statement regarding poorer ECOG PS is factually inaccurate. In the UK real-world cohort, [redacted] of the patients with reported ECOG PS scores had scores of 0 or 1. This percentage increased to [redacted] for patients with prior PD-(L)1 exposure, indicating that patients receiving immunotherapy may generally be fitter. To address concerns about missing ECOG scores, (56% of the sample) Johnson & Johnson have used a conservative worst-case imputation approach in our cost analysis. This method assumes poor PS for patients without ECOG scores and addresses the EAG's concerns regarding poor PS in the NHS population. This is confirmed by the largest UK study on real-world outcomes in mUC patients, where only 11.6% had an ECOG PS of 2, and fewer than 6 had a PS of 3. This recent population-based study in England showed that most patients receiving systemic therapy had a PS of 0 or 1. Patients with an ECOG PS >1 were up to 90% less likely to be treated than those with a PS of 0 ($P < 0.001$). The THOR trial reported 9.4% with ECOG PS >1, aligning closely with UK data (CSR, Table 10, page 48). Therefore, it is factually inaccurate to suggest that the THOR trial underrepresented patients with poorer PS. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7044411/, https://www.sciencedirect.com/science/article/pii/S1078143924005477#abs0002)	resolved for the ACM. However, it should be noted that key issue 3 included aspects not addressed in the comment by the company e.g., regarding the overrepresentation of Asians.
3	11, 51	1.1 and 3.2	Long-term effectiveness: The short median follow-	The median overall survival for metastatic or unresectable FGFR-positive urothelial cancer patients receiving second-line treatments is less than a year (references in the CS: Han et al. 2008; Kouno et al. 2007; Powles et al. 2018; Powles et al. 2021	Not a factual inaccuracy.

#	Page(s)	Section	Factual inaccuracy	Johnson & Johnson response	EAG response
			up (15.9 months) in the THOR trial raises uncertainty about the long-term effectiveness of erdafitinib, which could lead to overly optimistic cost effectiveness results.	and Rosenberg et al. 2016). Therefore, it is factually incorrect to describe the median duration of follow-up of 15.9 months in the THOR trial with the adjective "short" as the data should be considered as mature. This is a disease that progresses very quickly. In THOR, both arms reached median OS. In the erdafitinib arm, survival rate was 50% after a year and by 24 months, it reduced to 26% (CSR, Table 15, page 58). Moreover, long-term effectiveness was determined by elicitation results from clinical experts and not by the long follow-up data.	While the EAG acknowledges the argument regarding the progressive nature of the condition, the comments raised in Section 3.2.5 are not factual inaccurate.
4	15, 75	1.1, 1.4, 3.3 and 3.4	The EAG also recommends exploring methods to address the lack of FGFR status information in the RW data, such as using statistical techniques to adjust for potential differences in patient populations. However, the substantial reduction in sample size, reliance on retrospective data, and limitations in the matching	Johnson & Johnson acknowledges that the absence of FGFR information in the UK RWE data constitutes a limitation, as data availability is a common constraint associated with the use of RWE, particularly within UK RWE sources. We would like to rectify this factual inaccuracy as we do not interpret this lack of information as an indication of no FGFR alterations present. The MAIC analysis conducted between THOR and EV301 aimed to assess whether FGFR3 alterations could serve as treatment effect modifiers. The results indicated no differences in OS PFS and ORR for chemotherapy in both the untested population (EV301) and the FGFR-altered population (THOR). Currently, there is no evidence to support that FGFR3 alterations could act as treatment effect modifiers for chemotherapy. Statements such as "It is possible that FGFR3 alterations might be treatment effect modifying for only some forms of chemotherapy" is theoretical with no robust evidence base.	Not a factual inaccuracy. The EAG acknowledges the paucity of data, as evidenced by the use of MAIC as part of the CS. As highlighted by the company, exploring methods to address the lack of FGFR status indeed has certain limitation, however, extensive sensitivity analyses (suggested in key issue 5) could help

#	Page(s)	Section	Factual inaccuracy	Johnson & Johnson response	EAG response
			process highlight the need for caution when interpreting these findings, noting that: • Little difference does not imply no difference, and adjustment might mean insufficient power to detect differences. • Lack of information on FGFR status does not imply lack of FGFR alterations. • Little difference between the chemotherapy regimen mixes in THOR and EV-301 does not imply generalisability to only paclitaxel ± platinum or indeed any of the comparators from the scope or UK clinical practice not included in the ITC		understand the issue in more detail.

#	Page(s)	Section	Factual inaccuracy	Johnson & Johnson response	EAG response
			such as docetaxel or gemcitabine. It is possible that FGFR3 alterations might be treatment effect modifying for only some forms of chemotherapy. It also does not imply generalisability to atezolizumab.		
5	11 and 85	1.1 and 4.2.3	The EAG criticises that the CS did not incorporate data imputation methods for dealing with the missing data in the population adjustment.	It is inaccurate to state that the CS did not incorporate data imputation methods as both worst-case and best-case approaches are forms of imputation used to address missing data. The limitations stemming from the extent of missing data in the THOR and UK RW studies present challenges in applying these methods effectively. In this instance, a proportion of critical variables—27% for disease stage and 57% for ECOG PS—are missing. The missingness complicates any imputation process, including and especially multiple imputation methods. Given the lack of data and the risk of imputation methods not being able to predict reliable imputed data, Johnson & Johnson have chosen to take a conservative imputation approach and did a sensitivity analysis without multiple imputation of the data. In the worst-case imputation, we assume that patients with missing ECOG information are ECOG 2, this means that we will upweight the worst patients in THOR (those with ECOG 2) to match with the RWE data, therefore obtaining a very conservative estimate of the treatment effect between erdafitinib and paclitaxel ±	The EAG acknowledges that statements like "*the EAG would like to see a scenario analysis where the company handles the missing data using a data imputation method (e.g., multiple imputation)*" may suggest that the company's current worst-case approach is not an imputation method. The EAG therefore added minor

#	Page(s)	Section	Factual inaccuracy	Johnson & Johnson response	EAG response
				carboplatin. This means that any other imputation values would lead to a better treatment estimate (higher relative effect) for erdafitinib versus paclitaxel ± carboplatin. As a sensitivity analysis we did the opposite imputation, the best case which confirms our expectation that the relative treatment effect estimate is then more positive for erdafitinib.	changes to the EAG report.
6	11 and 87	1.1 and 4.2.4	Paclitaxel ± carboplatin was implemented as a basket of paclitaxel monotherapy and paclitaxel + carboplatin, which may bias the overall effectiveness of the comparator and may not be aligned with UK clinical practice.	Johnson & Johnson would like to state that UK clinical practice after PD-(L)1 treatment, established through the RW data and clinical expert opinion, is weekly paclitaxel monotherapy or 3-weekly paclitaxel in combination with carboplatin, and therefore the basket of paclitaxel ± carboplatin is aligned with UK clinical practice. The implementation of a basket of paclitaxel monotherapy and paclitaxel in combination with carboplatin was done to minimise uncertainty due to small sample sizes when treatments are split. Given the rarity of mUC, particularly in patients exposed to PD-(L)1 therapies, only a limited number of cases were documented through the NCRAS. Specifically, just 198 patients were recorded between 2016 and 2021. There were only 72 mUC patients who received treatments aligned with UK clinical practice, with 52 patients receiving paclitaxel monotherapy. The analysis of paclitaxel combined with carboplatin, only involves 18 patients, which could lead to significant bias and substantial uncertainty. The basket approach does not compromise the integrity of the comparison, as the median overall survival in mUC patients on paclitaxel monotherapy —comprising 75% of the patients—and on a combination of paclitaxel and carboplatin was similar. Consequently, the relative efficacy of erdafitinib observed in the paclitaxel monotherapy group was consistent with that of the combination of paclitaxel + carboplatin group. In addition, the methodology of comparing pooled treatments aligns with previous appraisals of pembrolizumab (TA692) and atezolizumab (TA525) in the context of	Not a factual inaccuracy.

#	Page(s)	Section	Factual inaccuracy	Johnson & Johnson response	EAG response
				previously treated mUC – docetaxel and paclitaxel were pooled as taxanes in both appraisals and were deemed appropriate.	
7	116	6.1.1.2	The EAG, in line with the existing guidelines and other relevant TA's (i.e. TA530 and TA692), applied a stopping rule to paclitaxel monotherapy and paclitaxel ± carboplatin at 24 weeks.	We acknowledge that we did not include the stopping rule in the CS, and we accept it. However, when we looked into the EAG model version, the stopping rule was not implemented correctly for paclitaxel + carboplatin administration costs, which resulted in a slight overestimation of those costs. Specifically, the rule should also be included in formulas in "column W" of the "Trace (PaclitaxelCarboplatin)" worksheet. This affects results of several EAG scenarios.	The EAG agrees and corrected the EAG model and EAG results.
8	94	4.2.6	Although the EAG appreciates the scenario analyses that were provided by the company in response to clarification to address the uncertainty surrounding the absence of PFS data for paclitaxel ± carboplatin in the UK RW mUC study, additional scenarios using the PFS of taxanes in TA525	We thank the EAG for their comment on the scenarios that we have provided. However, using PFS data from pooled taxane studies as a substitute for the PFS of paclitaxel ± carboplatin is inappropriate. The referenced data by the EAG originates from a distinct population that has not been previously exposed to PD-(L)1 inhibitors. Furthermore, the PFS data in question is a composite measure that includes both paclitaxel and docetaxel, with docetaxel not being a relevant comparator in this submission. Prior studies have also demonstrated a difference in PFS outcomes between paclitaxel and docetaxel. The suggested TA's are not suitable for decision-making regarding the population in this appraisal, and caution should be exercised when utilising this data.	Not a factual inaccuracy.

#	Page(s)	Section	Factual inaccuracy	Johnson & Johnson response	EAG response
			and TA692 would be informative.		
9	11 and 94-97	4.2.6	Issues related to the assessment of the best-fitting parametric survival curves.	Johnson & Johnson believe its inaccurate to state that there were issues related to the assessment of best fitting parametric curves. In the clarification questions, we included jointly fitted models which gave results similar to independent fits and hence were not included in the model. Johnson and Johnson explored the use of splines, which indeed had better (statistical) fits to the observed data but had long term extrapolations that were not fully aligned with clinical plausibility. Therefore Johnson & Johnson chose a more conservative approach with a lower long term OS extrapolation (lower tail) from the standard parametric fits for erdafitinib. However, we do partly agree with the EAG that a spline has a better statistical fit to the observed data. The parametric model choices were also influenced by the hazard functions and the long-term extrapolations derived through a semi-structured elicitation framework. In addition, the maturity of the data meant that most parametric models could describe the data well. Please also see a related response #15 below.	Not a factual inaccuracy.
10	101	4.2.8.3	Although the EAG acknowledges this potential limitation, the company's best fitting multivariable regression model included progression status and AEs, which are covariates that were tracked over time. Next to that, potential confounding effects	Johnson & Johnson would like to correct the inaccuracy in the rationale used by the EAG to use a multivariable regression model to derive utilities mainly to reduce bias in the estimates. It is unclear what confounding the EAG is specifically referring to, as confounding in general does not seem relevant to the purpose of HRQoL analysis in the context of economic modelling, where the goal is to simply generate utility estimates for each health state rather than establishing any causal effects. For example, the difference between utilities of progression-free and progressed disease health states should capture all differences between typical patients who are progression-free and who have progressed disease (who may differ in other respects), not just the independent effect of progression itself on an individual patient. Variables that may act as confounders when estimating the effect of progression (or other variables) on utility need to be adjusted for in that context. However, these same variables are not considered confounders when the objective	Not a factual inaccuracy.

#	Page(s)	Section	Factual inaccuracy	Johnson & Johnson response	EAG response
			may be missed by not considering additional covariates, which may result in potentially biased HSUVs.	is to obtain representative utility values for health states that are progression-free and progressed.	
11	106	4.2.9.9.3.	The EAG considers the company's evidence (a single expert opinion) insufficient to justify modelling different resource use for erdafitinib and paclitaxel ± carboplatin	Johnson & Johnson would like to correct that the company's evidence to justify modelling different resource use for erdafitinib and paclitaxel ± carboplatin was derived from a single advisor's opinion. The validation of HCRU was performed with 6 experts. Although we quote one clinician in the advisory board report (Steering Committee Report: Key Considerations for the Introduction of Erdafitinib in Locally Advanced/Metastatic Urothelial Cancer), the panel discussed and agreed to this point reaching consensus. The only difference in resource that we observed from the consensus in the advisory board, was the number of outpatient visits by patients on erdafitinib versus chemotherapy. This is logical and should not be controversial as it is driven by patients taking an oral medicine at home (taking oral erdafitinib) compared to those who must go and get their IV treatments at the hospital (for paclitaxel ± carboplatin patients).	Not a factual inaccuracy. The EAG's considerations are based on the evidence that was provided to the EAG.
12	11 and 108	1.1 and 4.2.10	However, although the EAG acknowledges that the patient numbers are low, the mean age and percentage females of the UK patients in THOR	Although Johnson & Johnson acknowledges that the EAG has used the 1.7x severity modifiers in the base case and all scenarios, we consider the EAGs conclusion that "calculating the severity weight based on UK population characteristics from THOR and from one clinical expert input results in a severity weight of x1.2" is factually inaccurate. The EAG does not have the clinical outcomes for the [redacted] UK patients in THOR. As such, it must be presumed that the EAG changed only the age and percentage	Not a factual inaccuracy.

#	Page(s)	Section	Factual inaccuracy	Johnson & Johnson response	EAG response
			study were higher than the overall THOR trial ([redacted]), which is also true for the mean starting age ([redacted]) suggested by an individual clinical expert during the advisory board. The EAG calculated the severity weight conditional on the EAG base-case assumptions, which in line with the company resulted in a severity weight of x1.7. However, calculating the severity weight based on UK population characteristics from THOR ([redacted]) and the clinical expert input ([redacted]) both resulted in a severity	females in these severity weight calculations. This is inappropriate and factually inaccurate as severity weight calculations should use consistent baseline characteristics and clinical outcomes. Further, J&J question the selection of the UK cohort of the THOR trial to inform baseline characteristics of the model when the largest UK-based study looking at real-world outcomes in patients with mUC is available showing median age is 66 years with 72.2% male patients. Similarly, a recent population-based study of 16,610 mUC patients in England reported the mean age of mUC treated patients as 67.5 years (https://www.sciencedirect.com/science/article/pii/S1078143924005477#abs0002).	

#	Page(s)	Section	Factual inaccuracy	Johnson & Johnson response	EAG response
			weight of x1.2. Based on these results and the PSA results (x1.7 and x1.2 severity weight in 51% and 49% of simulations respectively), the EAG considers it uncertain whether the x1.2 or x1.7 severity weight should be applied in the economic model.		
13	87	4.2.4.	Erdafitinib was modelled at an 8 mg dose once daily for 21 days, based to the anticipated MHRA and the THOR trial. In the THOR trial, however, 77% (n=104) of patients were up titrated to 9 mg of erdafitinib, while 17% of doses were skipped (based on a mean duration	Johnson & Johnson would like to clarify that the sentence "The company did correct for skipped doses in its economic model by applying an RDI of 98.8%." is incorrect because it does refer to the RDI of chemotherapy and not to erdafitinib. The proportion 17% of doses skipped was applied to erdafitinib, whereas the RDI of 98.8% was applied to chemotherapy, which is aligned with the RDI data for both treatments. It is also inaccurate to say that erdafitinib was modelled at an 8 mg dose and that up-titration was not incorporated. The dose of erdafitinib was not explicitly modelled. That is because different combinations of tablet strengths and pack sizes of erdafitinib that are expected to be used to achieve different daily doses of erdafitinib would result in the same cost per 28 days of therapy. Therefore up-titration (or other dose modifications) would not affect drug acquisition cost.	Regarding RDI: the EAG acknowledges the mix-up between the RDI of chemo-therapy and erdafitinib and corrected this in its EAG report. Regarding up-titration: not a factual inaccuracy.

#	Page(s)	Section	Factual inaccuracy	Johnson & Johnson response	EAG response
			of exposure of 206.8 days and a sample size of N=135). The company did correct for skipped doses in its economic model by applying an RDI of 98.8%. However, up titration to 9 mg seems not incorporated in the economic model, and the modelled erdafitinib dose (and potentially also treatment costs) is therefore likely to be underestimated.		
14	12, 20, 111	1.1, 1.3 and 5.1	The majority of the LY and QALY gains for erdafitinib, which was given until disease progression, were acquired in the PD health state	Johnson & Johnson would like to mention that the LY and QALY gains acquired in the PD health state are attributable to the mechanism of action of erdafitinib. Rapid uptake of erdafitinib into the lysosomal compartment of cells contributes to prolonged inhibition of FGFR signalling thus long-lasting anti-tumour activity. In addition, as highlighted in the response to the clarification questions, Johnson & Johnson highlighted that survival following progression may be related to deeper initial responses with erdafitinib treatment and the ability to tolerate (fewer residual toxicities after receiving erdafitinib) and respond to subsequent therapy due to differences in overall condition and residual toxicities following discontinuation of treatment, potentially allowing more patients who received erdafitinib to receive greater benefit from subsequent therapy.	Not a factual inaccuracy.

#	Page(s)	Section	Factual inaccuracy	Johnson & Johnson response	EAG response
15	96	4.2.6	Thirdly, the EAG noted that for erdafitinib, the standard parametric survival curves for the extrapolation of OS, PFS, TTD and TTNT did not seem to fit very well to the observed THOR data (underestimation of the observed data in the first few months and overestimation thereafter).	Johnson & Johnson would like to correct the factual inaccuracy that standard parametric curves did not fit very well to the observed THOR data. Visual assessment of model fit is inherently subjective, but Johnson & Johnson disagree that the standard survival curves "did not seem to fit very well", especially with regard to other outcomes other than OS. It is also inaccurate to describe the standard models as overestimating time to event at the end of observed period. This is especially clear in the case of OS: the log-logistic model selected for the base case predicted decreasing OS in the final months even as the decrease in Kaplan-Meier OS slowed and the curve reached a plateau. In the ATC population, the last Kaplan-Meier estimate of OS was 0.20, while OS predicted by the log-logistic model at the same time was only 0.08. The underestimation of OS by standard fits is further evident when they are compared with flexible (spline) fits, which usually fit observed data remarkably well. Indeed, spline fits captured the plateau in OS and hence predicted very long survival, which—while clinically implausible—was consistent with the observed trend.	Not a factual inaccuracy.
16	82	4.2.2	The main concerns of the EAG relate to: a) lack of a state transition model to verify the plausibility of the PSM extrapolations and b) use of 2017-2019 mortality risk data despite more recent mortality risk data being available.	The EAG are incorrect to state that “lack of a state transition model to verify the plausibility of the PSM extrapolations”. This is because without additional data sources or assumptions to inform transition probabilities, an STM would face the same data limitations as the PSM. Moreover, analysis of survival data for an STM would require discarding survival data of patients with unknown progression status after censoring for PFS. As there is no clear reason to prefer STM extrapolations over PSM ones, the former could not be used to verify the latter. The use of 2017-2019 was done deliberately to use data without the dilution of the impact of COVID-19 on mortality rates.	Not a factual inaccuracy.

NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Clinical expert statement

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

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Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

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 also

send a second version of your comments with that information redacted. See Health technology evaluations: interim methods and process guide for the proportionate approach to technology appraisals (section 3.2) for more information.

The deadline for your response is **5pm** on **Monday 18 November.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received, 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 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.

NICE National Institute for Health and Care Excellence

Part 1: Treating metastatic or unresectable FGFR-altered urothelial cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Robert Huddart
2. Name of organisation	Institute of Cancer Research and Royal Marsden Hospital
3. Job title or position	Professor of Urological Cancer and Hon Consultant Clinical Oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with metastatic or unresectable FGFR-altered urothelial cancer? ☐ A specialist in the clinical evidence base for metastatic or unresectable FGFR-altered urothelial cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☒ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for metastatic or unresectable FGFR-altered urothelial cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	The main aims of treatment are to prolong survival and improve/maintain quality of life
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A prolongation in Overall survival of 3 months and/or improvement/extension of quality life of 3 months
10. In your view, is there an unmet need for patients and healthcare professionals in metastatic or unresectable FGFR-altered urothelial cancer?	Yes, there is currently no limited satisfactory treatment options when treatment fails. (see below) I see this technology as the first personalised treatment in urothelial/bladder cancer.
11. How is metastatic or unresectable FGFR-altered urothelial cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.) • What impact would the technology have on the current pathway of care?	The current treatment algorithm (as per ESMO guidelines) of first line chemotherapy followed by adjuvant avelumab or second line atezoluzimab. A new alternative is Enfortumab vedotin/Pembroluzimab but this is not yet licensed/available in UK Apart from the occasional patient that can receive rechallenge chemotherapy, the only common option is third line taxane treatment with or without a carboplatin (usually without) which has toxicity including hair loss and has limited response and disease free survival. Antibody conjugate therapy (Enfortumab Vedotin) is licensed in UK in this space but is not NICE approved. ESMO treatment guidelines recommends use in this indication in suitable patients
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	This treatment will provide a new novel treatment option.

• How does healthcare resource use differ between the technology and current care? • In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	It should enable at least a subset of patients to improve survival and maintain quality of life. It will be the first oral treatment for metastatic bladder cancer so would minimise hospital visits for treatment and enable patients to perhaps spend time in the community whilst on active treatment. It will require some adjustment to practice 1. To find the sensitive population genomic screening will be required with 8-10 patients needing to be screened to find 1 suitable patient. Genomic screening has been only used to limited extent to date in urothelial cancers – in part as no NHS supported treatments are dependent on it – but its approval would necessitate a significant change in practice to ensure full benefit from the technology. There us a need for a companion diagnostic 2. There is defined and potentially toxicities not least of the skin, mucositis, lower bowel and ocular. These need careful management and can necessitate additional clinical reviews and supportive interventions 3. The management of toxicities may need increased involvement of dermatology and ophthalmic services that need consideration.
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care?	For those eligible for this treatment; Erdafitinib has a high response rate (around 40% compared to ~10% for chemotherapy) It had better PFS (doubled from 2.7 with chemotherapy to 5.6 months for Erdafitinib) and improved overall survival

• Do you expect the technology to increase health-related quality of life more than current care?	by an average of 4 months compared to clinician choice chemotherapy in this space in a randomised controlled trial. I have personally seen patients outlook transformed by its use which was why I was pleased to support its development in clinical trials.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	It has only been tested in FGFR 2/3 mutant patients so not suitable for patients without mutations. It has been shown that should be used after immunotherapy
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	It is difficult to say – it is probably easier to administer but Clinicians will need to get used to genomic screening (though this ahas been achieved successfully in similar patient groups like lung cancer). The side effect profile is different, more Skin. GI tract and ocular toxicity but akin to other Tyrosine Kinase inhibitors such as used in renal cancer so many clinicians will be familiar with these.
16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	I think the standard response rules would be used
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen	Oral admin is a plus- so less travel, time away from family and ability to work which may be difficult to capture Improved PFS/OS I would assume would be captured by QALY calcualtions

may be more easily administered (such as an oral tablet or home treatment) than current standard of care	
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	This is first targeted, personalised treatment in urothelial cancer so represents a major break through in this area. Potentially valuable for those not suitable for standard chemotherapy or those unable to receive immunotherapy (due to eg autoimmune disease or not eligible to receive due to lack of PDL1 expression)
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	See above Skin and Oral toxicity especially can have detrimental QoL impact but should be minimised by careful management with dose reductions and treatment breaks.
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting? • What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Yes In main trial patients had to have had immunotherapy and most had received previous chemotherapy (though wasn't entry criteria) Consideration needs to be given as above to those who cant receive immunotherapy and/or chemotherapy
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	no
22. How do data on real-world experience compare with the trial data?	I have limited experience outside trials but data seems reasonably consistent

23. NICE considers whether there are any equalities issues at each stage of an evaluation. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this evaluation could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation • lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	Not specifically Care should be taken to not discriminate in guidance against older people or less fit who may not be eligible for other treatments. There is little evidence if at all that previous treatment effects response to this technology. Efficacy seems similar whatever the prior treatment.

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

This is a novel targeted treatment in a population with unmet need

Technology has proven efficacy on overall survival in phase III trial

Will require more widespread tumour genomic screening than in current practice

Defined toxicities that could increase demand on supportive specialities (esp dermatology and ophthalmology)

Definitive step forward in patients with limited options and in particular in groups which are unable to access current standard treatments due co-morbiditties

Thank you for your time.

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NICE National Institute for Health and Care Excellence

Single Technology Appraisal

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

Patient expert statement

Thank you for agreeing to give us your views on this treatment and its possible use in the NHS.

Your comments are really valued. You can provide a unique perspective on conditions and their treatment that is not typically available from other sources

Information on completing this form

In part 1 we are asking you about living with metastatic or unresectable FGFR-altered urothelial cancer or caring for a patient with metastatic or unresectable FGFR-altered urothelial cancer. The text boxes will expand as you type.

In part 2 we are asking you to provide 5 summary sentences on the main points contained in this document.

Help with completing this form

If you have any questions or need help with completing this form please email the public involvement (PIP) team at pip@nice.org.uk (please include the ID number of your appraisal in any correspondence to the PIP team).

Please use this questionnaire with our hints and tips for patient experts. You can also refer to the Patient Organisation submission guide. **You do not have to answer every question** – they are prompts to guide you. There is also an opportunity to raise issues that are important to patients that you think have been missed and want to bring to the attention of the committee.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

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Your response should not be longer than 15 pages.

The deadline for your response is **5:00pm** on **Wednesday 27 November 2024.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

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

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Patient expert statement

NICE National Institute for Health and Care Excellence

Part 1: Living with this condition or caring for a patient with metastatic or unresectable FGFR-altered urothelial cancer

Table 1 About you, metastatic or unresectable FGFR-altered urothelial cancer, current treatments and equality

1. Your name	Jeannie Rigby
2. Are you (please tick all that apply)	☐ A patient with metastatic or unresectable FGFR-altered urothelial cancer? ☐ A patient with experience of the treatment being evaluated? ☐ A carer of a patient with metastatic or unresectable FGFR-altered urothelial cancer? ☒ A patient organisation employee or volunteer? ☐ Other (please specify):
3. Name of your nominating organisation	ACTION BLADDER CANCER UK
4. Has your nominating organisation provided a submission? (please tick all options that apply)	☐ No (please review all the questions and provide answers when possible) ☐ Yes, my nominating organisation has provided a submission ☐ I agree with it and **do not wish to** complete a patient expert statement ☒ Yes, I authored / was a contributor to my nominating organisations submission ☐ I agree with it and **do not wish to** complete this statement ☒ I agree with it and **will be** completing
5. How did you gather the information included in your statement? (please tick all that apply)	☐ I am drawing from personal experience ☒ I have other relevant knowledge or experience (for example, I am drawing on others' experiences). Please specify what other experience:

Patient expert statement

	Patient Benefit **This short statement is supplementary to the ABC UK Submission. The ABC UK Submission was written with patient input from the ABC UK patient focus group. This group has now provided further comments which they wish to be considered together with the ABC UK Submission.** ☐ I have completed part 2 of the statement **after attending** the expert engagement teleconference ☐ I have completed part 2 of the statement **but was not able to attend** the expert engagement teleconference ☐ I have not completed part 2 of the statement
6. What is your experience of living with metastatic or unresectable FGFR-altered urothelial cancer? **If you are a carer (for someone with metastatic or unresectable FGFR-altered urothelial cancer) please share your experience of caring for them**	
7a. What do you think of the current treatments and care available for metastatic or unresectable FGFR-altered urothelial cancer on the NHS? **7b. How do your views on these current treatments compare to those of other people that you may be aware of?**	
8. If there are disadvantages for patients of current NHS treatments for metastatic or unresectable FGFR-altered urothelial cancer (for example, how they are given or taken, side effects of treatment, and any others) please describe these	

9a. If there are advantages of erdafitinib over current treatments on the NHS please describe these. For example, the effect on your quality of life, your ability to continue work, education, self-care, and care for others? **9b. If you have stated more than one advantage, which one(s) do you consider to be the most important, and why?** **9c. Does erdafitinib help to overcome or address any of the listed disadvantages of current treatment that you have described in question 8? If so, please describe these**	**Patient Benefit** This short statement is supplementary to the ABC UK Submission. The ABC UK Submission was written with patient input from the ABC UK patient focus group. This group has now provided further thoughts which they wish to be considered together with the ABC UK Submission. **Patient impact of Testing** Patient concerns that this new treatment would require additional testing has been allayed by the knowledge that tissue samples required for testing for suitability for Erdafitinib can be taken from archived samples from earlier testing of tumours, or from the biopsy undertaken to confirm their diagnosis. Therefore no additional, or invasive, testing is required, and this testing could be undertaken as part of the treatment pathway. This also means no extra costs involved for the NHS. **Patient Impact of how treatment is administered** Erdafitinib is an oral drug which can be taken at home. This has significant advantages over the other available treatments. No drip is used, a patient does not have to endure frequent clinic appointments of long duration whilst sitting receiving drugs via a drip feed. Both these factors are of prime importance for quality of life. Currently, with chemotherapy, a significant amount of time is spent at hospital clinics receiving frequent treatment. This has a severe impact not only on the patient themselves, but also on their partner or the family member who is taking them to and from appointments and often remaining with them during treatment. More time can be spent at home, with their loved ones, or doing other things.

	Other than the impact of frequent attendance at hospital for treatment, chemotherapy can also have a significant impact on decline in the quality of life for a patient. ABC UK and our patients we consulted (this group includes patients who have undergone chemotherapy) feel strongly that this new therapy should be made widely available to patients and offer a real patient decision as to treatment, to provide a better quality of life for these patients, as well as improving outcomes.
10. If there are disadvantages of erdafitinib over current treatments on the NHS please describe these. For example, are there any risks with erdafitinib? If you are concerned about any potential side effects you have heard about, please describe them and explain why	
11. Are there any groups of patients who might benefit more from erdafitinib or any who may benefit less? If so, please describe them and explain why Consider, for example, if patients also have other health conditions (for example difficulties with mobility, dexterity or cognitive impairments) that affect the suitability of different treatments	
12. Are there any potential equality issues that should be taken into account when considering metastatic or unresectable FGFR-altered urothelial cancer and erdafitinib? Please explain if you think any groups of people with this condition are particularly disadvantage Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil	

partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here.	
13. Are there any other issues that you would like the committee to consider?	

Part 2: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Greatly improved quality of life for this patient group
- Improved outcomes for this patient group
- Patient choice of treatments (there is usually no choice in these circumstances)
- How treatment is administered would have less negative impact on patients than current alternative.
- Click or tap here to enter text.

Thank you for your time.

Your privacy

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