NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Tivozanib for treating renal cell carcinoma [ID591]

The following documents are made available to the consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Eusapharma
   - Kidney Cancer Support Network

   The Department of Health – had no comments
   Pfizer – had no comments

3. **Comments on the Appraisal Consultation Document received through the NICE website**

4. **Evidence Review Group (BMJ Group) addendum**

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

Tivozanib for treating renal cell carcinoma

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	EUSA Pharma	**1.1 General Comments:** **Overall assessment:** On the balance of the evidence presented in the Appraisal Consultation Document, we feel that the provisional recommendation might be unsound and unsuitable as a basis for guidance to the National Health Service. We are rather disappointed and view the initial recommendation not to support tivozanib in the indication of advanced renal cell carcinoma as potentially unsound. The European Medicines Agency has approved tivozanib for use in this indication, ruling that tivozanib is both efficacious and well tolerated. Furthermore, both patients and clinical experts agree that there is a clear unmet medical need for a more acceptable treatment in this indication. We strongly believe that tivozanib offers an important alternative to pazopanib and sunitinib in the first-line treatment of advanced renal cell carcinoma due to its preferential adverse event profile. **On clinical evidence:** Given the challenges of limited data availability and suboptimal statistical methods for data extrapolation, we agree that the interpretation of existing clinical evidence is reasonable. The European Medicines Agency concluded a favourable risk-benefit profile for tivozanib; an increase of 2.8 months in median progression free survival for tivozanib vs an active comparator is a clinically relevant outcome for patients in England & Wales. The benefit-risk balance of tivozanib in the first line treatment of adult patients with advanced renal cell carcinoma, and for adult patients who are vascular endothelial growth factor receptor and mammalian target of rapamycin pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced renal cell carcinoma, is favourable.	Thank you for your comments. Taking into account the estimated cost effectiveness of tivozanib, the clinicians' view, and unmet need, the committee recommended tivozanib as an option for treating advanced renal cell carcinoma in adults who have had no previous treatment. The committee concluded that it had not seen any additional evidence of benefits that were not captured in the measurement of QALYs. For further details, please see section 3.22 of the FAD. The committee concluded that neither the company's nor the ERG's network meta-analysis results were plausible or robust. This meant that the difference in effectiveness between tivozanib and current treatments in the NHS (sunitinib and pazopanib) was unclear. Please see section 3.10 of the FAD.

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			We note, and agree with the Committee, that the study design of the TIVO-1 study and the choice of comparator make it challenging to fully ascertain the magnitude of benefit associated with tivozanib compared with current treatment options. However, we believe that tivozanib does have a similar effect on health outcomes as pazopanib and sunitinib. Indeed, we are pleased that the Committee agreed with our assertions regarding the similar efficacy between tivozanib and the comparators in terms of progression free survival. **On cost-effectiveness evidence**: The interpretation of the cost-effectiveness evidence in the provisional recommendations could be considered unreasonable, since it appears to have ignored the impact of the uncertainty around the key drivers of the models, namely network meta-analyses and quality adjusted life years, and how they were derived. The quality adjusted life year is the main driver of the cost-effective models in submissions from both the Evidence Review Group and the Company. The utility scores used in deriving the quality adjusted life years relate to the three health states in renal cell carcinoma and apply equally in both the Evidence Review Group and Company models. Technically, therefore, any quality adjusted life year advantage observed between the two models would relate only to the transition probabilities and time spent in each health states for the different models, as predicted by the results of the network meta-analyses used in the different models. The most impactful clinical outcome of the models is the extrapolated overall survival comparator results derived from the network meta-analyses conducted by the Evidence Review Group and the Company. As confirmed by the Committee, deriving these data provided the greatest source of uncertainty in both models. However, we have reasons to query the robustness of the Evidence Review Group network meta-analysis, as relates to the level of evidence of the studies used in their analyses. The Evidence Review Group network meta-analysis included some studies that we believe could be considered as inappropriate (small numbers, heterogeneous populations) and which we believe should have been excluded from the network meta-analysis. We are certain that the Committee would have been more inclined to support the Company's model and results if they had considered the integrity of the network meta-analyses provided as a source of data for the various models. We appeal	The committee noted the concerns raised about including the Cross-J-RCC trial in the evidence network. However, the committee was not presented with results based on the network without Cross-J-RCC. The committee concluded that the structure of the network and the trials included in it were appropriate. Please see section 3.8 of the FAD. The committee agreed that the results of the company and the ERG's network meta-analyses used to compare tivozanib with pazopanib and sunitinib lacked face validity, and both analyses differed substantially. For further details, please see section 3.10 of the FAD. The committee agreed that tivozanib is reasonably well tolerated, but that it was not clear whether it was better tolerated than pazopanib or sunitinib. Please see section 3.11 of the FAD.

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			to the Committee to consider this point carefully, as the safety of its judgement may be seen to hang on a technical issue that could be considered unsafe. **Adverse events and health related quality of life:** The provisional recommendation could not be considered fair, sound and suitable basis for NHS guidance for this population of patients who are not only suffering from renal cell carcinoma but also dealing with unpleasant and debilitating side effects from their treatment, resulting in a considerable impact on quality of life. The key differences between tivozanib and comparators are those that affect quality of life – notably, fatigue, diarrhoea and hand and foot syndrome. It appears that the significance of these may have been largely ignored in the appraisal. **Conclusion:** Working with the Committee to meet the needs of patients Given the high unmet need of patients in England & Wales, and the quality of life and tolerability profile benefits associated with tivozanib described in the data, we are willing to enter into cost arrangements to support patients who currently need an alternative, efficacious but better-tolerated treatment for renal cell carcinoma.	The committee considered analyses including the patient access scheme. Please see section 3.21 of the FAD.
2	Company	EUSA Pharma	*evidence does not clearly show that the side effects with tivozanib are better tolerated than those with sunitinib or pazopanib* Whilst there may be uncertainty in the evidence for efficacy, the evidence for side effects is clear. Data shows that adverse events which patients find most troublesome (fatigue, diarrhoea and hand and foot disease) and which impact most on their quality of life are less likely and less severe with tivozanib compared with currently used agents (sunitinib and pazopanib). In TIVO-1, rates of fatigue were 19% with tivozanib vs 16% with sorafenib, rates of diarrhoea were 23% vs 33% and rates of hand foot syndrome were 14% vs 54%. Most fatigue, diarrhoea and hand foot syndrome with tivozanib was mild to moderate; in contrast, 17% of sorafenib patients had hand foot syndrome of grade 3 or above [Motzer, 2013]. Rates of fatigue, diarrhoea and hand foot syndrome with pazopanib and sunitinib in the COMPARZ study were considerably higher – fatigue: 55% with pazopanib	Comment noted. The committee considered this data. The committee concluded that tivozanib is reasonably well tolerated, but that it was not clear whether it was better tolerated than pazopanib or sunitinib. Please see section 3.11 of the FAD.

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			vs 63% with sunitinib, diarrhoea: 63% vs 57%, and hand foot syndrome: 29% vs 50%. Diarrhoea, fatigue and hand foot syndrome were severe (grade 3 or above) in 9%, 10% and 6% of pazopanib patients and 8%, 17%, 11% of sunitinib patients, respectively [Motzer, 2013b]. Evidence comparing rates of treatment discontinuation, dose reduction and dose interruptions due to adverse events also suggest that tivozanib is more acceptable to patients than sunitinib or pazopanib. In TIVO-1, dose reductions and dose interruptions due to adverse events was 14% and 19% for tivozanib, respectively, vs 43% and 36% for sorafenib. Discontinuation rates to adverse events in the TIVO-1 study were 4% with tivozanib vs 5% with sorafenib. Rates of dose reduction, interruption and discontinuation due to adverse events in the COMPARZ study were considerably higher than tivozanib – dose reduction: 44% vs 51%, dose interruption: 44% vs 49% and discontinuation 24% vs 20%. The key differences between tivozanib and comparators are those that affect patient quality of life, notably fatigue, diarrhoea and hand and foot disease. The significance of these have been largely ignored in the appraisal. These impact of these clinically relevant side effects of treatment have been documented clearly in two publications which look at adverse events from the patients' perspective. Regardless of line of therapy, patients find the side effects of targeted therapy for renal cell carcinoma troublesome – in particular, severe fatigue/tiredness, diarrhoea and hand foot syndrome. Mohamed et al (2011) highlighted that although progression free survival was of most importance to patients in terms of improvement, severe fatigue/tiredness and diarrhoea were rated as the most troublesome tolerability effects of renal cell carcinoma treatment. Increasing progression free survival by 10 months was found to be almost as important as avoiding severe fatigue/tiredness. This is further supported by a publication by Wong et al (2012), which similarly highlighted that although progression free survival was the most important attribute, patients would be willing to forego a period of progression free survival to avoid adverse events.	The committee considered this data. The committee concluded that the company's and ERG's modelling already captured any benefits from differences in adherence. Please see section 3.17 of the FAD.

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			The authors presented benefit equivalents as measured in progression free survival. These represent the amount of benefit (months of progression free survival) that patients generally require to accept adverse events of varying severities. The authors also stated that these measures can be interpreted as the amount of benefit that patients would be willing to forego to avoid toxicities. progression free survival. Indeed, patients would be willing to forgo 4.4 months of progression free survival to avoid mild-to-moderate-severe fatigue, 3.5 months to avoid mild-to-moderate-severe stomach problems and 2.1 months to avoid mild-to-moderate-severe hand foot syndrome. Please see point 7 for further clarification. **References** Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol 2013a;31(30):3791-9. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013b;369(8):722-31. Mohamed AF, Hauber AB, Neary MP. Patient benefit-risk preferences for targeted agents in the treatment of renal cell carcinoma. Pharmacoeconomics 2011; 29(11): 977-88. Wong MK, Mohamed AF, Hauber AB, et al. Patients rank toxicity against progression free survival in second-line treatment of advanced renal cell carcinoma. J Med Econ 2012; 15(6): 1139-48.	
3	Company	EUSA Pharma	2. Typo 4weeks should be 4 weeks	Comment noted. This section has been updated in the FAD.
4	Company	EUSA Pharma	3.4 *The pivotal trial, TIVO-1, has limited relevance to clinical practice in England* We believe that it might be more accurate to state that "*The pivotal trial, TIVO-1, has **some** relevance to clinical practice in England*" This wording is used in the conclusion of this section and we believe better reflects the evidence discussed in this section.	Comment noted. The committee considered that TIVO-1, has limited generalisability to clinical practice in England. No changes to the FAD are needed.
5	Company	EUSA	3.7	Comment noted. No changes to the FAD are

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		Pharma	*patients in the sorafenib group were more likely to have more therapies than patients in the tivozanib group* We believe that it might be more accurate to state "*patients in the sorafenib group were more likely to have more **targeted** therapies than patients in the tivozanib group",* since the majority of patients in the sorafenib arm switched to tivozanib, a targeted therapy (see Table 13 of the Evidence Review Group report).	needed.
6	Company	EUSA Pharma	3.7 *and that it was the Company's preferred method of adjusting for crossover* We believe that it might be more accurate to explain the Company's rationale for using the Inverse Probability Censoring Weighting method. The following copy edit is proposed: "*that it was the Company's preferred method of adjusting for crossover **because it adjusts for the more favourable performance status observed in the sorafenib arm, which may have impacted on overall survival rates."***	Comment noted. No changes to the FAD are needed.
7	Company	EUSA Pharma	3.11 We believe that evidence comparing rates of treatment discontinuation, dose reduction and dose reductions due to adverse events have not been included in the Appraisal Consultation Document. The evidence, although indirect, suggests that tivozanib may be acceptable to patients than sunitinib or pazopanib and that patients receive a higher dose intensity of treatment. We note in our original submission (page 112) that: Low rates of treatment discontinuation due to adverse events were seen in the TIVO-1 study – 4% with tivozanib vs 5% with sorafenib. Patients randomised to tivozanib experienced fewer dose reductions due to adverse events (19% vs 36%) and dose interruptions due to adverse events (14% vs 43%) than those on sorafenib [Motzer, 2013a]. The discontinuation rate with tivozanib compares favourably with that for pazopanib (24% in COMPARZ vs sunitinib and 14% in the pivotal study vs placebo) and sunitinib (20% in COMPARZ and 19% in the pivotal trial vs interfereron). Dose reductions and interruptions were more common with	The committee considered this data. The committee concluded that the company's and ERG's modelling already captured any benefits from differences in adherence. Please see section 3.17 of the FAD.

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			pazopanib and sunitinib than with tivozanib, in the COMPARZ study dose reductions were 44% with pazopanib and 51% with sunitinib; dose interruptions were 44% and 49% respectively [Motzer, 2013b]. These data suggest that, by indirect comparison, tivozanib is more acceptable to patients than either sunitinib or pazopanib. Real world evidence from a retrospective medical record review of patients receiving sunitinib for first-line treatment of renal cell carcinoma across Europe (41% of patients from the United Kingdom) revealed that patients with reduced dose intensity (<70%) or treatment discontinuation had significantly reduced survival times, illustrating the importance of maintaining patients on the full dose [Porta, 2014]. The Appraisal Consultation Document reflects these differences and notes that dose intensity with tivozanib is improved over sunitinib and pazopanib (94% vs 86%). Therefore, we feel that Section 3.11 should also include a mention that the tolerability of tivozanib means that more patients are able to remain on the full dose of treatment compared with sunitinib and pazopanib. We suggest insertion of the following copy in 3.11 after treatments (line 4) ***"However, patients receiving tivozanib have fewer discontinuations, dose reductions and dose interruptions due to adverse events compared with the comparators, as reflected in higher dose intensity (94% vs 86%)."*** **References** Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol 2013a;31(30):3791-9. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013b;369(8):722-31. [data in appendix] Porta C, Levy A, Hawkins R, et al. Impact of adverse events, treatment modifications, and dose intensity on survival among patients with advanced renal cell carcinoma treated with first-line sunitinib: a medical chart review across ten centers in five European countries. Cancer Medicine 2014;3(6):1517-26. doi: 10.1002/cam4.302	

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8	Company	EUSA Pharma	3.19 *In the Evidence Review Group's base-case results, both pazopanib and sunitinib dominated tivozanib, that is, they were more effective and less costly.* On review of the Evidence Review Group report (Table 86) we note that tivozanib is marginally more costly than pazopanib (by [redacted]) but less costly than sunitinib (by [redacted]), therefore this statement is incorrect. These cost differences are minor compared with the total cost of treatment, with all three agents costing between [redacted] (pazopanib) [redacted] (sunitinib). It might be more appropriate to say ***In the Evidence Review Group's base-case results, both pazopanib and sunitinib were more effective than tivozanib, at a similar cost***.	Comment noted. This is not a factual inaccuracy, as the statement referred to the ERG results including all confidential comparator patient access scheme discounts, which are not included in the ERG report. The FAD has been updated to clarify that any analyses referred to include all confidential comparator patient access scheme discounts.
9	Company	EUSA Pharma	3.20 *This included consideration of a scenario in which the Evidence Review Group assumed that tivozanib, sunitinib and pazopanib were all equally effective in extending progression-free and overall survival. The Committee appreciated that this analysis was likely to be optimistic because the results from the network meta-analysis suggested that overall survival could be shorter with tivozanib compared with pazopanib and sunitinib (see section 3.10). The Committee noted that the results showed that tivozanib was more costly than pazopanib and sunitinib even when this optimistic approach was taken*. Table 88 of the Evidence Review Group report shows that in a scenario analysis assuming equal efficacy tivozanib is more expensive than sunitinib [redacted] and pazopanib [redacted]). We note that these cost differences are minor (particularly in the case of sunitinib). We believe it might be more appropriate to state ***slightly more costly*** which reflects the actual cost differences.	Comment noted. This is not a factual inaccuracy, as the statement referred to the ERG results including all confidential comparator patient access scheme discounts, which are not included in the ERG report. The FAD has been updated to clarify that any analyses referred to include all confidential comparator patient access scheme discounts.
1	Patient organisation	Kidney Cancer Support Network	Tivozanib is a potent, selective, long half-life inhibitor of all three vascular endothelial growth factor (VEGF) receptors (VEGF-1, VEGF-2 and VEGF-3) that is designed to optimise VEGF blockade while minimising side effects, resulting in a more tolerable treatment than is currently available for mRCC, especially in combination with other therapies. A tolerable side effect profile renders tivozanib a useful candidate for combination with	Thank you for your comments. The committee noted that patient groups consider tivozanib a more specific treatment than other treatments for metastatic renal cell carcinoma. However, the committee was not presented with evidence about the extent to which these benefits were

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			immunotherapy drugs, such as nivolumab, to further improve the overall survival of patients with recurrent or metastatic RCC.	realised in practice. The committee concluded that it had not seen any additional evidence of benefits that were not captured in the measurement of QALYs. Please see section 3.21 of the FAD.
2	Patient organisation	Kidney Cancer Support Network	Tivozanib has proven to be effective in extending progression free survival by nearly 3 months compared to sorafenib, with a tolerable side effect profile. Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including patient experience as well as overall survival, it is vital that innovative new drugs with different modes of action are made available to patients in order that they have the best care possible. If these drugs are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to the rest of Europe and North America.	The committee concluded that tivozanib increased progression-free survival compared with sorafenib. However, sorafenib is not used in the NHS, and compared with pazopanib and sunitinib which are used in the NHS, the committee concluded that the available evidence suggested that at best tivozanib may be similar to pazopanib and sunitinib. Please see sections 3.6 and 3.10 of the FAD.
3	Patient organisation	Kidney Cancer Support Network	Current first-line treatments offer an important, but sometimes short-lived period of stability, but not all patients respond to these treatments and most patients become refractory after a period of time. Biomarkers for the treatment of RCC are yet to be identified, and unfortunately clinicians are not able to predict which patients will respond to which drug. Therefore, selection of the most effective treatment for individual patients is accomplished by trial and error. Without a choice of treatment alternatives in the second-line and beyond, most patients will face disease progression, including worsening of symptoms, such as severe pain, fatigue and shortness-of-breath. Patients require choice in second- and third-line therapy to continue managing their disease, and to maintain quality of life.	Comment noted. Tivozanib was being considered within its marketing authorisation for untreated advanced renal cell carcinoma only. Please see section 3.2 of the FAD.
4	Patient organisation	Kidney Cancer Support Network	A number of clinical trials of tivozanib have been conducted or are ongoing in recurrent and/or metastatic RCC patients in the UK. The patients who participated in these trials did so in the expectation that their data would enable other patients in the UK to benefit from this drug. If the government and the pharmaceutical industry cannot agree a price that allows the use of tivozanib within the NHS, we question whether patients will continue to support future research by taking part in clinical trials. Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from new, innovative and clinically effective drugs if the precedent for these drugs is rejection by NICE.	Taking into account the estimated cost effectiveness of tivozanib, the clinicians' view, and unmet need, the committee recommended tivozanib as an option for treating advanced renal cell carcinoma in adults who have had no previous treatment.

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5	Patient organisation	Kidney Cancer Support Network	Current treatments have proven to shrink tumours and delay disease progression in some patients, but adding tivozanib as a choice in the second-line (and beyond) enables patients and clinicians to have individualised treatment plans to better control this disease and maintain a high quality of life. It could also address the massive unmet need for treatment options in the third-line and beyond.	Comment noted. Tivozanib was being considered within its marketing authorisation for untreated advanced renal cell carcinoma only. Please see section 3.2 of the FAD.
1	Web comment	Ipsen	NICE guidance recommends cabozantinib for use in both 2nd and 3rd line treatment. At present, this ACD appears to contradict not only that published guidance, but also the ACD for lenvatinib+everolimus (Sections 3.1 and 3.3). We suggest that the wording is amended to reflect the most up-to-date recommendations.	Comment noted. Section 3.3 of the FAD has been updated to remove the reference to subsequent treatments.

Tivozanib for treating renal cell carcinoma [ID591]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 4 September 2017 please upload to NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	EUSA Pharma
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

Tivozanib for treating renal cell carcinoma [ID591]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 4 September 2017 please upload to NICE DOCS

	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**1.1 General Comments:** **Overall assessment:** On the balance of the evidence presented in the Appraisal Consultation Document, we feel that the provisional recommendation might be unsound and unsuitable as a basis for guidance to the National Health Service. We are rather disappointed and view the initial recommendation not to support tivozanib in the indication of advanced renal cell carcinoma as potentially unsound. The European Medicines Agency has approved tivozanib for use in this indication, ruling that tivozanib is both efficacious and well tolerated. Furthermore, both patients and clinical experts agree that there is a clear unmet medical need for a more acceptable treatment in this indication. We strongly believe that tivozanib offers an important alternative to pazopanib and sunitinib in the first-line treatment of advanced renal cell carcinoma due to its preferential adverse event profile. **On clinical evidence:** Given the challenges of limited data availability and suboptimal statistical methods for data extrapolation, we agree that the interpretation of existing clinical evidence is reasonable. The European Medicines Agency concluded a favourable risk-benefit profile for tivozanib; an increase of 2.8 months in median progression free survival for tivozanib vs an active comparator is a clinically relevant outcome for patients in England & Wales. The benefit-risk balance of tivozanib in the first line treatment of adult patients with advanced renal cell carcinoma, and for adult patients who are vascular endothelial growth factor receptor and mammalian target of rapamycin pathway inhibitor-naïve following disease progression after one prior treatment with cytokine therapy for advanced renal cell carcinoma, is favourable. We note, and agree with the Committee, that the study design of the TIVO-1 study and the choice of comparator make it challenging to fully ascertain the magnitude of benefit associated with tivozanib compared with current treatment options. However, we believe that tivozanib does have a similar effect on health outcomes as pazopanib and sunitinib. Indeed, we are pleased that the Committee agreed with our assertions regarding the similar efficacy between tivozanib and the comparators in terms of progression free survival. **On cost-effectiveness evidence**: The interpretation of the cost-effectiveness evidence in the provisional recommendations could be considered unreasonable, since it appears to have ignored the impact of the uncertainty around the key drivers of the models, namely network meta-analyses and quality adjusted life years, and how they were derived. The quality adjusted life year is the main driver of the cost-effective models in submissions from both the Evidence Review Group and the Company. The utility scores used in deriving the quality adjusted life years relate to the three health states in renal cell carcinoma and apply equally in both the Evidence Review Group and Company models. Technically, therefore, any quality adjusted life year advantage observed between the two models would relate only to the transition probabilities and time spent in each health states for the different models, as predicted by the results of the network meta-analyses used in the different models. The most impactful clinical outcome of the models is the extrapolated overall survival comparator results derived from the network meta-analyses conducted by the Evidence Review Group and the Company. As confirmed by the Committee, deriving these data provided the greatest source of uncertainty in both models. However, we have reasons to query the robustness of the Evidence Review Group network meta-analysis, as relates to the level of evidence of the studies used in their analyses. The Evidence Review Group network meta-analysis included some studies that we believe could be considered as inappropriate (small numbers, heterogeneous populations) and which we

	believe should have been excluded from the network meta-analysis. We are certain that the Committee would have been more inclined to support the Company's model and results if they had considered the integrity of the network meta-analyses provided as a source of data for the various models. We appeal to the Committee to consider this point carefully, as the safety of its judgement may be seen to hang on a technical issue that could be considered unsafe. **Adverse events and health related quality of life:** The provisional recommendation could not be considered fair, sound and suitable basis for NHS guidance for this population of patients who are not only suffering from renal cell carcinoma but also dealing with unpleasant and debilitating side effects from their treatment, resulting in a considerable impact on quality of life. The key differences between tivozanib and comparators are those that affect quality of life – notably, fatigue, diarrhoea and hand and foot syndrome. It appears that the significance of these may have been largely ignored in the appraisal. **Conclusion:** Working with the Committee to meet the needs of patients Given the high unmet need of patients in England & Wales, and the quality of life and tolerability profile benefits associated with tivozanib described in the data, we are willing to enter into cost arrangements to support patients who currently need an alternative, efficacious but better-tolerated treatment for renal cell carcinoma.
2	*evidence does not clearly show that the side effects with tivozanib are better tolerated than those with sunitinib or pazopanib* Whilst there may be uncertainty in the evidence for efficacy, the evidence for side effects is clear. Data shows that adverse events which patients find most troublesome (fatigue, diarrhoea and hand and foot disease) and which impact most on their quality of life are less likely and less severe with tivozanib compared with currently used agents (sunitinib and pazopanib). In TIVO-1, rates of fatigue were 19% with tivozanib vs 16% with sorafenib, rates of diarrhoea were 23% vs 33% and rates of hand foot syndrome were 14% vs 54%. Most fatigue, diarrhoea and hand foot syndrome with tivozanib was mild to moderate; in contrast, 17% of sorafenib patients had hand foot syndrome of grade 3 or above [Motzer, 2013]. Rates of fatigue, diarrhoea and hand foot syndrome with pazopanib and sunitinib in the COMPARZ study were considerably higher – fatigue: 55% with pazopanib vs 63% with sunitinib, diarrhoea: 63% vs 57%, and hand foot syndrome: 29% vs 50%. Diarrhoea, fatigue and hand foot syndrome were severe (grade 3 or above) in 9%, 10% and 6% of pazopanib patients and 8%, 17%, 11% of sunitinib patients, respectively [Motzer, 2013b]. Evidence comparing rates of treatment discontinuation, dose reduction and dose interruptions due to adverse events also suggest that tivozanib is more acceptable to patients than sunitinib or pazopanib. In TIVO-1, dose reductions and dose interruptions due to adverse events was 14% and 19% for tivozanib, respectively, vs 43% and 36% for sorafenib. Discontinuation rates to adverse events in the TIVO-1 study were 4% with tivozanib vs 5% with sorafenib. Rates of dose reduction, interruption and discontinuation due to adverse events in the COMPARZ study were considerably higher than tivozanib – dose reduction: 44% vs 51%, dose interruption: 44% vs 49% and discontinuation 24% vs 20%. The key differences between tivozanib and comparators are those that affect patient quality of life, notably fatigue, diarrhoea and hand and foot disease. The significance of these have been largely ignored in the appraisal. These impact of these clinically relevant side effects of treatment have been documented clearly in two publications which look at adverse events from the patients' perspective. Regardless of line of therapy, patients find the side effects of targeted therapy for renal cell carcinoma troublesome – in particular, severe fatigue/tiredness, diarrhoea and hand foot syndrome.

	Mohamed et al (2011) highlighted that although progression free survival was of most importance to patients in terms of improvement, severe fatigue/tiredness and diarrhoea were rated as the most troublesome tolerability effects of renal cell carcinoma treatment. Increasing progression free survival by 10 months was found to be almost as important as avoiding severe fatigue/tiredness. This is further supported by a publication by Wong et al (2012), which similarly highlighted that although progression free survival was the most important attribute, patients would be willing to forego a period of progression free survival to avoid adverse events. The authors presented benefit equivalents as measured in progression free survival. These represent the amount of benefit (months of progression free survival) that patients generally require to accept adverse events of varying severities. The authors also stated that these measures can be interpreted as the amount of benefit that patients would be willing to forego to avoid toxicities. progression free survival. Indeed, patients would be willing to forgo 4.4 months of progression free survival to avoid mild-to-moderate-severe fatigue, 3.5 months to avoid mild-to-moderate-severe stomach problems and 2.1 months to avoid mild-to-moderate-severe hand foot syndrome. Please see point 7 for further clarification. **References** Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol 2013a;31(30):3791-9. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013b;369(8):722-31. Mohamed AF, Hauber AB, Neary MP. Patient benefit-risk preferences for targeted agents in the treatment of renal cell carcinoma. Pharmacoeconomics 2011; 29(11): 977-88. Wong MK, Mohamed AF, Hauber AB, et al. Patients rank toxicity against progression free survival in second-line treatment of advanced renal cell carcinoma. J Med Econ 2012; 15(6): 1139-48.
3	2. Typo 4weeks should be 4 weeks
4	3.4 *The pivotal trial, TIVO-1, has limited relevance to clinical practice in England* We believe that it might be more accurate to state that "*The pivotal trial, TIVO-1, has **some** relevance to clinical practice in England"* This wording is used in the conclusion of this section and we believe better reflects the evidence discussed in this section.
5	3.7 *patients in the sorafenib group were more likely to have more therapies than patients in the tivozanib group* We believe that it might be more accurate to state "*patients in the sorafenib group were more likely to have more **targeted** therapies than patients in the tivozanib group",* since the majority of patients in the sorafenib arm switched to tivozanib, a targeted therapy (see Table 13 of the Evidence Review Group report).
6	3.7 *and that it was the Company's preferred method of adjusting for crossover* We believe that it might be more accurate to explain the Company's rationale for using the Inverse Probability Censoring Weighting method. The following copy edit is proposed: "*that it was the*

	Company's preferred method of adjusting for crossover ***because it adjusts for the more favourable performance status observed in the sorafenib arm, which may have impacted on overall survival rates."***
7	3.11 We believe that evidence comparing rates of treatment discontinuation, dose reduction and dose reductions due to adverse events have not been included in the Appraisal Consultation Document. The evidence, although indirect, suggests that tivozanib may be acceptable to patients than sunitinib or pazopanib and that patients receive a higher dose intensity of treatment. We note in our original submission (page 112) that: Low rates of treatment discontinuation due to adverse events were seen in the TIVO-1 study – 4% with tivozanib vs 5% with sorafenib. Patients randomised to tivozanib experienced fewer dose reductions due to adverse events (19% vs 36%) and dose interruptions due to adverse events (14% vs 43%) than those on sorafenib [Motzer, 2013a]. The discontinuation rate with tivozanib compares favourably with that for pazopanib (24% in COMPARZ vs sunitinib and 14% in the pivotal study vs placebo) and sunitinib (20% in COMPARZ and 19% in the pivotal trial vs interfereron). Dose reductions and interruptions were more common with pazopanib and sunitinib than with tivozanib, in the COMPARZ study dose reductions were 44% with pazopanib and 51% with sunitinib; dose interruptions were 44% and 49% respectively [Motzer, 2013b]. These data suggest that, by indirect comparison, tivozanib is more acceptable to patients than either sunitinib or pazopanib. Real world evidence from a retrospective medical record review of patients receiving sunitinib for first-line treatment of renal cell carcinoma across Europe (41% of patients from the United Kingdom) revealed that patients with reduced dose intensity (<70%) or treatment discontinuation had significantly reduced survival times, illustrating the importance of maintaining patients on the full dose [Porta, 2014]. The Appraisal Consultation Document reflects these differences and notes that dose intensity with tivozanib is improved over sunitinib and pazopanib (94% vs 86%). Therefore, we feel that Section 3.11 should also include a mention that the tolerability of tivozanib means that more patients are able to remain on the full dose of treatment compared with sunitinib and pazopanib. We suggest insertion of the following copy in 3.11 after treatments (line 4) ***"However, patients receiving tivozanib have fewer discontinuations, dose reductions and dose interruptions due to adverse events compared with the comparators, as reflected in higher dose intensity (94% vs 86%)."*** **References** Motzer RJ, Nosov D, Eisen T, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. J Clin Oncol 2013a;31(30):3791-9. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. N Engl J Med 2013b;369(8):722-31. [data in appendix] Porta C, Levy A, Hawkins R, et al. Impact of adverse events, treatment modifications, and dose intensity on survival among patients with advanced renal cell carcinoma treated with first-line sunitinib: a medical chart review across ten centers in five European countries. Cancer Medicine 2014;3(6):1517-26. doi: 10.1002/cam4.302
8	3.19 *In the Evidence Review Group's base-case results, both pazopanib and sunitinib dominated*

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	tivozanib, that is, they were more effective and less costly. On review of the Evidence Review Group report (Table 86) we note that tivozanib is marginally more costly than pazopanib (by commercial in confidence information removed) but less costly than sunitinib (by commercial in confidence information removed), therefore this statement is incorrect. These cost differences are minor compared with the total cost of treatment, with all three agents costing between commercial in confidence information removed (pazopanib) and commercial in confidence information removed (sunitinib). It might be more appropriate to say ***In the Evidence Review Group's base-case results, both pazopanib and sunitinib were more effective than tivozanib, at a similar cost***.
9	3.20 *This included consideration of a scenario in which the Evidence Review Group assumed that tivozanib, sunitinib and pazopanib were all equally effective in extending progression-free and overall survival. The Committee appreciated that this analysis was likely to be optimistic because the results from the network meta-analysis suggested that overall survival could be shorter with tivozanib compared with pazopanib and sunitinib (see section 3.10). The Committee noted that the results showed that tivozanib was more costly than pazopanib and sunitinib even when this optimistic approach was taken*. Table 88 of the Evidence Review Group report shows that in a scenario analysis assuming equal efficacy tivozanib is more expensive than sunitinib (commercial in confidence information removed) and pazopanib (commercial in confidence information removed). We note that these cost differences are minor (particularly in the case of sunitinib). We believe it might be more appropriate to state ***slightly more costly*** which reflects the actual cost differences.

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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

unlawful or otherwise inappropriate.

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

Tivozanib for treating renal cell carcinoma [ID591]

NICE National Institute for Health and Care Excellence

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Kidney Cancer Support Network
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments

Tivozanib for treating renal cell carcinoma [ID591]

NICE National Institute for Health and Care Excellence

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	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	Tivozanib is a potent, selective, long half-life inhibitor of all three vascular endothelial growth factor (VEGF) receptors (VEGF-1, VEGF-2 and VEGF-3) that is designed to optimise VEGF blockade while minimising side effects, resulting in a more tolerable treatment than is currently available for mRCC, especially in combination with other therapies. A tolerable side effect profile renders tivozanib a useful candidate for combination with immunotherapy drugs, such as nivolumab, to further improve the overall survival of patients with recurrent or metastatic RCC.
2	Tivozanib has proven to be effective in extending progression free survival by nearly 3 months compared to sorafenib, with a tolerable side effect profile. Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including patient experience as well as overall survival, it is vital that innovative new drugs with different modes of action are made available to patients in order that they have the best care possible. If these drugs are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to the rest of Europe and North America.
3	Current first-line treatments offer an important, but sometimes short-lived period of stability, but not all patients respond to these treatments and most patients become refractory after a period of time. Biomarkers for the treatment of RCC are yet to be identified, and unfortunately clinicians are not able to predict which patients will respond to which drug. Therefore, selection of the most effective treatment for individual patients is accomplished by trial and error. Without a choice of treatment alternatives in the second-line and beyond, most patients will face disease progression, including worsening of symptoms, such as severe pain, fatigue and shortness-of-breath. Patients require choice in second- and third-line therapy to continue managing their disease, and to maintain quality of life.
4	A number of clinical trials of tivozanib have been conducted or are ongoing in recurrent and/or metastatic RCC patients in the UK. The patients who participated in these trials did so in the expectation that their data would enable other patients in the UK to benefit from this drug. If the government and the pharmaceutical industry cannot agree a price that allows the use of tivozanib within the NHS, we question whether patients will continue to support future research by taking part in clinical trials. Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from new, innovative and clinically effective drugs if the precedent for these drugs is rejection by NICE.
5	Current treatments have proven to shrink tumours and delay disease progression in some patients, but adding tivozanib as a choice in the second-line (and beyond) enables patients and clinicians to have individualised treatment plans to better control this disease and maintain a high quality of life. It could also address the massive unmet need for treatment options in the third-line and beyond.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted,

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please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.

- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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Comments on the ACD Received from the Public through the NICE Website

Name	Ipsen
Role	Pharmaceutical Industry
Location	England
Conflict	I work for the manufacturer of one of the comparators in this appraisal (cabozantinib, Ipsen)
Notes	
Comments on individual sections of the ACD:	
NICE guidance recommends cabozantinib for use in both 2nd and 3rd line treatment. At present, this ACD appears to contradict not only that published guidance, but also the ACD for lenvatinib+everolimus (Sections 3.1 and 3.3). We suggest that the wording is amended to reflect the most up-to-date recommendations.	

Tivozanib for treating renal cell carcinoma [ID591]

ERG review of the company's response to the ACD

September 2017

This report was commissioned by the NIHR HTA Programme as project number 16/56/14

BMJ Technology Assessment Group

1 ERG REPLY TO COMPANY COMMENTS

1.1 Studies included in the network meta-analysis

In point 1 of the company's response, the company question the robustness of the Evidence Review Group's (ERG's) network meta-analysis (NMA) (Box 1**Error! Reference source not found.**).

Box 1. Company comment regarding the ERG's network meta-analysis

…we have reasons to query the robustness of the Evidence Review Group network meta-analysis, as relates to the level of evidence of the studies used in their analyses. The Evidence Review Group network meta-analysis included some studies that we believe could be considered as inappropriate (small numbers, heterogeneous populations) and which we believe should have been excluded from the network meta-analysis. We are certain that the Committee would have been more inclined to support the Company's model and results if they had considered the integrity of the network meta-analyses provided as a source of data for the various models. We appeal to the Committee to consider this point carefully, as the safety of its judgement may be seen to hang on a technical issue that could be considered unsafe.
Abbreviations: none

At the clarification stage, the ERG suggested that the company's original network meta-analyses (NMAs), which included up to 19 studies, be simplified to networks based on four studies linking tivozanib with pazopanib and sunitinib to minimise clinical heterogeneity. Subsequently, all of the company and ERG network meta-analyses were based on the same four studies which provided the clinical effectiveness evidence for the economic model: TIVO-1[1] (n = 362 treatment naïve), COMPARZ[2] (n = 1110), SWITCH (n = 365), and CROSS-J-RCC (n = 120). At clarification, the company provided a table of the population and study methodology of relevant RCTs (Table 3, clarification response), a table of baseline characteristics of patients in the relevant trials in the NMA (Table 4, clarification response), and a discussion of the similarities and differences between the trials (clarification response to question A1). The company did not raise any concerns about the inclusion of these four trials in the network meta-analysis, either in the clarification response or the factual accuracy check received by the ERG.

The ERG included a full critique of the conduct and populations of the four trials in Sections 4.3.1 and 4.3.2 of the ERG report.

1.2 Comparing rates of fatigue, diarrhoea and hand-foot syndrome

In Point 2 of their response to the ACD, the company provides a naive comparison of the percentages of fatigue, diarrhoea and hand-foot syndrome (HFS) observed in the tivozanib group of TIVO-1[1] with the percentages observed in the head-to-head COMPARZ[2] study of sunitinib and pazopanib. The company propose that these three adverse events (AEs) are particularly important to patients' quality

of life. The ERG would like to reiterate that the impact of AEs on quality of life, and the costs associated with the AEs, are incorporated in the company's and the ERG's assessment of cost-effectiveness, which include severe fatigue, diarrhoea and hand-foot syndrome (Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 and above). The ERG found that changes to the modelling of AEs had a minimal impact on the overall ICERs. The company's response to the ACD also mentions differences in rates of AEs of any grade; any differences in less severe AEs are not reflected in the company's or the ERG's assessment of cost-effectiveness as the company state the cost burden of less severe AEs are likely to be non-significant and because only Grade 3 and above were used in the NMAs.

The use of CTCAE grading of AEs in all four trials comprising the NMA reduces measurement variation between the trials, but naïve comparisons are subject to confounding because within-trial randomisation is broken. The ERG considers NMA a more appropriate method of comparing treatment safety. NMAs linking TIVO-1[1] and COMPARZ[2] via two studies comparing sunitinib with sorafenib (SWITCH[3] and CROSS-J-RCC[4]) are likely to provide a more robust comparison because the benefits of randomisation are maintained. SWITCH[3] and CROSS-J-RCC[4] also provide additional adverse event data for sunitinib which are overlooked in the naïve comparisons put forward by the company. Table 53 of the ERG report (reproduced here as Table 1) highlights the variation in percentages of adverse events for the same treatment across different studies. NMA incorporates all available data and variation is reflected in the uncertainty around the estimates.

Table 1. Adverse event rates observed in trials included in the simplified NMA

% of patients with Grade 3 or 4 AEs	Tivozanib	Sorafenib			Sunitinib			Pazopanib
	TIVO-1 naïve (N=181)	TIVO-1 naïve (N=181)	CROSS-J-RCC (N=63)	SWITCH (N=177)	CROSS-J-RCC (N=57)	SWITCH (N=176)	COMPARZ (N=548)	COMPARZ (N=554)
Anaemia	0.6	1.7	5	NR	12	NR	7	2
Fatigue/asthenia	5	2.8	2	4.5	16	7.4	20	13
HFS	2	16	25	12	12	5.7	12	6
Hypertension	25	16	17	9	18	12	15	15
Diarrhoea	2.2	6.1	6	5.1	0	2.8	8	9

Notes: TIVO-1 data are for the 70% in each group that were naïve to systemic therapy. Data for CROSS-J-RCC and SWITCH are first-line therapy experience only (i.e. not post-crossover)
Abbreviations in table: AE, adverse effects; HFS, hand-foot syndrome; N, number of patients; NR, not reported

1.3 Comparing rates of treatment discontinuation, dose reduction and dose interruptions due to adverse events

The company present data for treatment discontinuations, dose reductions and dose interruptions due to adverse events in the tivozanib group of TIVO-1[1] compared with the sunitinib and pazopanib groups of the COMPARZ[2] study (Points 2 and 7 of the company's response to the ACD). The ERG's comments regarding naïve comparisons in Section 1.2 are similarly applicable to these data, but the ERG considers these data particularly difficult to compare across trials. While lower treatment discontinuations,

interruptions and dose reductions may indicate better tolerability of a drug, they may be confounded by differences in drug administration and study protocol, even within a trial. The ERG wishes to highlight the following for consideration when interpreting these data:

- TIVO-1[1] and COMPARZ[2] were both open-label studies which increases the potential for investigator bias in the decision to stop or interrupt treatment, or reduce dose.

- Dose availability and study protocol may influence a clinician's decision to reduce dose in a trial. Sunitinib and pazopanib can both be reduced and increased in increments (sunitinib in 12.5 mg increments between 25 and 75 mg, and pazopanib in 200 mg increments) whereas tivozanib is only available in two doses (1,340μg and 890μg). Importantly, in TIVO-1,[1] tivozanib could not be increased again if the dose was reduced.

- Dose interruptions may be defined differently based on drug regimen. For example, tivozanib is administered for 3 weeks in a 4-week cycle and sunitinib for 4 weeks in a 6-week cycle.

In Point 7 of the company's response to the ACD, the company reports discontinuations due to AEs were 4% for tivozanib and 5% for sorafenib, which are the percentages of patients discontinuing the study drug due to an AE judged by the investigator to be related to the study drug. The proportion of patients discontinuing the study drug due to any AE was 14.7% in the tivozanib group and 13.2% in the sorafenib group (Table 49 of the final clinical study report (CSR)).[5] However, the ERG wishes to highlight that the clinical benefit observed in the relevant trials are reflective of the dose received and so any differences in dose received are already accounted for in the clinical effectiveness of each drug, which has been used to inform the economic model. As such, the ICERs produced by the model inherently include the impact of differences in doses received and the impact on PFS and OS.

2 REFERENCES

1. Motzer RJ, Nosov D, Eisen T, Bondarenko I, Lesovoy V, Lipatov O, et al. Tivozanib versus sorafenib as initial targeted therapy for patients with metastatic renal cell carcinoma: results from a phase III trial. Journal of Clinical Oncology. 2013;31(30):3791-9.
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