NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

GUIDANCE EXECUTIVE (GE)

Review of TA219; Everolimus for the second-line treatment of advanced renal cell carcinoma

Final recommendation post consultation
Everolimus TA219 should be reviewed alongside other treatments for renal cell carcinoma after failure of prior systemic treatment, including sunitinib and sorafenib (part review of TA178) and any new treatments such as axitinib through the Multiple Technology Appraisal (MTA) Process.

1. Background

This guidance was issued in April 2011.

At the GE meeting of 20 May 2014 it was agreed that we would consult on the recommendations made in the GE proposal paper. A four week consultation has been conducted with consultees and commentators and the responses are presented below.

2. Proposal put to consultees and commentators

The guidance should be transferred to the ‘static guidance’ list.

3. Rationale for selecting this proposal

Little new clinical evidence on everolimus has become available since the guidance was issued. That data which is available will not change the guidance recommendations. The ongoing STA appraisal of axitinib in the same population of previously treated renal cell carcinoma will not have an impact on the everolimus recommendations. In addition, no new comparator data has become available that will change the everolimus recommendations.

4. Summary of consultee and commentator responses

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Respondent: Novartis **Response to proposal:** Disagree Executive summary: NICE have provisionally decided to refer TA219 to the static list. This preliminary decision is based on the conclusion that there is very little change in the evidence base since TA219 was published. We disagree with this conclusion because there are several data sources that can potentially inform the review of TA219 and result in change in the current guidance. • Since 2009 the treatment paradigm for the treatment of metastatic renal cell carcinoma has significantly changed. Best Supportive Care (BSC) is no longer an acceptable treatment option as patients now have the option of anti VEGF targeted therapies. • There is new evidence comparing everolimus with targeted therapies in line with changing clinical practice. • A literature review of everolimus compared with BSC is unlikely to show new evidence. However a literature search of everolimus compared with targeted therapies shows that there is new evidence since 2009 that is relevant for TA219 and can lead to a change in the guidance. • The search strategy from the original assessment for TA219 is no longer fit for purpose as clinical practice has evolved since everolimus came into market. The search strategy should not be limited to a comparison of everolimus with BSC. • We disagree with NICE on the fact that the on-going axitinib appraisal will not have an impact on the everolimus recommendations. Axitinib is now standard second line therapy and therefore a new comparator treatment for everolimus. We urge NICE to therefore reconsider the provisional decision to refer TA219 to the static list and review the guidance.	**Comment from Technology Appraisals** Comment noted. Everolimus was appraised in TA219 through the Single Technology Appraisal (STA) Process. No new evidence has become available comparing everolimus with best supportive care which would be likely to change the recommendations of the original guidance. However, recognising that the treatment paradigm has changed because in established clinical practice tyrosine kinase inhibitors are used, best supportive care is therefore not the only comparator. This change in clinical practice is reflected in the updated scope for the ongoing STA of axitinib for renal cell carcinoma after failure of prior systemic treatment [ID518] with sunitinib, pazopanib and best supportive care all included as comparators for the prior-cytokine group. Updated evidence is available for the comparison of everolimus with tyrosine kinase inhibitors such as sunitinib and sorafenib, which may lead to a change in guidance.

Supporting information a) Recent studies comparing everolimus to targeted therapies 1. *A Randomized Phase II Study of GDC-0980 Versus Everolimus in Metastatic Renal Cell Carcinoma Patients After VEGF-Targeted Therapy (ROVER study)* Patients with clear cell mRCC who progressed on or after VEGF-targeted therapy were randomized (1:1) to receive GDC-0980 (40 mg PO QD) or everolimus (10 mg PO QD). Please note that the patient population in this trial is similar to that of everolimus from the RECORD-1 trial. The results from this trial showed that median PFS was significantly longer in the everolimus arm compared with the GDC-0980 arm (median PFS for GDC -0980 vs everolimus was 3.7 vs 6.1 months respectively, (95% HR 2.12; CI: 1.23; 3.63, p < 0.01). Median OS was not statistically significantly different but trended in favor of everolimus after 48 events (27 for the GDC-0980 arm; 21 for the everolimus arm) ORR was 7% for GDC-0980 and 12% for everolimus. The authors concluded that in the ROVER trial, everolimus produced statistically significantly longer PFS compared with GDC-0980 in mRCC patients who were previously treated with VEGF-targeted therapy. This trial provides new evidence of everolimus' efficacy against an active comparator, with significant PFS and OS data that should inform the review of TA219. [redacted]	Everolimus TA219 should therefore be reviewed alongside other treatments for renal cell carcinoma after failure of prior systemic treatment, including sunitinib and sorafenib TA178 and any new treatments such as axitinib through the Multiple Technology Appraisal (MTA) Process. Comments noted.

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[redacted] [redacted] These data are the most comprehensive updates since TA219 was published showing the PFS and OS benefit of everolimus in metastatic RCC patients who have failed prior targeted therapy. This evidence is likely to impact on the current TA219 guidance as this data were not available when TA219 was published. For completeness we have included the relevant publications with this response. b) Relevance of axitinib as a comparator We do not agree with NICE's conclusion that the on-going appraisal of axitinib will not have an impact on the everolimus recommendations. Axitinib is now commonly used in the second line setting (funded via the Cancer Drugs Fund (CDF) and is therefore the appropriate comparator for everolimus. The draft axitinib recommendation is positive and is likely to remain this way. On that basis axitinib might soon become a NICE approved comparator for everolimus. In addition the AXIS trial provides new comparative data to indirectly compare everolimus to axitinib given that both trials have similar patient populations. Indirect treatment comparison is a commonly used methodology to compare treatments that do not have head to head evidence. Although there is an ongoing axitinib appraisal, this does not distract from the fact that axitinib is a genuine comparator for everolimus and can be indirectly compared via the RECORD 1 and AXIS trials. We therefore does not agree with the conclusions in the GE proposal paper suggesting that no new relevant new interventions or comparators have come to market since the original guidance was issued. The health economics case presented as part of TA219 was mainly based on the RECORD-1 trial, which compared everolimus with BSC. With the licensing of axitinib, everolimus	Comments noted. Comments noted.

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should be indirectly compared with axitinib and the results of such an analysis are unlikely to be the same as those of the original health economics case presented in 2009. The monthly cost of everolimus is lower than that of axitinib and an indirect analysis conducted by Novartis shows that everolimus is more efficacious when compared with axitinib. It is therefore reasonable to conclude that the cost effectiveness analysis of everolimus compared with axitinib can only yield better cost effectiveness results compared with the original analysis comparing everolimus to BSC. It is therefore inaccurate for NICE to suggest that the inclusion of axitinib or the axitinib appraisal will not have an impact on TA 219. If recommended, everolimus will provide clinicians and patients with a treatment choice that is currently only currently available, via the Cancer Drugs Fund and therefore in the interests of patients NICE should review TA219. As highlighted earlier, there is new evidence for everolimus and comparator treatments, in particular axitinib that justifies a new health economics case. c) Significance of other comparators not recommended by NICE NICE concludes that all the new evidence compared everolimus with sorafenib (first- and second-line), sunitinib (second-line) or temsirolimus (first-line) which are not recommended by NICE. We understand that all these drugs that everolimus is compared with are routinely funded on the CDF and are therefore part of standard clinical care. We also received communication from NICE confirming that drugs that are funded via the CDF (after a negative NICE recommendation) will now be considered as comparators for appraisals. Thus there is new evidence comparing everolimus to other targeted therapies such as sunitinib and sorafenib and it is relevant for this review of TA219. The fact that they were not recommended by NICE is no longer a justification for excluding them as comparators. The communication from NICE stating that CDF treatments can now be considered as comparators is included with this response. d) Matrix of consultees and commentators We have noticed inconsistencies between the GE proposal paper and the matrix of consultees and commentators. The GE proposal paper suggests that there have been no new comparator treatments since the publication of TA219 (We do not agree with this as	Comments noted.

explained earlier). However in the matrix of consultees and commentators, NICE have included the manufacturer of axitinib as a comparator manufacturer. This inclusion brings with it the ability to comment and be involved with the appraisal of TA219. It is therefore unclear how the manufacturer of axitinib qualifies to be a comparator manufacturer when their drug is not considered by the GE proposal to be relevant for the appraisal. We believe that the manufacturer of axitinib can only be a comparator manufacturer if their drug is a comparator for this potential appraisal. As mentioned earlier, axitinib is now the standard of care in second line setting and therefore is a relevant comparator for TA219. If this is so the Health Economics case for everolimus will be different to that presented in 2009 (based on a comparison with BSC) justifying the need for a review of TA219. However in the unlikely event that NICE insists that axitinib (and the on-going appraisal of axitinib) is not relevant to TA219, then accordingly the manufacturer of axitinib should be excluded from the list of consultees and commentators for TA219. Conclusion There is new evidence on everolimus and its comparators that justifies a review of TA219. This new evidence includes both everolimus and other targeted therapies that are now in routine clinical use. Of particular relevance is axitinib that covers a similar population to everolimus and is now the standard of care. As highlighted earlier, the introduction of axitinib in English clinical practice changes the health economics case for everolimus to that presented in 2009 when everolimus was compared with BSC. TA219 should therefore not be referred to the static list, but should be reviewed so that the new evidence on both everolimus and its comparators can be assessed and new guidance issued for the benefit of patients who have limited NICE approved treatment options in the second line setting. References/Attachments 1. The ROVER study ASCO poster 2. [redacted] Communication from NICE confirming the use of CDF treatments as comparators	Comments noted. Comments noted.

Confidential information has been removed.

Respondent: National Cancer Research Institute; Royal College of Physicians; Royal College of Radiologists; Association of Cancer Physicians; Kidney Cancer UK **Response to proposal:** Disagree I write on behalf of the NCRI/RCP/RCR/ACP/JCCO who work together to produce joint submissions to NICE oncological consultations. We are grateful for the opportunity to comment and would like to make the following joint response on the above review proposal. Please note that this position is also supported by the Kidney Cancer UK. Our expert clinicians treating renal cancer do not believe that the guidance should be transferred to the 'static guidance list'. Instead we believe it would be opportune for NICE to review the evidence for the use of everolimus after failure of VEGFR TKIs. The new data are: 1. A randomised phase II trial of everolimus in which the UK was a major recruiter (Powles et al ASCO 2014). This further confirmed the benefits of everolimus and suggested survival may be longer than previously seen. 2. There is now extensive UK experience of using everolimus in metastatic renal cancer after failure of at least one VEGFR TKI. In England, this is funded by the Cancer Drugs Fund and data support the efficacy in this patient population. Furthermore, we believe it is important that treatment throughout the UK is harmonised to bring it in line with international norms. Currently, in England this is the case because of the Cancer Drugs Fund. The situation in Scotland and Wales is less favourable for patients and we, along with patient groups, feel this inequality is inappropriate. Most importantly we feel all patients in the UK should have optimal access to palliative treatment options for the management of metastatic renal cancer. This comprises initial VEGFR TKI therapy (pazopanib or sunitinib) followed by axitinib and/or everolimus, both of which should be available after failure of prior VEGFR TKI therapy - currently the optimal choice is unclear and this remains a matter of clinical judgment.	**Comment from Technology Appraisals** Everolimus was appraised in TA219 through the Single Technology Appraisal (STA) Process. No new evidence has become available comparing everolimus with best supportive care which would be likely to change the recommendations of the original guidance. However, recognising that the treatment paradigm has changed because in established clinical practice tyrosine kinase inhibitors are used, best supportive care is therefore not the only comparator. This change in clinical practice is reflected in the updated scope for the ongoing STA of axitinib for renal cell carcinoma after failure of prior systemic treatment [ID518] with sunitinib, pazopanib and best supportive care all included as comparators for the prior-cytokine group. Updated evidence is available for the comparison of everolimus with tyrosine kinase inhibitors such as sunitinib and sorafenib, which may lead to a change in guidance. Everolimus TA219 should therefore be reviewed alongside other treatments for renal cell carcinoma after failure of prior systemic treatment, including sunitinib and sorafenib TA178 and any new treatments such as axitinib through the Multiple

	Technology Appraisal (MTA) Process.

Respondent: Healthcare Improvement Scotland **Response to proposal:** No comment Healthcare Improvement Scotland has no comment to make on the proposal to move the existing guidance to the static list.	**Comment from Technology Appraisals** Comment noted.

Respondent: James Whale Fund for Kidney Caner **Response to proposal:** Disagree James Whale Fund for Kidney Cancer is disappointed at the proposal to move the existing NICE guidance for everolimus for the second-line treatment of metastatic renal cell carcinoma (mRCC) to the static list. It is our understanding that when on the static list, guidance will not be reviewed for at least 3 years, and any data that are generated or come to light during this period will not be included in the guidance until July 2017 at the earliest. Currently, mRCC patients can access everolimus through the Cancer Drugs Fund in England; however, it is likely the CDF will come to an end in April 2016, and the only means to access this drug after this time will be through participation in clinical trials (which are few and far between). Standard practice for the treatment of mRCC is surgery followed by first-line treatment with sunitinib or pazopanib. These treatments have given mRCC patients hope, but at the cost of severe side effects and limited progression free survival. Sunitinib and pazopanib can both keep the disease at bay and extend life by, on average, about 11 months. For those patients who are unable to tolerate the side effects to these first-line drugs, or those for whom their disease no longer responds to treatment, there are	**Comment from Technology Appraisals** Comments noted. Everolimus TA219 should be reviewed alongside other treatments for renal cell carcinoma after failure of prior systemic treatment, including sunitinib and sorafenib TA178 and any new treatments such as axitinib through the Multiple Technology Appraisal (MTA) Process.

currently no second-line treatments available via NHS England. Second-line treatments, such as axitinib, everolimus or sorafenib, are available through the CDF or through participation in clinical trials, which requires a high degree of commitment from patients in terms of clinic visits and patient monitoring. Axitinib has been provisionally recommended as a second-line treatment, and could be available through NHS England by the end of the year; however, for those patients who are intolerant or unresponsive to VEGF tyrosine kinase inhibitors, such as sunitinib, pazopanib and axitinib, everolimus (an mTOR inhibitor) offers a viable second-line alternative. Without access to second-line treatment, the only treatment available to these patients is palliative care to make their last months of life as comfortable as possible. We strongly recommend that everolimus be kept off the static list for the time being, to enable the guidance to be updated with any new data that could impact the recommendations laid out in the guidance as and when those data come to light. This could eventually enable mRCC patients to access everolimus via NHS England, without having the uncertainty of obtaining funding for the drugs they need through the CDF, or having to participate in clinical trials, both of which for many patients is too much to take during their last months of life.	Comments noted.

Respondent: Pfizer **Response to proposal:** Agree Pfizer has no further comments, and supports the move of everolimus to the static list.	**Comment from Technology Appraisals** Comments noted.

Paper signed off by: Frances Sutcliffe – Associate Director, Technology Appraisals – 19 November 2014

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