

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Final draft guidance

**Erdafitinib for treating unresectable or
metastatic urothelial cancer with FGFR3
alterations after a PD-1 or PD-L1 inhibitor**

1 Recommendation

- 1.1 Erdafitinib is recommended, within its marketing authorisation, as an option for treating unresectable or metastatic urothelial cancer with susceptible FGFR3 genetic alterations in adults after at least 1 line of treatment for unresectable or metastatic cancer that included a PD-1 or PD-L1 inhibitor. Erdafitinib is only recommended if the company provides it according to the commercial arrangement (see [section 2](#)).

Why the committee made this recommendation

Usual treatment for unresectable or metastatic urothelial cancer with FGFR3 genetic alterations after at least 1 line of treatment that included a PD-1 or PD-L1 inhibitor is paclitaxel with or without carboplatin, or best supportive care.

Erdafitinib has not been directly compared in a clinical trial with paclitaxel with or without carboplatin, or best supportive care. But indirect comparisons with each of these comparators suggest that erdafitinib increases how long people have before their cancer gets worse and how long they live.

When considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, erdafitinib is recommended.

2 Information about erdafitinib

Marketing authorisation indication

- 2.1 Erdafitinib (Balversa, Johnson & Johnson) is indicated for ‘the treatment of adult patients with unresectable or metastatic urothelial carcinoma (UC), harbouring susceptible FGFR3 genetic alterations who have previously received at least one line of therapy containing a PD-1 or PD-L1 inhibitor in the unresectable or metastatic treatment setting’.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics for erdafitinib](#).

Price

- 2.3 The list price for erdafitinib is £12,750 per 28 days (excluding VAT; company submission).
- 2.4 The company has a commercial arrangement (simple discount patient access scheme). This makes erdafitinib available to the NHS with a discount. The size of the discount is commercial in confidence.

3 Committee discussion

The [evaluation committee](#) considered evidence submitted by Johnson & Johnson, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

The condition

Unresectable or metastatic urothelial carcinoma

- 3.1 Urothelial carcinoma is cancer of the transitional cells that form the inner lining of the bladder, urethra, ureter, or renal pelvis, with most cases originating in the bladder. Urothelial cancer accounts for approximately 90% of all bladder cancers. Fibroblast growth factor receptors (FGFR) regulate cell growth, and alterations in these receptors can promote

uncontrolled growth of urothelial carcinoma tumours. Around 15% to 20% of people with advanced urothelial carcinoma have alterations in the FGFR3 gene. FGFR3 alterations are more common in a subtype of urothelial cancer called luminal urothelial cancer. The clinical experts explained that the luminal subtype may be slower growing but might also have reduced responses to chemotherapy and immunotherapy.

Symptoms of urothelial cancer include blood in the urine, problems urinating and pain. The patient experts explained that unresectable or metastatic urothelial cancer significantly affects quality of life. They explained that people with the condition are often shocked to learn about the poor prognosis and the limited treatment options that are available. The patient experts added that currently available treatment options require frequent hospital visits, which are very burdensome, and are associated with significant side effects. The patient experts explained that they experienced severe pain and mental exhaustion, linked to both the cancer and the current treatment options. They felt that reducing pain was a very important factor in treatments. The clinical and patient experts explained that erdafitinib (which targets the FGFR3 gene) would be the first targeted treatment available for unresectable or metastatic urothelial cancer. The committee concluded that unresectable or metastatic urothelial cancer is a debilitating condition with poor outcomes and has a substantial impact on quality of life.

Clinical management

Treatment pathway

- 3.2 The clinical experts explained that first-line treatment for unresectable or metastatic urothelial cancer could be either platinum-based chemotherapy (cisplatin or carboplatin) or, for people whose cancer is PD-L1 positive, atezolizumab. They explained that cisplatin was unsuitable for some people (for example, people with renal or hearing issues) and that these people might have carboplatin instead. If the disease did not progress after a course of treatment with platinum-based chemotherapy, then people could have maintenance treatment with avelumab. If the disease

did progress on treatment with platinum-based chemotherapy, then people could not have avelumab but could have atezolizumab as a second-line treatment. The clinical experts explained that if the cancer progressed during treatment with atezolizumab or avelumab then there would be no further treatment with either. They explained that once these treatment options had been exhausted, people might have paclitaxel with or without carboplatin or best supportive care (BSC). The clinical experts explained that many people at this point in the pathway are not well enough to have further chemotherapy and that even those who are well enough may not want to have chemotherapy because of its limited benefit, the need for frequent hospital visits and the risk of adverse events. The clinical experts thought that around 70% of people at this point in the pathway may be well enough to be offered chemotherapy but that only 30% to 50% of people would actually have it, with the rest having BSC. The committee discussed the treatment options available and noted that the patient experts had said that once there was disease progression after avelumab or atezolizumab there were very limited treatment options. It concluded that new and effective treatment options would be highly valued by people with unresectable or metastatic urothelial cancer.

Relevant comparators

- 3.3 At the first committee meeting, the company thought that paclitaxel with or without carboplatin was the most relevant comparator. The company did a retrospective real-world metastatic urothelial cancer (RW mUC) study using datasets from the National Cancer Registration and Analysis Service (NCRAS; see [section 3.7](#)). The study showed that for people who had a PD-1 or PD-L1 inhibitor (atezolizumab or avelumab) and then had further treatment, paclitaxel with or without carboplatin was the most frequently used treatment. The company did not consider docetaxel to be a relevant comparator because real-world evidence and clinical expert opinion suggest it is not frequently used in NHS clinical practice. The clinical experts explained that docetaxel and paclitaxel are both taxanes. They would expect both treatments to have similar efficacy, but there is limited evidence directly comparing them. The clinical experts explained

that paclitaxel is preferred in the NHS, because it is less likely than docetaxel to suppress blood cell production in the bone marrow (myelosuppressive). So, docetaxel is rarely used. The committee recalled that many people would choose to have BSC at this point in the treatment pathway. The clinical experts explained that some people who are currently only able to have BSC may be able to have erdafitinib because it is an oral tablet and has a more favourable toxicity profile. The company noted that the datasets used in its RW mUC study did not capture data for people having BSC. It also explained that it was unable to find any other sources of health outcome data for people who have had BSC, after having a PD-1 or PD-L1 inhibitor. This meant that a comparison of BSC against erdafitinib was difficult. The committee concluded that atezolizumab and docetaxel were not relevant comparators. It acknowledged the challenges of obtaining estimates of the health outcomes experienced by people having BSC among the population that erdafitinib would be offered to in NHS clinical practice. But, at the first committee meeting, it thought that BSC is an appropriate comparator given that a large proportion of people who are likely to be offered erdafitinib currently have BSC. So, the committee concluded that the relevant comparators were paclitaxel with or without carboplatin, and BSC and that these should be included in the cost-effectiveness modelling.

Clinical effectiveness

Clinical evidence for erdafitinib

- 3.4 The clinical trial evidence for erdafitinib came from THOR. This was an international, phase III, randomised, open-label trial. The trial compared erdafitinib with chemotherapy (vinflunine or docetaxel) in people with advanced urothelial cancer and FGFR2 or FGFR3 alterations whose condition had progressed on or after 1 or 2 prior treatments. The company's base case used data from a cohort in the study in which at least 1 of the prior treatments was a PD-1 or PD-L1 inhibitor. The company explained that this cohort was in line with the marketing-authorisation population for erdafitinib and the population that would be

offered erdafitinib in NHS clinical practice. The primary endpoint was overall survival (OS), which was statistically significantly higher in the erdafitinib arm (12.06 months) than in the chemotherapy arm (7.79 months, hazard ratio [HR] 0.64; 95% confidence interval [CI] 0.47 to 0.88). A statistically significant improvement was also observed for progression-free survival in the erdafitinib arm (5.55 months) compared with the chemotherapy arm (2.73 months, HR 0.58; 95% CI 0.44 to 0.78). The committee noted that the chemotherapy regimens used in the trial were not those used in NHS clinical practice (see [sections 3.2 and 3.3](#)). The committee concluded that erdafitinib was associated with statistically significant improvements in progression-free survival (PFS) and OS compared with docetaxel and vinflunine.

Age of the relevant population

- 3.5 The EAG noted that the median age of people in the erdafitinib arm of the model was 66 years, but the average age of people from the UK in the THOR trial was higher. (The THOR UK average age was considered confidential by the company and cannot be reported here.) The EAG noted that the starting age in the model would affect the results and the severity-modifier calculations (see [section 3.22](#)). The EAG noted that a clinical expert at the company's advisory board meeting had also suggested that the UK average patient age at diagnosis was higher. The company explained that the sample size of people from the UK in THOR was small. But it explained that the median age of the people in the RW mUC study who informed the indirect treatment comparison (ITC; see [section 3.8](#)) was 65.5 years, which was similar to the median age in the THOR trial (66 years). It also said that previous appraisals for metastatic urothelial cancer treatments have used data from studies in which the populations had similar median ages. At the first committee meeting, clinical experts explained that they expected people who might have erdafitinib in the NHS to be slightly older than in THOR and suggested an average age of 70 years. At the second committee meeting, the company shared evidence from [Mahmoudpour et al. \(2024\)](#), which showed that the mean age of people treated for metastatic urothelial cancer in England

was 67.5 years. It thought that the 70-year age estimate cited by clinical experts related to the entire metastatic urothelial cancer population. It thought that the population eligible for erdafitinib would be younger because it was people who had been deemed fit for systemic immunotherapy. The company also shared median overall-survival estimates for people below 65 years and over 65 years (14.0 and 10.9 months, respectively). It explained that these results show consistent efficacy in all age groups and thought that this limited the generalisability concerns. The NHS England Cancer Drugs Fund clinical lead (from here, Cancer Drugs Fund lead) shared data from NHS England that showed that the mean age of people having immunotherapy in England for this population was 69 to 71 years. The committee concluded that the model starting age should reflect clinical practice and be set at 70 years.

Generalisability of clinical evidence

- 3.6 A generalisability concern was that most people in the THOR study had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 1. The EAG explained that this may indicate a healthier population than would be expected in NHS clinical practice. The EAG noted that the company had attempted to address these concerns by reweighting the THOR trial to better match UK clinical practice (see [section 3.8](#)). But the EAG was still concerned about generalisability to NHS clinical practice, particularly because of age and ECOG status (see [sections 3.5 and 3.6](#)). The committee noted that clinical studies often recruit younger and healthier people than expected in NHS clinical practice. It also noted that the subgroup analysis for OS suggested erdafitinib may be less effective in people over the age of 65. So, it thought that there was a risk that the clinical effectiveness results might not be generalisable to the NHS clinical practice population. But it acknowledged comments from the company and clinical experts that the trial was not powered to assess treatment effectiveness within subgroups and that the confidence intervals for the age subgroups overlapped. The EAG explained that the subgroup analysis not being powered to assess treatment effect within subgroups could mean that real differences in

treatment effect were not detected. It said that overlapping confidence intervals did not preclude a discussion of a possible effect. The EAG thought that the available analysis from THOR may signal that treatment outcomes may not be uniform across all patient subgroups. So, at the first committee meeting, the committee concluded that it was plausible that age was a treatment-effect modifier and that there was some uncertainty around the generalisability of the THOR trial to NHS clinical practice. At the second committee meeting, the company explained that its base case uses worst-case imputation for ECOG to align the baseline characteristic with the UK population. The committee concluded that some uncertainty remained around the generalisability of the THOR trial to NHS clinical practice.

Real-world evidence study

- 3.7 The clinical evidence for paclitaxel with or without carboplatin came from the company's RW mUC retrospective cohort study. The company said that the study aimed to provide clarity on current treatment practices. The company used NCRAS datasets to obtain health outcomes data for a cohort of people with metastatic urothelial cancer in the UK that reflected the population that would have erdafitinib in NHS clinical practice. The RW mUC study included 72 people. Fifty-four of these people had paclitaxel monotherapy and 18 had paclitaxel with carboplatin. Paclitaxel with or without carboplatin as a group is referred to as a 'basket' comparator. PFS data was not available in the NCRAS datasets, so time-to-next treatment (TTNT) data was used in place of PFS data when comparing erdafitinib against paclitaxel with or without carboplatin in an ITC. The committee concluded that the RW mUC study was an appropriate data source to inform the clinical effectiveness of paclitaxel with or without carboplatin in NHS clinical practice.

Indirect treatment comparisons

- 3.8 Because the THOR study did not compare erdafitinib with a relevant comparator (see [section 3.3](#)), the company did an indirect comparison of erdafitinib against paclitaxel with or without carboplatin. The company did

ITCs of OS and TTNT using erdafitinib data from THOR and paclitaxel with or without carboplatin data from its RW mUC study for the:

- paclitaxel basket comparator (n=72; see [section 3.12](#))
- paclitaxel monotherapy comparator (n=54)
- paclitaxel plus carboplatin comparator (n=18).

The ITC used the inverse probability weighting (IPW) method, which adjusts a trial population (by reweighting people in the analysis) to better match a target population. The company used a form of IPW called average treatment effect for the control (ATC) in its base case. This reweighted the THOR trial population towards the RW mUC target population. It did this because the RW mUC study was thought to be more reflective of NHS clinical practice than THOR. Erdafitinib was associated with a statistically significant improvement in TTNT compared with the comparators:

- paclitaxel basket comparator: HR 0.53 (95% CI 0.37 to 0.76)
- paclitaxel monotherapy: HR 0.59 (95% CI 0.39 to 0.87)
- paclitaxel plus carboplatin: HR 0.34 (95% CI 0.18 to 0.64).

Erdafitinib was also associated with improved OS compared with the comparators:

- paclitaxel basket comparator: HR 0.35 (95% CI 0.23 to 0.52)
- paclitaxel monotherapy: HR 0.38 (95% CI 0.25 to 0.59)
- paclitaxel plus carboplatin: HR 0.22 (95% CI 0.11 to 0.44).

The EAG agreed that the ATC form of IPW was appropriate, and it also used this in its base case. The committee thought that the ATC approach to IPW was likely to give the estimates that were most reflective of NHS clinical practice. But it noted that there was very little difference in the HR for OS between the IPW-adjusted and unadjusted comparisons and thought that this was somewhat counterintuitive and

associated with uncertainty. It concluded that the company's base-case ITC suggested that erdafitinib had better TTNT and OS when compared with carboplatin with or without paclitaxel. It also concluded that it would consider this approach in its decision making (see [section 3.23](#)).

FGFR3 status

3.9 The EAG noted that the RW mUC study did not have any information on FGFR3 alteration status, so it was unclear how well this study matched the potential NHS clinical practice population. The company did a matching-adjusted indirect comparison (MAIC). The MAIC compared people who had:

- vinflunine and docetaxel in the THOR trial (which was FGFR3 specific), with
- similar chemotherapies in the EV-301 trial (which compared enfortumab vedotin with investigator-chosen chemotherapy [standard docetaxel, paclitaxel, or vinflunine] and was not specific for FGFR3).

The MAIC found no statistically significant differences in PFS or OS between the 2 populations. The company thought that this showed that paclitaxel with or without carboplatin would have similar efficacy regardless of FGFR3 status. The committee recalled the clinical experts' position on FGFR3 alteration status (see [section 3.1](#)) but thought that FGFR3 alteration status did not appear to be an effect modifier for chemotherapy. So, it concluded that the lack of FGFR3 status in the RW mUC study was unlikely to be a major limitation.

Missing data

3.10 At the first committee meeting, the company noted that disease-stage data was missing for 27% of people in the THOR study, while ECOG performance status data was missing for 57% of people in the UK RW mUC study. In its base case, the company chose to assume the worst possible value for the missing data. The company thought that this was a

conservative approach as it meant that the ITC put more weight on people in THOR who had characteristics of worse health. The EAG used the same approach in its base case. But it noted that the scenario in which people with missing data were removed resulted in a more conservative estimate of the effectiveness and cost effectiveness of erdafitinib. The EAG thought that scenario analysis using imputation methods such as multiple imputation or assuming the best possible value for the missing data would be informative. The company said that because data is only available for a small number of variables, estimates generated using multiple imputation might not be robust. The EAG thought that if the available data was unsuitable for multiple imputation, then this could also bring into question the reliability of the ITC that is the basis of the company's model (see [section 3.8](#)). The committee thought that the substantial amount of missing data brought uncertainty to the ITC results. At the first committee meeting, the committee concluded that it would like to see analyses using alternative imputation methods, such as multiple imputation or assuming the best possible value for the missing data, to explore this uncertainty. At the second committee meeting, the company shared results using multiple imputation to account for missing data. It highlighted that the approach was informative, but not suitable for decision making. This was because the adjusted OS for erdafitinib with multiple imputation was greater than the results from the THOR trial. It explained that it was highly improbable for adjusted survival data to be greater than data from a randomised controlled trial. The EAG agreed with the company but noted it would have liked to see analyses assuming the best possible value for the missing data. The committee thought that the company had explored some of the uncertainty around missing data, and that missing data did not appear to have a large effect on the cost-effectiveness estimates in this case. But, because only one approach had been considered, the robustness of these results was not known and the impact of missing data was still uncertain. The committee concluded that the company's approach that assumed the worst possible value for the missing data was appropriate for decision making.

Economic model

Company's modelling approach

3.11 The company presented a 3-state partitioned-survival model. The model consisted of health states for progression free, progressed disease and death. The company said that this model structure is the simplest possible structure that meets the needs of the decision problem and captures the benefits of erdafitinib and the comparator. The company highlighted that 3-state partitioned-survival models are frequently used in NICE's technology appraisals in oncology. The EAG noted that [NICE Decision Support Unit \(DSU\) TSD19](#) recommends that state-transition modelling is done alongside partitioned-survival modelling, to verify the plausibility of the extrapolations and explore key uncertainties. The EAG thought that, given the uncertainties in extrapolating the observed data from THOR (see [section 3.15](#)), state-transition modelling may have been informative. But the EAG also recognised that a state-transition modelling approach would need significant resources and time. The company said that one of the benefits of state-transition modelling is that it can more easily handle adjustments for subsequent treatment mixes. The company thought that this potential benefit was not relevant in this appraisal. Although the committee would have liked to see a more thorough exploration of structural uncertainty, it concluded that the model structure was acceptable for decision making.

Modelling of paclitaxel with or without carboplatin

3.12 The company assumed in the basket comparator that 75% of people have paclitaxel monotherapy and 25% of people have paclitaxel in combination with carboplatin. The company explained that the ratio of individual comparators was informed by the RW mUC study (see [section 3.7](#)) in which 3 times as many people had paclitaxel monotherapy as had paclitaxel in combination with carboplatin. It also explained that the ratio was supported by consensus from its UK-based advisory board meeting. At the first committee meeting, the clinical experts agreed that the ratio broadly represented the ratio of chemotherapy in NHS clinical practice.

The EAG thought that modelling the comparators as a basket could bias the overall effectiveness estimates. It noted that the hazard ratios for TTNT and OS for erdafitinib compared with paclitaxel monotherapy were somewhat higher (making erdafitinib less effective) than those for erdafitinib compared with paclitaxel in combination with carboplatin (see [section 3.8](#)). The EAG also noted that the observed median TTNT (6.51, 95% CI 3.68 to 7.03) and OS (6.90, 95% CI 5.13 to 7.69) for paclitaxel monotherapy was higher than for median TTNT (4.19, 95% CI 1.74 to 6.08) and OS (4.19, 95% CI 1.74 to 6.08) for paclitaxel in combination with carboplatin. The EAG felt this to be counterintuitive because it expected that adding a second treatment (carboplatin) would improve health outcomes compared with paclitaxel monotherapy alone. The company responded that there was overlap in confidence intervals between the various medians and that it did not consider that there was evidence of a difference. The EAG thought that, even with overlapping confidence intervals, it was plausible that there was a difference. The clinical experts said that the reasons for any difference were uncertain. But they thought that, usually, healthcare professionals are more likely to offer paclitaxel with carboplatin to fitter people and paclitaxel monotherapy to people who are less well. They explained that healthcare professionals might be more cautious about treating aggressive disease in less well patients (instead opting for BSC, see [section 3.2](#)). But they also explained that healthcare professionals might offer combination treatment, which would be considered more likely to result in a response, to people with more aggressive disease. This could then create a selection bias in which paclitaxel monotherapy was more likely to be given to people with less aggressive disease. The committee thought that this selection bias was a plausible explanation for the counterintuitive results. But it noted that there was no clinical evidence or additional details on the people included in the RW mUC study to support it. The committee also noted the small sample size of the RW mUC study. It thought that, while it was possible that the combination therapy had worse outcomes than the monotherapy because of selection bias, it was unclear if the numerical difference between the 2

treatments would occur in NHS clinical practice. A clinical expert thought that the results for the combination therapy were broadly in keeping with their experience, but that the results for the monotherapy appeared slightly high. They noted that they would not expect people having paclitaxel monotherapy for unresectable or metastatic urothelial cancer to live for 6 months. The committee thought that the results from the ITC were associated with uncertainty. But it noted that the proportions used in the basket appeared to reflect the breakdown of chemotherapy in NHS clinical practice and that modelling the comparators as a basket made use of all the available data. It concluded that it was appropriate to model paclitaxel with or without carboplatin as a basket.

Modelling of BSC

- 3.13 At the second committee meeting, the company provided cost-effectiveness estimates for BSC as a standalone comparator and as part of the basket comparator. It assumed 50% of the basket comparator was chemotherapy (with a 3-to-1 ratio of paclitaxel to carboplatin with paclitaxel) and 50% BSC. The company did not model any subsequent treatments for people having BSC after disease progression. The company was not aware of any sources of health outcome data for people who have had BSC, after having a PD-1 or PD-L1 inhibitor. So, it used clinical outcomes from the RW mUC study for people having paclitaxel and carboplatin as a proxy for BSC. The company did not use the costs of chemotherapy as a proxy for BSC. The company noted that this approach probably overestimated the treatment effect of BSC. The EAG agreed that this approach would probably lead to conservative cost-effectiveness estimates for erdafitinib. At the second committee meeting, the committee concluded that the company had provided acceptable cost-effectiveness estimates comparing erdafitinib with BSC. The committee said that this was still the case when BSC was included as part of the basket comparator that incorporated all the relevant comparators.

Stopping rule for paclitaxel with or without carboplatin

- 3.14 At the first committee meeting, the company's base case assumed people continue to have paclitaxel with or without carboplatin until disease progression. The EAG highlighted that, according to existing guidelines, clinical experts and the company's response to clarification, people in NHS clinical practice have paclitaxel with or without carboplatin for a maximum of 6 treatment cycles. The company acknowledged this. The EAG assumed in its base case that people have paclitaxel with or without carboplatin for up to a maximum of 6 cycles by setting time to treatment discontinuation (TTD) to zero after 25 weeks. The EAG explained that TTD was not captured in the RW mUC study. So, its base case assumes TTD is equal to PFS. But the EAG said that people may stop treatment for reasons other than disease progression, so this approach may still overestimate TTD. At the first committee meeting, the committee concluded that a 6-cycle stopping rule for paclitaxel with or without carboplatin should be applied in the modelling.

Erdafitinib OS extrapolation

- 3.15 In the company's base case, OS for erdafitinib was modelled by fitting a log-logistic curve to the data from the ITC. The EAG thought that median follow up in THOR was relatively short at 15.9 months. It explained that a short follow up introduces uncertainty about the long-term effectiveness of erdafitinib. The EAG noted that in the THOR study there were only a few people at risk for all outcomes at relatively early time points. It noted that this meant that a substantial part of the data that was used for extrapolating outcomes was based on a small number of people. It highlighted that in the erdafitinib OS data approximately 6% of people were at risk after 30 months. The EAG thought that fitting parametric curves to observed data including few people at risk for a substantial period adds uncertainty to the extrapolation. The EAG also thought that the standard parametric curves appeared to provide a poor fit to the observed data. The committee considered the estimates of OS used in the company's base case alongside the most optimistic and pessimistic estimates, generated using standard parametric models. The committee thought that when compared with the most optimistic and pessimistic

models the log-logistic curve provided an acceptable fit to the observed data and plausible estimates of long-term survival. The committee concluded that, although it was associated with uncertainty, the log-logistic distribution would be appropriate to extrapolate OS for erdafitinib if the ITC was used to model the relative effect of erdafitinib against the basket comparator.

PFS extrapolation for paclitaxel with or without carboplatin

- 3.16 In the company's base case, PFS for the comparators was estimated by fitting a log-logistic curve to data from [Vaishampayan et al. \(2005\)](#). The company said that median PFS in the Vaishampayan study was in line with median PFS observed in other studies. The EAG highlighted that Vaishampayan et al. is a relatively old study and none of the people in the study were from the UK. The EAG thought that the lack of PFS data for paclitaxel with or without carboplatin was a major limitation. The EAG preferred to use TTNT data from the RW mUC study as a proxy to inform the PFS estimates because the data was from people with metastatic urothelial cancer in NHS clinical practice. The committee thought that there was uncertainty in the PFS predictions. But it noted that the choice of either the company's or the EAG's preferred approach had very similar long-term predictions and only a small impact on the cost-effectiveness estimates. The committee concluded that, although uncertain, it preferred the EAG's approach to modelling PFS for paclitaxel with or without carboplatin and, by extension, BSC (see [section 3.13](#)).

Plausibility of modelled results

- 3.17 The company's base case predicted that, for people who have erdafitinib, the majority of life years (65%) and quality-adjusted life years (QALYs) (62%) gained would occur in the progressed-disease health state. The EAG thought that this was implausible given that people having erdafitinib do so until disease progression. The EAG explained that this observation could be because of uncertainty in the OS projections for erdafitinib (see [section 3.15](#)). But the EAG noted that the majority of the life years and QALYs gained in the observed erdafitinib trial data also occurred in the

progressed-disease health state. At the first committee meeting the company said that it believed that the estimates of the time spent in the progressed and progression-free health states in its base case were plausible. In particular, it believed that the time spent in the progression-free health state would be similar for both erdafitinib and the basket of paclitaxel with or without carboplatin. The clinical expert said that people who had treatment with erdafitinib would probably be healthier overall when their disease progresses than people who had chemotherapy and so might spend more time in the progressed-disease health state. They noted that people who had only chemotherapy might have a short time between disease progression and death. The clinical expert thought that this could explain the much higher benefits that erdafitinib accrues in the progressed-disease health state than chemotherapy. The committee acknowledged this and thought that it could offer some explanation as to why erdafitinib has greater gains in the progressed-disease health state. But it recalled that the median TTNT estimated using the ITC was higher for erdafitinib (8.02 months, 95% CI 6.47 to 9.00) than for the basket comparator (5.36 months, 95% CI 3.68 to 6.77). It also recalled that median PFS for erdafitinib was longer than for chemotherapy in the THOR study (see [section 3.4](#)). So, at the first committee meeting, the committee thought it implausible that the time spent in the progression-free health state would be very similar for both erdafitinib and the basket comparator. At the second committee meeting, the company thought that the lack of PFS data from the RW mUC study is an inherent limitation for a rare condition with high unmet need. It also noted that the MAIC indicates that the PFS for paclitaxel monotherapy is comparable to that of erdafitinib. Also, TTNT for erdafitinib and paclitaxel is more aligned with OS, so PFS could be overestimated. At the second committee meeting, the committee concluded that this issue added some uncertainty to the analyses.

Alternative modelling approaches

- 3.18 The committee reflected on the uncertainties in the ITC (see [section 3.10](#) and [section 3.12](#)) and the possibly implausible estimates of the time spent

in each health state (see [section 3.17](#)). It understood the company's reasons for not using data from THOR directly in the model. But the committee said that it would always want to see results using key trial data directly, because not presenting the results increases uncertainty. So, the committee concluded that, in addition to the company's current approach, it would like to see an analysis using data from THOR to capture the health benefits associated with both erdafitinib and chemotherapy. The committee recalled that the clinical experts considered docetaxel and paclitaxel to have similar efficacy (see [section 3.3](#)). Given this, the committee decided that it would like to see exploratory analyses using the results from THOR to directly inform the model alongside its preferred assumptions (see [section 3.23](#)). The committee noted that [section 4.6.16 of NICE's health technology evaluations manual](#) states that observational studies can be used to quantify the baseline risk of health outcomes. The manual also states that relative treatment effects seen in randomised trials may then be applied to data on the baseline risk of health outcomes. So, at the first committee meeting, the committee also decided that it would like to see another additional analysis applying the relative treatment effect from THOR to data on baseline risk of OS and TTNT from the RW mUC study. The company provided these analyses at the second committee meeting, and used the results from THOR to directly inform the model. But it considered the results inappropriate because of the further assumptions that were needed. Using the relative treatment effect from THOR assumes that TTD for erdafitinib is similar to TTD from THOR because of a lack of TTD data in the RW mUC study, which adds uncertainty. The company felt that using the results directly from THOR meant that the model would be comparing against docetaxel and vinflunine, which were not relevant comparators. The EAG agreed that the results were informative but should only be considered exploratory. At the second meeting, the committee noted that the additional analyses did not appear to have a large effect on the estimates of cost effectiveness and concluded that they reduced the uncertainty in the ITC to a limited extent.

Utility values

Source of utility values

3.19 The THOR trial collected health-related quality of life data. The company's base case included utility values estimated using a mixed models for repeated measures (MMRM) approach. This approach estimated utility values for the progression-free and progressed-disease health states in separate models. The company also provided analysis estimating utility values using a multivariable regression model, which estimates utility values for progression-free and progressed-disease health states in the same model. The company said that multivariable regression models including baseline characteristics may not be valid unless the distribution of those characteristics is tracked over time. The company explained that, because baseline characteristics may change over time, using initial baseline values in the model may bias the results. It also said that in the multivariable regression model approach health-related quality of life before disease progression would influence the estimated post-progression utilities. It thought that this was undesirable, especially when people with the condition spend longer with progressed disease than progression free. The company said that the utility values derived using the MMRM approach were very close to those used in [NICE's technology appraisal guidance on pembrolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable](#) (TA522). But the company considers the utility values to be confidential so they cannot be reported here. The EAG's base case used the utility values derived using the multivariable regression model. The EAG acknowledged that using initial baseline characteristics is a limitation. But it explained that the model did include progression status and adverse events, which were covariates that were tracked over time. It also explained that by not considering additional covariates potential confounding effects could be missed. The EAG agreed that the utility values estimated using the MMRM approach were close to those used in TA522. But it noted that the pre-progression utility value estimated using the multivariable regression model approach was even closer. The

committee considered both approaches and concluded that the results from the multivariable regression model as used in the EAG's base case were more appropriate for decision making.

Costs

Healthcare resource-use costs

3.20 In the company's base case, it was assumed that people who had erdafitinib would need less frequent outpatient visits than people who had paclitaxel with or without carboplatin. So, the progression-free per-cycle resource-use cost was assumed to be lower in the erdafitinib arm. The company said that the assumption that people who have erdafitinib would need less frequent outpatient visits was supported by clinical expert consensus at its advisory board meeting. The EAG preferred to assume the same progression-free per-cycle resource-use cost for both treatment arms. It thought that the evidence provided by the company was insufficient to justify a difference in resource-use assumptions. At the first committee meeting, clinical experts agreed with the company that people having erdafitinib would probably need less frequent outpatient visits, in part because erdafitinib is administered orally. The committee agreed that people having erdafitinib would need less frequent outpatient hospital visits. So, it concluded that the resource-use costs per cycle used in the company's base case were suitable for decision making.

Testing costs

3.21 Erdafitinib is indicated for a population with susceptible FGFR3 genetic alterations. The final scope for this appraisal specified that the economic modelling should include the costs associated with diagnostic testing for FGFR3 alterations in people with urothelial cancer who would not otherwise have been tested. The company's base case included a cost of £37.33 for adding a mutation test to a next-generation sequencing panel. The company divided that cost by the expected prevalence of FGFR3 alterations (16.6%) to give a total cost of £224.85 to identify a single person with FGFR3 mutation-positive unresectable or metastatic urothelial

cancer. This approach was based on previous appraisals, namely NICE's technology appraisal guidance on:

- [pemigatinib for treating relapsed or refractory advanced cholangiocarcinoma with FGFR2 fusion or rearrangement](#)
- [amivantamab for treating EGFR exon 20 insertion mutation-positive advanced non-small-cell lung cancer after platinum-based chemotherapy](#)
- [ivosidenib for treating advanced cholangiocarcinoma with an IDH1 R132 mutation after 1 or more systemic treatments.](#)

The Cancer Drugs Fund lead explained that the £37.33 in the company's base case was the cost of adding a mutation to a panel that was already being used in routine practice. The situation for erdafitinib was different because there are currently no targeted treatments (see [section 3.1](#)) and people with unresectable or metastatic urothelial cancer do not routinely have genomic testing. So, the full cost of implementing a genomic testing panel would be incurred. The Cancer Drugs Fund lead explained that the NHS England National Genomic Test Directory (NGTD) included a much higher cost (which is confidential and cannot be reported here) to cover the cost of implementing both a DNA and an RNA panel.

The committee noted that the previous appraisals the company based their calculations on were all related to conditions for which an existing multi-panel test was routine. It thought that the cost per test used in the company's base case did not reflect the cost to the NHS of implementing new FGFR3 testing for unresectable or metastatic urothelial cancer. It thought this because, currently, people with the condition do not routinely have a next-generation sequencing (NGS) test. At the first committee meeting, the committee concluded that the full cost of implementing a genomic testing panel for FGFR3 mutations should be applied in the modelling using the:

- cost provided by the Cancer Drugs Fund lead
- expected prevalence of FGFR3 alterations of 16.6%.

At the second committee meeting, the NHS Genomic Medicine Service (GMS) provided a submission to clarify information previously shared by the Cancer Drugs Fund lead. It explained that the cost preferred by the company relates to the cost of adding an FGFR target to a panel that was already in routine use. But this cost is inappropriate because people with metastatic urothelial cancer are not routinely tested for eligibility for other treatments. The company thought that FGFR3 could be tested for using polymerase chain reaction (PCR) testing, which is much cheaper. But the GSM outlined that the NGTD recommends 2 panels (DNA and RNA) for FGFR3 detection, each of which attracts a tariff. It explained that a marginal tariff rate (which is confidential and cannot be reported here), instead of a full tariff, could be used. This is to recognise that FGFR3 tests are already listed on the NGTD and available for use (but are not used in routine practice) and to recognise that testing costs might reduce in the future. The committee thought that testing costs could reduce in the future as NGS testing becomes more widespread and the technology improves, but it was unclear by how much. It also noted that testing costs could reduce if other treatments for urothelial cancer that require a targeted test become available. But the committee was not aware of any such treatments that could become available soon. So, the committee concluded that the marginal testing costs provided by the GSM at the second committee meeting were appropriate for decision making.

Severity

- 3.22 The committee considered the severity of the condition (the future health lost by people living with the condition and having standard care in the NHS). The committee may apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. The company provided absolute and proportional QALY shortfall

estimates in line with [NICE's health technology evaluations manual](#). The committee recalled its conclusion that modelling paclitaxel with or without comparators as a basket was its preferred approach (see [section 3.12](#)). But it also recalled that the basket comparator should also include BSC, which it currently does not. The committee considered that including BSC in the basket comparator would probably increase the estimates of the future health lost. The committee noted that in the company's and the EAG's base case the proportional QALY shortfall estimates qualified for a QALY weighting of 1.7. But the EAG explained that the QALY weighting was sensitive to the assumed age of the population. The EAG noted that the company's and the EAG's base case both assumed an average age of 67 years, based on the average age in the adjusted THOR population. The committee recalled that the clinical experts had explained that they would expect people having erdafitinib in NHS clinical practice to be older than in THOR. The clinical experts had suggested an average age of 70 years (see [section 3.5](#)). But the company said that the average age in the RW mUC population, who would have erdafitinib if it was recommended in NHS clinical practice, was lower at 65.5 years (see [section 3.5](#)). The committee noted that assuming an average age of 70 years results in a lower proportional QALY shortfall estimate, which qualifies for a lower QALY weight of 1.2. The company said that it was unreasonable to change the average age of the population without making corresponding changes to the data used to obtain the total QALYs expected for people having the basket comparator. The committee also heard from patient and clinical experts about how people with unresectable or metastatic urothelial cancer often have very few treatment options, a poor prognosis and a substantially decreased quality of life.

At the first committee meeting, the committee concluded that, although uncertain, the severity weight of 1.7 applied to the QALYs was likely to be appropriate. But it noted that it would reconsider the severity weighting once the additional comparator of BSC had been explored. At the second committee meeting, the company shared results that included BSC as a comparator, and the updated QALY shortfall estimates qualified for a

QALY weighting of 1.7. The committee was satisfied that the QALY shortfall estimates would still qualify for a severity weighting of 1.7 with the new model starting age (see section 3.5). The committee also recalled that it was plausible that the total QALYs for the basket comparator had been overestimated because of how BSC was modelled (see [section 3.13](#)). So, the committee confirmed its conclusion that the severity weight of 1.7 applied to the QALYs was appropriate.

Cost-effectiveness estimates

Committee's preferred assumptions

3.23 The committee recalled its preferences for the cost-effectiveness modelling, which was to use:

- both paclitaxel with or without carboplatin and BSC as relevant comparators (see [section 3.3](#))
- the company's 3-state partitioned-survival model (see [section 3.11](#))
- a basket comparator including paclitaxel with carboplatin, paclitaxel monotherapy and BSC (see [section 3.12](#))
- a ratio of 3 to 1 paclitaxel monotherapy to paclitaxel plus carboplatin within the chemotherapy component of the basket (see section 3.12)
- a 6-cycle stopping rule for paclitaxel with or without carboplatin (see [section 3.14](#))
- TTNT data from the RW mUC study as a proxy to inform the PFS for paclitaxel with or without carboplatin (see [section 3.16](#))
- the multivariable regression model as used in the EAG's base case to estimate utility values (see [section 3.19](#))
- lower progression-free per-cycle resource-use costs in the erdafitinib arm as used in the company's base case (see [section 3.20](#))
- the marginal tariff rate of testing costs provided by the GMS (see [section 3.21](#)).

At the second committee meeting, the committee recalled that when its

preferred assumptions were incorporated into the model, some uncertainties remained, including the:

- generalisability of the THOR trial data to NHS clinical practice (see [section 3.6](#))
- amount of time spent in the progression-free health state for each intervention (see [section 3.17](#)).

The company's and EAG's base cases produced a deterministic incremental cost-effectiveness ratio (ICER) of £28,182 for erdafitinib compared with the basket comparator. The committee's preferred base case (which reflected its preferred assumptions listed above) was the company's and EAG's base case with the GMS FGFR3 testing cost included (see section 3.21). The ICER that includes this testing cost was towards the upper end of the range that NICE normally considers a cost-effective use of NHS resources. (This ICER is confidential because the preferred testing cost is confidential and cannot be reported here.)

Acceptable ICER

- 3.24 [NICE's manual on health technology evaluations](#) notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects, including uncaptured health benefits. The committee noted the remaining uncertainties after the second committee meeting (see [section 3.23](#)). But the committee also noted the high level of unmet need experienced by people with unresectable or metastatic urothelial cancer and that erdafitinib would be the first targeted treatment available (see [section 3.1](#)). It also thought that treatment effectiveness for the BSC comparator may be overestimated (see [section 3.13](#)). Also, testing costs would probably reduce in the future as use becomes more widespread,

the technology improves or other drugs that require targeted testing are recommended (see [section 3.21](#)). So, the committee concluded that an acceptable ICER would be towards the upper end of the range that NICE considers a cost-effective use of NHS resources (£30,000 per QALY gained).

Other factors

Equality

- 3.25 The committee considered equality issues that had been raised during the appraisal process. Patient experts raised concerns that where a person lives might affect their ability to access diagnostic testing and erdafitinib. The committee noted that FGFR3 testing was available for all patients but was not currently used in clinical practice. It agreed that its recommendation applies to all people within the marketing authorisation and does not restrict access to treatment for some people over others. The committee noted that this was the case for other comments from the patient experts that women with unresectable or metastatic urothelial cancer experience worse outcomes than men. The patient experts said that the use of the severity modifier may disadvantage older people. But the committee agreed that it should use the methods and processes outlined in [NICE's health technology evaluations manual](#). These include assessing the severity of unresectable or metastatic urothelial cancer by considering both the associated absolute and proportional QALY shortfall. The use of both absolute and proportional QALY shortfall intends to capture different impacts of disease on people's quality of life. The committee also recalled its conclusion that, based on the current evidence and analyses, a severity weight of 1.7 applied to the QALYs was likely to be appropriate (see [section 3.22](#)). The committee concluded that no equality issues were raised that would have an impact on its decision making.

Uncaptured benefits

- 3.26 The committee considered whether there were any uncaptured benefits of erdafitinib. It did not identify additional benefits of erdafitinib not captured in the economic modelling. So, the committee concluded that all additional benefits of erdafitinib had already been taken into account.

Conclusion

Recommendation

- 3.27 The committee concluded that the most plausible ICER for erdafitinib was towards the upper end of the range NICE normally considers a cost-effective use of NHS resources. So, erdafitinib is recommended as an option for treating unresectable or metastatic urothelial cancer with susceptible FGFR3 genetic alterations in adults after at least 1 line of treatment for unresectable or metastatic cancer that included a PD-1 or PD-L1 inhibitor.

4 Implementation

- 4.1 Section 7 of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.
- 4.2 Chapter 2 of [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The

[NHS England Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.

- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.
- 4.4 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has unresectable or metastatic urothelial cancer with susceptible FGFR3 genetic alterations in adults after at least 1 line of treatment for unresectable or metastatic cancer that included a PD-1 or PD-L1 inhibitor and the healthcare professional responsible for their care thinks that erdafitinib is the right treatment, it should be available for use, in line with NICE’s recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee C](#).

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The [minutes of each evaluation committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Stephen O'Brien

Chair, technology appraisal committee C

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Ross Wilkinson and Owen Swales

Technical leads

Samuel Slayen

Technical adviser

Leena Issa

Project manager

Lorna Dunning

Associate director

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