

Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

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Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

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1 Guidance

- 1.1 Axitinib is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine, only if the company provides axitinib with the discount agreed in the patient access scheme.
- 1.2 At the time of publication (February 2015), axitinib has a UK marketing authorisation only for use after failure with first-line sunitinib or a cytokine. If it is considered for use after any other first-line treatments, the prescriber should obtain and document informed consent and follow the relevant guidance published by the General Medical Council.^[1]
- 1.3 Because the remit referred to NICE by the Department of Health for this technology appraisal only includes adults who have been previously treated with sunitinib, the use of axitinib after treatment with other tyrosine kinase inhibitors is not subject to statutory funding.

^[1] For further information see the General Medical Council's [Prescribing guidance: prescribing unlicensed medicines](#).

2 The technology

- 2.1 Axitinib (Inlyta, Pfizer) is an oral multi-targeted tyrosine kinase inhibitor with anti-tumour activity. Axitinib selectively inhibits vascular endothelial growth factor receptors 1, 2 and 3, platelet-derived growth factor receptor, and c-kit, which may inhibit angiogenesis in tumours. Axitinib has a marketing authorisation for 'the treatment of adult patients with advanced renal cell carcinoma, after failure of prior treatment with sunitinib or a cytokine'.
- 2.2 The summary of product characteristics lists the following adverse reactions for axitinib: diarrhoea, hypertension, fatigue, dysphonia, nausea, decreased appetite, palmar–plantar erythrodysesthesia (hand–foot syndrome), hypothyroidism, headache, dysgeusia, haemorrhage, vomiting, stomatitis, constipation, rash, dry skin, proteinuria, asthenia and mucosal inflammation. For full details of adverse reactions and contraindications, see the summary of product characteristics.
- 2.3 Axitinib is available in 1-mg and 5-mg film-coated tablets at net prices of £703.40 and £3517 per 56-tablet pack respectively (excluding VAT, 'British national formulary' [BNF] November 2014). Axitinib is administered orally at a recommended starting dose of 5 mg twice daily. This dose may be increased to 7 mg and then up to 10 mg, or decreased to 3 mg and then down to 2 mg, depending on individual safety and tolerability. The company has agreed a patient access scheme with the Department of Health. The size of the discount is commercial in confidence. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The company's submission

The Appraisal Committee ([section 7](#)) considered evidence submitted by the company of axitinib and a review of this evidence by the Evidence Review Group (ERG; [section 8](#)).

Clinical-effectiveness evidence

- 3.1 The company conducted a systematic literature search and identified 1 randomised controlled trial (AXIS) that assessed axitinib for the second-line treatment of people with advanced renal cell carcinoma. AXIS was a phase III, international, multicentre, randomised, open-label, active-controlled trial comparing axitinib with sorafenib for treating advanced or metastatic renal cell carcinoma after failure of first-line systemic therapy. The trial was carried out in 175 centres in 22 countries and lasted for 3 years. The clinical-effectiveness evidence presented in the company's submission was based mainly on this trial, but because it had no best supportive care comparator as defined in the scope, additional studies were used for an indirect comparison of axitinib with best supportive care.
- 3.2 Patients were eligible to enter the AXIS trial if they had measurable and progressive disease according to the Response Evaluation Criteria In Solid Tumours (RECIST) at least 2 weeks after 1 systemic first-line treatment with sunitinib, temsirolimus or cytokine(s), or at least 4 weeks or more treatment with bevacizumab plus interferon alfa-2a. The trial randomised 723 patients in a 1:1 ratio to receive either 5 mg axitinib twice daily or 400 mg sorafenib twice daily. The dose for axitinib was either maintained, or increased to 7 mg and then up to 10 mg twice daily, or reduced to 3 mg and then down to 2 mg twice daily, depending on individual safety and tolerability and at the discretion of the treating physician. If there were sorafenib-related adverse reactions, the dose could be reduced to 400 mg once daily and, if necessary, further reduced to 400 mg on alternate days. No other chemotherapy or experimental anticancer medications were allowed in the trial period. Palliative care was allowed for pain control only of bone disease present at baseline and for disease-related symptoms. Baseline patient characteristics were balanced across the 2 treatment groups. The mean age was approximately 60 years (66% of the patients were less than 65 years), 72% were men and approximately 76% were white. The previous systemic therapies used were also similar across the 2 groups (in both groups, 54% of patients had received sunitinib, 35% had

received cytokines, 8% had received bevacizumab and 3% had received temsirolimus). There were no notable differences between the treatment groups in terms of disease history.

- 3.3 The primary outcome in the AXIS trial was progression-free survival as measured by an independent review committee (IRC), and this was defined as the time from randomisation to first disease progression or death from any cause (whichever occurred first). Secondary outcomes included progression-free survival as assessed by the investigator, overall survival, defined as the time from randomisation to the date of death from any cause, and patient-reported outcomes (quality of life). Quality of life was assessed using the 15-item Functional Assessment of Cancer Therapy Kidney Symptom Index (FKSI-15), which measures symptoms and quality of life in people with advanced kidney disease; and the FKSI Disease-Related Symptoms subscale (FKSI-DRS), which measures symptoms related to advanced kidney cancer disease. The EQ-5D was also used to assess generic health status.
- 3.4 Subgroup analyses of the primary and secondary end points were performed for the stratification factors based on Eastern Cooperative Oncology Group (ECOG) performance score (0 and 1) and prior treatment regimen (sunitinib, a cytokine, bevacizumab or temsirolimus). The evidence in the company's submission was based on the subgroups of patients who were previously treated with sunitinib or a cytokine (such as interferon alfa or interleukin 2), in line with the marketing authorisation for axitinib. These subgroups are referred to as the prior-sunitinib group and the prior-cytokine group in this document. Subgroups were also predefined for the secondary end points based on baseline patient characteristics of age (less than 65 years or 65 years or more); sex; ethnic origin (white or non-white); geographical region (Asia, Europe, North America or other); and Memorial Sloan-Kettering Cancer Centre (MSKCC) risk groups (favourable, intermediate or poor).
- 3.5 In the main trial population, there was a statistically significant difference of 2 months in the IRC-assessed median progression-free survival, which was 6.7 months in the axitinib group compared with 4.7 months in the sorafenib group. The hazard ratio (HR) for progression was 0.67 (95% confidence interval [CI] 0.54 to 0.81, $p < 0.0001$), adjusted for the stratification factors (ECOG performance score and prior systemic therapy). However, the improvement in overall survival (20.1 months in the axitinib group compared with 19.2 months

in the sorafenib group) was not statistically significant (HR 0.97, 95% CI 0.80 to 1.17, $p=0.37$).

- 3.6 FKSI-15, FKSI-DRS and EQ-5D quality-of-life data were collected at day 1, every 4 weeks thereafter, at the end of trial treatment or withdrawal, and on day 28 of the follow-up period. Higher FKSI-15, FKSI-DRS and EQ-5D scores indicate better quality of life. A repeated measures mixed-effects model was used to compare differences in quality of life between the 2 treatment groups. There were no statistically significant differences at follow-up between axitinib and sorafenib using the 3 health measures. For FKSI-15, there was no statistically significant difference between axitinib and sorafenib after treatment ($p=0.4833$) and no statistically significant interaction between treatment and time ($p=0.3943$), and quality of life was maintained while patients remained on axitinib and sorafenib treatment. The axitinib group had mean FKSI-DRS scores 0.12 higher than the sorafenib group, measured using the FKSI-DRS measure for the main trial population (95% CI -0.45 to 0.69, $p=0.67$). For EQ-5D, the overall between-treatment comparison for axitinib compared with sorafenib was not statistically significant (no p value given); however, quality of life was maintained while patients remained on treatment and declined when patients stopped trial medication. The quality-of-life differences for the prior-cytokine group and the prior-sunitinib group are academic in confidence, and therefore cannot be reported here.
- 3.7 The safety analysis was performed for all patients who received at least 1 dose of axitinib or sorafenib in the AXIS trial ($n=714$). Diarrhoea was the most common treatment-emergent adverse event, occurring proportionately in both treatment groups (54.9% in the axitinib group and 53.2% in the sorafenib group). The most common additional adverse events in the axitinib group were hypertension, dysphonia, nausea and hypothyroidism. Hand-foot syndrome, rash and alopecia were more common in the sorafenib group than in the axitinib group. The sorafenib group had a higher occurrence of grade 3 (51.3% compared with 50.4%) and grade 4 (10.1% compared with 5.8%) adverse events compared with axitinib. Serious adverse events resulting in death, hospitalisation, significant disability and birth defects in children of patients in the trial occurred equally in both treatment groups in the full trial population. The sorafenib group was associated with higher proportions of adverse events leading to dose reductions or interruptions (62% compared with 55.4%) and permanent discontinuation of trial medication (13% compared with 9.2%)

compared with axitinib. The adverse event data for the prior-cytokine and the prior-sunitinib groups are academic in confidence.

Prior-cytokine group

- 3.8 For the prior-cytokine group in the AXIS trial, the axitinib group had a statistically significant IRC-assessed median progression-free survival of 12.1 months compared with 6.5 months in the sorafenib group (HR 0.46, 95% CI 0.32 to 0.68, $p < 0.0001$). There was also a statistically significant 3.7-month higher investigator-assessed progression-free survival in the axitinib group compared with the sorafenib group (HR 0.64, 95% CI 0.45 to 0.90, $p = 0.0049$). However, there was no statistically significant improvement in overall survival, which was 29.4 months in the axitinib group and 27.8 months in the sorafenib group (HR 0.81, 95% CI 0.56 to 1.19, $p = 0.14$).

Indirect treatment comparison

- 3.9 In a systematic review of the literature, the company identified 1 relevant trial, known as TARGET, that was considered suitable for an indirect comparison of axitinib compared with best supportive care. For the purpose of this appraisal, the company used placebo from the TARGET and RECORD-1 trials (see section 3.14) as a proxy for best supportive care. TARGET was a phase III, multicentre, randomised, double-blind, placebo-controlled trial comparing sorafenib with placebo for people with metastatic renal cell carcinoma who had received 1 prior systemic therapy. However, TARGET was made up mostly of patients who had received first-line cytokine therapy only (interferon alfa or interleukin 2), and also did not have a prior-sunitinib subgroup. Therefore, an indirect comparison of axitinib with best supportive care was possible only for the cytokine-refractory subgroup. The patients in TARGET were similar to the patients in the AXIS trial in terms of age, sex and nephrectomy status. However, only 2 metastatic sites (lung and liver) were reported in TARGET, whereas AXIS reported more than 8 sites. MSKCC risk scores and prior treatments also differed between the 2 trials. Median progression-free survival was 5.5 months for sorafenib compared with 2.8 months for placebo using the intention-to-treat (ITT) population, and mean overall survival was 17.8 months for sorafenib compared with 14.3 months for placebo in the ITT population censored for crossover.
- 3.10 The indirect comparison was performed using Bayesian Markov-chain Monte

Carlo sampling to determine the relative efficacy of the treatments. Sampling was performed using WinBUGS. The hazard ratios from AXIS (median progression-free survival [HR 0.46, 95% CI 0.32 to 0.68, $p < 0.0001$] and overall survival median [HR 0.81, 95% CI 0.56 to 1.19, $p = 0.14$]) and TARGET (median progression-free survival [HR 0.54, 95% CI 0.45 to 0.64, $p < 0.001$], and median overall survival censored for crossover [HR 0.78, 95% CI 0.62 to 0.97, $p = 0.029$]) were used in a fixed-effects model with an assumption of proportional hazards. Point estimates of the hazard ratio for each pair of treatments and 95% credible intervals (CrI) were calculated. The result of the indirect comparison showed a 75% reduction in disease progression for axitinib compared with placebo (assumed here to be equivalent to best supportive care; progression-free survival was 11 months for the axitinib group compared with 3.5 months for the best supportive care group [median HR 0.25, 95% CrI 0.17 to 0.38], approximation based on 3 extrapolated curves). For overall survival (33.5 months for the axitinib group compared with 23.5 months for the best supportive care group), the median hazard ratio for death censored for crossover was 0.63 (95% CrI 0.41 to 0.99).

- 3.11 The company identified some limitations in the evidence networks from the AXIS and TARGET trials that had an impact on the indirect comparison. The company stated that in the AXIS trial, the relative efficacy as measured by overall survival (which was not statistically significant) may have been diluted because an active comparator (sorafenib) was used in the trial. The overall survival results may also have been confounded because of the subsequent treatments received after progression. In the prior-cytokine subgroup, 46.4% of patients in both the axitinib and sorafenib groups received subsequent treatments after progression. In the prior-sunitinib subgroup, 60% of patients in the axitinib group and 65.2% of patients in the sorafenib group received subsequent treatments. The company also stated that the overall survival analysis may have been affected by the relatively long survival after progression because of the patient heterogeneity usually seen in advanced renal cell carcinoma, the likelihood of receiving subsequent therapy, and the variability in treatment decisions made after progression.
- 3.12 The company stated that in the TARGET trial, the overall survival result may have been confounded by crossover from the placebo arm to the sorafenib treatment arm. It said that the method of adjusting for crossover (censoring of the patients) was not appropriate because it could lead to selection bias. The

company stated that the rank-preserving structural failure time (RPSFT) method used in the NICE technology appraisal guidance on [everolimus for the second-line treatment of advanced renal cell carcinoma](#) would have been more appropriate, and that the method usually improves the hazard ratio in favour of the active treatment. Another limitation with the evidence from TARGET was the absence of a prior-sunitinib group. The company stated that the prior-cytokine group (patients who have never received a tyrosine kinase inhibitor such as sunitinib) and the prior-sunitinib group were considered to be clinically different populations that were not interchangeable. First-line therapy was considered to have failed more rapidly in the prior-cytokine group than in the prior-sunitinib group. Therefore, the prior-cytokine group may benefit more from second-line treatment, as shown by the higher median progression-free survival. Because of this, separate evidence was presented for the prior-sunitinib group.

Prior-sunitinib group

- 3.13 For the subgroup of patients who were previously treated with sunitinib in the AXIS trial, there was a statistically significant difference in the IRC-assessed median progression-free survival of 1.4 months (4.8 months in the axitinib group compared with 3.4 months in the sorafenib group, HR 0.74, 95% CI 0.57 to 0.96, $p=0.0107$), adjusted for performance status. The axitinib group also had a statistically significant 2-month longer investigator-assessed progression-free survival than the sorafenib group (HR 0.64, 95% CI 0.49 to 0.82, $p=0.0002$). The hazard ratio for median overall survival was 0.997 (95% CI 0.78 to 1.27, $p=0.49$), based on 15.2 months median overall survival in the axitinib group and 16.5 months in the sorafenib group.

Simulated treatment comparison

- 3.14 The company identified 1 trial (RECORD-1) in an additional systematic review of the literature in which sunitinib-refractory patients received best supportive care after disease progression. This was used to provide a link between axitinib and best supportive care in a prior-sunitinib population. The RECORD-1 trial compared everolimus plus best supportive care with placebo plus best supportive care, in patients with metastatic renal cell carcinoma that progressed after treatment with a tyrosine kinase inhibitor. As there was no direct link between the treatments used in the AXIS trial and those used in RECORD-1, the company performed a simulated treatment comparison to

create an adjusted indirect comparison between the axitinib prior-sunitinib group from AXIS and the best supportive care prior-sunitinib group from RECORD-1. The aim of the comparison was to estimate how the prior-sunitinib group from the AXIS trial would have performed if they had been treated with placebo, using data from RECORD-1. Patients in RECORD-1 were allowed to cross over to the everolimus arm, although the impact of the crossover was adjusted for using the RPSFT method, which the company considered to be valid. The company stated that 2 different figures for median progression-free survival for the everolimus arm of the prior-sunitinib group were published by 2 different authors (5.6 months and 3.9 months). The company chose the 3.9-month figure and this resulted in a hazard ratio of 0.34 (95% CI 0.23 to 0.51) when compared with 1.8 months for placebo in the prior-sunitinib group. The median overall survival was 14.8 months for everolimus in the prior-sunitinib group compared with 10.0 months for placebo in the ITT population (HR 0.53, confidence intervals not reported).

- 3.15 The company highlighted several differences between the AXIS and RECORD-1 trials. Firstly, 14% of patients in RECORD-1 had stopped prior treatment because of intolerance, rather than disease progression as in the AXIS trial. Secondly, only 43 patients in the everolimus arm of RECORD-1 had received prior sunitinib only, in contrast to the 194 prior-sunitinib patients in the axitinib arm of the AXIS trial. The company noted that some of the 43 patients in RECORD-1 may have had sunitinib intolerance rather than sunitinib-refractory disease, which may have led to potential bias because sunitinib-intolerant patients would be expected to respond better to subsequent treatment than patients with sunitinib-refractory disease. Thirdly, patients in RECORD-1 had received 1 or more prior treatments, whereas patients in AXIS had received only 1 first-line treatment. In RECORD-1, median progression-free survival was assessed in a prior-sunitinib-only subgroup (n=56). However, the overall survival and patient characteristics for this subgroup were not assessed. As a result, 2 approaches were taken in the simulated treatment comparison to compare axitinib with best supportive care in a prior-sunitinib population. The first compared the axitinib prior-sunitinib group in AXIS with the best supportive care ITT group in RECORD-1, and assumed that the ITT group would have the same overall survival and patient characteristics as the prior-sunitinib group in RECORD-1. The second approach compared the axitinib prior-sunitinib group with the everolimus prior-sunitinib group, and then applied the RPSFT-adjusted hazard ratio for everolimus to best supportive care to create a

modelled prior-sunitinib group.

- 3.16 The simulated treatment comparison was performed by analysing patient-level data from the axitinib arm of the AXIS trial to derive parametric failure-time (survival) equations incorporating baseline predictors of the end points (progression-free survival and overall survival). Five distributions were examined, but only the 2 best fitting (log-normal and Weibull) were used in the comparison, and an assumption of proportional hazards was applied. The results of the comparison suggested a progression-free survival and overall survival benefit from axitinib treatment compared with best supportive care and everolimus treatment when the log-normal and Weibull distributions were used. The estimated increase in mean progression-free survival and overall survival for the best supportive care ITT and everolimus prior-sunitinib simulated treatment comparison curves are commercial in confidence. The progression-free survival hazard ratio (0.34) for the prior-sunitinib group and adjusted overall survival hazard ratio (0.53) for the ITT group of RECORD-1 were applied to the everolimus simulated treatment comparison curves to generate modelled AXIS-like, prior-sunitinib progression-free survival and overall survival curves for best supportive care. This resulted in an estimated median progression-free survival of 1.7 months for the group of patients referred to in the company's submission as 'axitinib-like patients' if they had received placebo, compared with 5.8 months if they had received axitinib (HR not reported), a difference of 4.1 months. The median overall survival estimated for these patients was 8.3 months for placebo compared with 15.2 months for axitinib (HR not reported).

Indirect treatment comparison (RENCOMP)

- 3.17 The company also provided an additional analysis, using retrospective observational data from a Swedish database (Renal Comparison; RENCOMP) to estimate the overall survival hazard ratio for people who received sorafenib or best supportive care after first-line treatment with sunitinib. Patient characteristics such as age, sex and nephrectomy status were similar across the 2 treatment groups (sorafenib and best supportive care). However, the sorafenib and best supportive care groups differed in terms of year of diagnosis, lead time between metastatic disease and first prescription of sunitinib, diagnosis of primary metastatic disease and place of treatment. A multivariate Cox proportional regression analysis was performed using variables with

significance at the 5% level to adjust for uncertainty resulting from confounding, and an assumption of proportional hazards was applied. This resulted in a median overall survival hazard ratio of 0.62 (95% CI 0.41 to 0.94, $p=0.023$). The results from RENCOMP were used in an indirect comparison with the results from the prior-sunitinib group in the AXIS trial (median progression-free survival HR 0.74 [95% CI 0.57 to 0.96] and median overall survival HR 0.997 [95% CI 0.78 to 1.27]), to generate indirect hazard ratios for axitinib and best supportive care in the prior-sunitinib group. The results showed that axitinib was associated with an improvement in overall survival compared with best supportive care in a sunitinib-refractory population (HR 0.62, 95% CrI 0.38 to 0.997).

Cost-effectiveness evidence

- 3.18 The company conducted a systematic review of the literature and identified 3 studies on the cost effectiveness of active treatments compared with best supportive care for advanced and metastatic renal cell carcinoma after failure of a systemic therapy. None of the studies identified included axitinib, so the company carried out a de novo analysis on the cost effectiveness of axitinib compared with best supportive care for treating advanced renal cell carcinoma after failure of treatment with sunitinib or a cytokine. The economic evaluation was based on the 2 separate populations specified in the marketing authorisation for axitinib (the groups of people in whom treatment with sunitinib or cytokines has failed, also referred to as the prior-sunitinib and the prior-cytokine groups).
- 3.19 A 3-state Markov cohort model was developed, based on previous modelling of metastatic cancer using Microsoft Excel. All patients entered the model in the 'progression-free' health state and in each cycle could progress to the 'progressed disease' health state, progress from either of these health states to 'death', or remain in their current health state. The model had a lifetime horizon of 10 years consisting of 4-weekly cycles, included a half-cycle correction, and both costs and benefits were discounted at 3.5%. The analysis was performed from the perspective of the NHS and personal social services.
- 3.20 The proportion of patients in each health state at each point in time was calculated directly from parametric survival function equations. For the axitinib prior-cytokine group, the Weibull distribution was used to extrapolate the

overall survival and progression-free survival data because it was considered to provide the best model fit. Survival models based on log-logistic and Gompertz parametric distributions were used in a sensitivity analysis for overall survival because, of the 5 parametric distributions tested by the company, they provided the next-best model fit. However, the log-normal and Gompertz distributions were used in the sensitivity analysis to extrapolate progression-free survival. For the best supportive care group, parametric survival curves were generated by applying the hazard ratios from the indirect comparison (see section 3.10) to the parametric survival functions used to model the axitinib treatment group.

3.21 For the axitinib prior-sunitinib group, the log-normal distribution was used in the base case to extrapolate overall survival data because it provided the best model fit. The Weibull and Gompertz distributions provided the next-best fits, so these were explored in a sensitivity analysis. The Weibull distribution was used for progression-free survival data in the base-case analysis, whereas the log-normal and Gompertz distributions were explored in the sensitivity analysis. For the best supportive care group, the prior-sunitinib progression-free survival and the ITT population-adjusted hazard ratios (see section 3.16) were applied to the everolimus simulated treatment comparison curves to generate modelled AXIS-like, prior-sunitinib progression-free survival and overall curves. Only the Weibull distribution was used in the economic model for the survival curves, because the log-normal distribution did not support the use of hazard ratios. In a sensitivity analysis, the overall survival hazard ratio generated from the indirect comparison of the RENCOMP analysis and the prior-sunitinib overall survival analysis from the AXIS trial was applied to the axitinib parametric survival functions to generate parametric survival curves for the best supportive care group.

3.22 The utility values used in the model were derived from the AXIS trial using the EQ-5D questionnaire. The analysis was based on the full AXIS population because the p values indicated no statistically significant difference between the prior-sunitinib and prior-cytokine subgroups. The mean utility value for the progression-free health state was 0.69, based on the average of the EQ-5D index value at each time point in the AXIS trial and weighted by the number of patients still on treatment at that time point. The utility value for the progressed disease health state was 0.61, based on the weighted average of the mean utility at the end of treatment. The utility values used in the model were assumed to reflect the adverse event profile of the treatment from the AXIS trial. In a

systematic review of the literature, the company did not identify any sources reporting utility values for people with advanced renal cell carcinoma receiving best supportive care after sunitinib treatment has failed. Therefore, the company assumed that people receiving best supportive care would have the same utility value as people receiving axitinib in the model. Utility values from previous NICE technology appraisals, derived from a phase II study of sunitinib in a cytokine-refractory population, were explored in a sensitivity analysis. Quality of life was assumed to remain constant for each health state in the post-trial period.

- 3.23 The average cycle (4 weeks/28 days) costs of axitinib were estimated by applying the proposed patient access scheme, which is commercial in confidence and so cannot be shown here. This was based on the recommended dosing schedule of 5 mg twice daily until disease progression. The cost was adjusted for the relative dosing intensity observed in the AXIS trial, which was 102%. A dosing intensity of 80% was assumed in a scenario analysis to reflect the lower intensities observed in clinical practice and previous NICE technology appraisals. Drug discontinuation occurred because of disease progression or adverse events. The probabilities of discontinuation per cycle applied in the model were 0.80% and 1.26% for the prior-cytokine and prior-sunitinib groups respectively, although the discontinuation rates from adverse events alone were assumed to be the same. No administration cost was included in the company's model because axitinib is taken orally and the patient access scheme is a simple discount applied at the point of invoice. No drug costs were assumed for best supportive care.
- 3.24 The company stated that the costs associated with routine medical monitoring were based on those used in NICE's technology appraisal guidance on bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma and on everolimus for the second-line treatment of advanced renal cell carcinoma. The company also stated that these assumptions were validated with expert clinical opinion to ensure consistency with current clinical practice in the UK. These costs were applied equally to the axitinib and best supportive care groups in the company's model because patients were assumed to receive the same management regardless of their treatment. For the progression-free state, the total cost per cycle (£109.69) was based on 1 GP visit per cycle, 1 tumour scan per 3 cycles and 1 blood test per

cycle. The total cost per cycle for the progressed disease state was £319, and this included 1 GP visit per cycle, 3 visits by a specialist community nurse every 2 cycles, and 28 vials of pain medication per cycle. A scenario analysis was explored in which patients visited an oncologist rather than their GP. This resulted in a total management cost per cycle of £176.69 for the progression-free state and £386 for the progressed disease state. Costs associated with adverse events were included in the model for the progression-free state only, and were assumed by the company to be similar for the prior-sunitinib and prior-cytokine groups. Only the costs for grades 3 and 4 adverse events (which occurred in over 5% of the patient population) were included. For the axitinib group, the included adverse events were hypertension (£424 per episode) and diarrhoea (£544 per episode), and the cost of anaemia (£2068.47 per episode) was applied to the best supportive care group in a sensitivity analysis.

Before the appeal: company's additional clinical- and cost-effectiveness evidence

3.25 In response to the first consultation, the company presented evidence to support the robustness and reliability of the results for the prior-sunitinib group by developing the simulated treatment comparison analysis to include estimates of the standard errors and confidence intervals for the adjustment factors. Estimates of the standard error of the logarithm of the median progression-free survival and crossover-adjusted overall survival were obtained from RECORD-1. The delta method was used to estimate the standard error for the adjustment factors to enable the calculation of a 95% confidence interval. The company also provided a second set of 95% confidence intervals that only considered uncertainty in the derived axitinib equation and not the uncertainty in the survival estimates for the best supportive care population in the RECORD-1 trial. The 2 sets of confidence intervals estimated for progression-free survival were similar, but the confidence interval that accounted for uncertainty in the overall survival estimate was wider than the one excluding the uncertainty. The company stated that this difference in the overall survival confidence intervals was a result of the wide 95% confidence intervals for the acceleration factor from the RPSFT analysis used to adjust for crossover in RECORD-1.

3.26 In response to the first consultation, the company also provided its reasoning

for the plausibility of the survival gains of axitinib compared with best supportive care generated by its simulated treatment comparison in terms of the ratio of progression-free survival gain to overall survival gain. It stated that this relationship between the survival gains was also observed in some placebo-controlled trials for advanced renal cell carcinoma such as RECORD-1 (1 to 1.6 months, progression-free survival to overall survival gain) and TARGET (1 to 1.3 months, progression-free survival to overall survival gain considering the censoring method of adjusting for crossover). The company also presented the results in the context of a meta-analysis of 28 trials of advanced renal cell carcinoma that compared an active therapy with placebo or best supportive care. In this study, a subgroup of 24 studies without crossover resulted in a 1 to 1.61 months progression-free survival to overall survival gain, whereas another subgroup of 16 studies in which patients received prior therapy resulted in a 1 to 1.42 months progression-free survival to overall survival gain. The company also stated that in NICE's technology appraisal guidance on [everolimus for the second-line treatment of advanced renal cell carcinoma](#) the Committee had accepted a 1 to 1.4 months progression-free survival to overall survival gain relationship.

- 3.27 The company presented updated economic analyses that included a revised patient access scheme agreed with the Department of Health. The size of the discount is commercial in confidence. The company's updated results, including the various sensitivity analyses, include the revised patient access scheme unless stated otherwise.
- 3.28 The updated economic analyses incorporated a 15-year time horizon to address the ERG's concern that the 10 years used in the original model may not be in line with real-life expectancy. The company also applied prior-cytokine and prior-sunitinib subgroup specific utility values and relative dose intensity rates rather than the estimates for the ITT population used in the original model. In addition, a value of 0% for the percentage of people with hypertension, which was less than 1% in the TARGET trial, was applied to the revised model; this was assumed to be 2% in the original model. The probabilistic sensitivity analyses were also updated to include the use of standard errors rather than standard deviations for the progression-free health state utility (standard error [SE] =0.0035), progressed disease health state utility (SE=0.0175) and relative dosing intensity (SE=1.86%). The standard error of the cost of death was also applied in the revised analysis. Finally, the company identified and corrected a

transcript error that involved the timescale of the simulated treatment analysis. The correction reduced the estimated mean costs and quality-adjusted life years (QALYs) in all cases for both arms and this only had a marginal impact on the incremental cost effectiveness ratios (ICERs) for the 2 populations.

Prior-cytokine group

- 3.29 The results of the updated economic analysis showed that the additional QALY gains from axitinib treatment were observed in the progression-free state. The base-case assumptions resulted in an ICER of £55,284 per QALY gained (with the patient access scheme applied) for axitinib compared with best supportive care after failure of a cytokine. All the incremental costs and QALYs gained in the company's submission are commercial in confidence.
- 3.30 The company performed a univariate deterministic sensitivity analysis by varying some of the model input parameters using the 95% confidence interval. The cost-effectiveness result for the prior-cytokine group was most sensitive to changes in the overall survival hazard ratio and the post-progression utilities for axitinib and best supportive care in the univariate deterministic sensitivity analysis. The ICERs ranged from approximately £40,000 to more than £100,000 per QALY gained for changes in the utilities and more than £350,000 per QALY gained for changes in overall survival (with the patient access scheme applied). The base-case ICER was also sensitive to changes in the values of the survival parameters for the axitinib group. Changes in the cost estimates (such as GP visits, specialist nurse visits and tumour scans), discontinuation because of adverse events, relative dose intensity of axitinib, changes in the progression-free utility for the best supportive care group, and changes in the IRC-assessed progression-free survival hazard ratio from the AXIS trial had very little effect on the base-case results.
- 3.31 The probabilistic sensitivity analysis indicated that axitinib would have a 42% chance of being cost effective compared with best supportive care, if the maximum acceptable ICER was £50,000 per QALY gained with the patient access scheme applied to the prior-cytokine group. The company did not present the probability of axitinib being cost effective if the maximum acceptable ICERs were £20,000 per QALY gained or £30,000 per QALY gained.
- 3.32 The company also explored various scenario analyses to account for the

uncertainties associated with some of the assumptions in the base-case model. All results included the patient access scheme. The scenario analyses explored the effect on the ICER of:

- using alternative parametric distributions (log-normal, log-logistic and Gompertz) to extrapolate survival
- using external data to estimate utility values
- reducing the dosing intensity of axitinib to 80%
- assuming an oncologist visit instead of a GP visit for estimating costs in the progression-free state.

The results showed that the base-case ICER, when applying the patient access scheme, was most sensitive to the method of extrapolation of overall survival (£21,959 per QALY gained for the log-logistic method and £72,537 per QALY gained for the Gompertz method); whereas other scenarios resulted in ICERs close to the revised base case.

Prior-sunitinib group

- 3.33 The results of the economic analysis showed that there were additional QALY gains with axitinib before and after progression, although most of the additional QALYs gained were observed before progression. The base-case analysis resulted in an ICER of £33,538 per QALY gained (with the patient access scheme applied) for axitinib compared with best supportive care for the prior-sunitinib group. All the incremental costs and QALYs gained are commercial in confidence.
- 3.34 The univariate sensitivity analysis performed for the prior-sunitinib group showed that the ICER was most sensitive to changes in the survival parameter values for the axitinib group, with ICERs ranging from approximately £25,000 to £48,000 per QALY gained (with the patient access scheme applied). The base-case ICER was also sensitive to changes in the progressed disease utility values for the axitinib and best supportive care groups and progression-free utility value for the axitinib group; the resulting ICERs ranged from approximately £29,000 to £40,000 per QALY gained (with the patient access scheme applied). Changes in the cost estimates (such as GP visits, specialist nurse visits and tumour scans), discontinuation because of adverse events,

relative dose intensity of axitinib and changes in the progression-free utility for the best supportive care group had little impact on the base-case result.

3.35 The probabilistic sensitivity analysis showed that axitinib would have a 65% chance of being cost effective compared with best supportive care, if the maximum acceptable ICER was £50,000 per QALY gained and uncertainty around the median crossover-adjusted overall survival for best supportive care was considered (when applying the patient access scheme). However, when the uncertainty was excluded from the second set of the confidence intervals used, the probability of axitinib being cost effective compared with best supportive care increased to 90% at a maximum acceptable ICER of £50,000 per QALY gained, applying the patient access scheme. The company did not present the probability of axitinib being cost effective if the maximum acceptable ICERs were £20,000 per QALY gained or £30,000 per QALY gained.

3.36 Several scenario analyses were also performed by the company to explore the effect on the ICER of:

- using alternative parametric distributions (Weibull, log-normal and Gompertz) to extrapolate survival
- using alternative methods of comparison with best supportive care
- using external data to estimate utility values
- reducing the dosing intensity of axitinib to 80%
- assuming an oncologist visit instead of a GP visit for estimating costs in the progression-free state.

The ICER was most sensitive to the use of the Weibull and Gompertz distributions to extrapolate overall survival using the RENCAMP method of comparison (£47,515 and £39,479 per QALY gained respectively, with the patient access scheme applied), and reducing the dosing intensity of axitinib (£27,324 per QALY gained, with the patient access scheme applied). It was least sensitive to the use of alternative distributions to extrapolate overall survival using the simulated treatment method of comparison and costing based on an oncologist visit (ICERs ranged from £28,958 to £34,722 per QALY gained, with the patient access scheme applied). The company also applied the assumption of no QALY or survival gain post-progression used in the ERG's exploratory analysis to the updated analysis. The ICER estimated using this

- assumption and the updated analysis (including the patient access scheme) was £52,850 per QALY gained.

After the appeal: company's additional clinical and cost-effectiveness evidence

Company's submission addendum after the appeal for the prior-cytokine subgroup

- 3.37 After the appeal hearing, NICE issued an updated scope that included sunitinib and pazopanib as comparators in addition to best supportive care for the post-cytokine subgroup. The company carried out a literature review to identify trials that provided evidence on the efficacy and safety of axitinib, sunitinib and pazopanib in people with advanced renal cell carcinoma who had received previous cytokine therapy. The company identified 1 randomised controlled trial that compared axitinib with sorafenib (AXIS, see sections 3.1 to 3.8), 2 open-label, single-arm trials designed to assess the efficacy and safety of sunitinib (RTKC-0511-014 and A6181006/NCT00077974) and 1 randomised controlled trial that compared pazopanib with placebo (VEG105192).
- 3.38 RTKC-0511-014 was an open-label, single-arm, multicentre trial with 63 patients, designed to assess the efficacy and safety of sunitinib in patients with metastatic clear-cell renal cell carcinoma after failure of cytokine therapy. Median time to progression was 8.7 months (95% CI 5.5 to 10.7), and median overall survival was 16.4 months (95% CI 10.8 to NA). A6181006/NCT00077974 was an open-label, single-arm, multicentre trial with 106 patients, designed to confirm the anti-tumour efficacy of sunitinib monotherapy in patients with metastatic clear-cell renal cell carcinoma after failure of cytokine therapy. In A6181006/NCT00077974, median progression-free survival was 8.3 months (95% CI 7.8 to 14.5) and median overall survival was 23.9 months (95% CI 14.1 to 30.7) for sunitinib.
- 3.39 VEG105192 was designed to determine the efficacy and safety of pazopanib compared with placebo in patients with advanced and/or metastatic renal cell carcinoma who had not been previously treated or who had previously received cytokine therapy. The evidence submitted by the company was limited to the patients who had previously received cytokine therapy. Pazopanib statistically significantly increased progression-free survival compared with placebo (7.4 months compared with 4.2 months, HR 0.54, 95% CI 0.35 to 0.84, $p < 0.001$), but did not statistically significantly increase overall survival compared with placebo (22.7 months compared with 18.7 months, HR 0.82, 95% CI

0.57 to 1.16) in the ITT population. There was 54% crossover after progression from placebo to pazopanib.

- 3.40 Because there were no trials directly comparing axitinib with sunitinib, the company carried out a naive comparison of survival data for axitinib and sunitinib. The company stated that it was not possible to carry out an indirect comparison because the existing sunitinib studies were either single-arm or compared sunitinib with itself (administered at different times of the day). The company reported that, directly comparing axitinib and sunitinib through the naive comparison, axitinib increased progression-free survival by 3.3 months and overall survival by 5.5 months compared with sunitinib. A comparison with sunitinib in the post-cytokine subgroup was not included in the indirect comparison, because no randomised controlled trial evidence was available.
- 3.41 Because there were no trials directly comparing axitinib with pazopanib, the company undertook a naive comparison for overall survival and an indirect comparison for progression-free survival. Progression-free survival results were used in the network of evidence for the indirect comparison, but overall survival results were not included in the indirect comparison because of the issue of crossover between the placebo and treatment group. In the naive analysis, axitinib increased progression-free survival by 4.7 months and overall survival by 6.7 months compared with pazopanib. In the progression-free survival indirect comparison, axitinib increased progression-free survival compared with pazopanib in the post-cytokine population (median HR 0.465, 95% CrI 0.255 to 0.852).
- 3.42 The company did not provide a full incremental analysis of axitinib compared with sunitinib and pazopanib in the prior-cytokine population. Instead it provided a naive economic comparison based on the base-case ICER with the patient access scheme of £55,284 per QALY gained for axitinib compared with best supportive care (see section 3.29). In the naive comparison, best supportive care had a numerically higher median overall survival than either sunitinib or pazopanib (24 months compared with 23.9 months and 22.7 months respectively). The company stated that best supportive care has a lower cost than either sunitinib or pazopanib, and therefore it dominates (that is, it is more effective and less costly than) both sunitinib and pazopanib. The company stated that an estimate for overall survival for best supportive care using the lower 95% CI of 17.6 months was a more realistic estimate than 24 months. The

company provided alternative ICERs for axitinib compared with best supportive care, sunitinib and pazopanib using the median overall survival for best supportive care of 17.6 months. This generated an ICER of £36,493 per QALY gained for axitinib compared with best supportive care (typographical error corrected from £33,000 per QALY gained in the response to the second consultation), and an ICER of £55,000 per QALY gained as an upper limit for the ICER of axitinib compared with sunitinib or pazopanib. The company's view was that if the median overall survival for best supportive care was 17.6 months, then end-of-life criteria should be applied by the Committee, because axitinib is expected to offer at least 3 months additional benefit for both progression-free survival and overall survival over best supportive care, sunitinib and pazopanib; patients with advanced or metastatic renal cell carcinoma are expected to survive less than 24 months in the prior-cytokine subgroup; and the population of advanced or metastatic renal cell carcinoma patients who have received treatment with cytokines represent a small patient population.

Company's comments and analysis based on an abstract and presentation by Grunwald et al. for the post-sunitinib subgroup

- 3.43 Following the appeal, the company provided further data on the overall survival benefit attributable to tumour size reduction based on Grunwald et al. These data were a summary of the abstract and comments from the company, the presentation at the European Cancer Congress (hosted by the European Cancer Organisation [ECCO] and European Society for Medical Oncology [ESMO]) 2013 on the Grunwald analysis, and data on file from the company on the ECCO ESMO 2013 presentation.
- 3.44 Grunwald et al. was a retrospective cohort study correlating tumour shrinkage with overall survival in patients with metastatic renal cell carcinoma treated with systemic therapy (tyrosine kinase inhibitors, mTOR inhibitors and/or interferon). It included a total of 2749 patients, of whom 359 were treated with axitinib. The hazard ratios for the maximal tumour shrinkage were 0.267 (95% CI 0.201 to 0.354) for $\leq -100\%$ to $< -60\%$ tumour shrinkage, 0.697 (95% CI 0.589 to 0.825) for $\leq -60\%$ to $< -30\%$ tumour shrinkage, 1.618 (95% CI 1.383 to 1.893) for ≤ 0 to $< +20\%$ tumour shrinkage (that is, tumour growth), 1.918 (95% CI 1.540 to 2.389) for $\geq +20\%$ tumour shrinkage (that is, tumour growth), and 4.369 (95% CI 3.607 to 5.292) for the group with no post-baseline scan, relative to the $\leq -30\%$ to $< 0\%$ tumour shrinkage group, which showed that

tumour shrinkage is an independent predictor of overall survival for first- and second-line therapy. The company used the results from Grunwald et al. to weight the estimates of median overall survival for best supportive care from RECORD-1, by multiplying the median overall survival by the proportion of patients, giving a weighted estimate of 8.194 months (95% CI academic in confidence, and therefore not shown here). The company stated that this was consistent with the 8.3 months overall survival results from the simulated treatment comparison (see section 3.16), and that these results were consistent with the company's base-case analyses using the simulated treatment comparison, which gave an ICER of £33,538 per QALY gained in the prior-sunitinib group (see section 3.33).

Evidence Review Group comments

Company's clinical-effectiveness evidence

- 3.45 The ERG stated that there were a few limitations with the literature search conducted by the company, some of which were addressed by the company after clarification. Despite these limitations, the ERG considered that the search was adequate and accurately reflected the research question. It stated that AXIS, TARGET and RECORD-1 were good-quality clinical trials with sound methodologies, except for the method used to adjust for crossover in TARGET (censoring of patients). The ERG considered that censoring often introduces bias and it agreed that the method used to account for the crossover that occurred in RECORD-1 (RPSFT) was more appropriate. The ERG noted that, although the outcomes reported in the AXIS trial corresponded with those in the final scope, only progression-free survival and overall survival outcomes were presented for the comparison of axitinib with best supportive care.
- 3.46 The ERG noted that baseline patient characteristics were not reported separately for the prior-cytokine groups in either the AXIS or the TARGET trials. Therefore, the indirect comparison of the trial populations was based on the ITT groups in the 2 trials. The ERG noted that the patient characteristics of the ITT groups in the AXIS and TARGET trials were reasonably similar, with slight differences observed only in the MSKCC scores and the number of metastatic sites. The ERG considered that the potential bias associated with the hazard ratio for overall survival in TARGET may limit the robustness of the indirect comparison in the prior-cytokine group.

3.47 The ERG noted that the patient characteristics reported by the company for the AXIS and RECORD-1 trials were taken from the prior-sunitinib group of the axitinib and everolimus arms and the ITT group of the sorafenib and placebo arms. The ERG also noted the differences between the AXIS and RECORD-1 trials that were highlighted by the company (see section 3.15), which could limit the evidence available for comparing axitinib with best supportive care in a prior-sunitinib group. The ERG was uncertain whether a simulated treatment comparison presents a valid and reliable estimate of the clinical effectiveness of axitinib compared with best supportive care in this group of patients. The ERG considered that there could be potential bias associated with the simulated treatment comparison because it involves a comparison of 2 single treatment arms and not a comparison of randomised treatment allocation. The ERG also stated that the results of the comparison could not be verified because individual patient data from the AXIS trial were used and were not provided by the company. However, the ERG indicated that the analysis seemed to have been performed correctly and the reporting of methods, results and limitations was clear despite the issues identified. The ERG agreed with the company that combining observational data (a lower level of evidence) from the RENCOMP database with the data from the AXIS trial was a potential source of uncertainty because patients were not randomly allocated to receive the second-line treatments and the reasons for discontinuing first-line treatments were not known.

Company's cost-effectiveness evidence

3.48 The ERG was satisfied with the company's modelling approach, which was consistent with other published economic studies of advanced renal cell carcinoma and used a population that reflected the actual clinical population. At the time of the company's submission, the ERG re-emphasised that only approximately 6% of patients will receive cytokines as a first-line treatment. The ERG was satisfied that the best supportive care comparator used in the model reflected recommended UK clinical practice and was in line with the original scope for this appraisal.

3.49 The ERG accepted the company's choice of the distributions used in the base-case and scenario analyses. The ERG noted the company's clarification that patients who withdrew from treatment prematurely because of adverse events were still followed up in the trial, and were included in the estimates of

progression-free survival and the overall survival curves for the axitinib arm rather than the best supportive care arm. The ERG stated that this approach would only be valid if the patients were followed up for progression as well, and not for survival only. The ERG considered that the estimate of the QALYs in the axitinib group may have been affected if they were not followed up for progression, because disease is expected to progress earlier once patients stop treatment. It also noted that, because of earlier progression to the progressed disease state, the overall costs would be higher for the axitinib group compared with the cost in the model, which was set at 'zero' for the patients who withdrew. The ERG indicated that making this adjustment in the model would increase the base-case ICERs, although the impact would be limited by the relatively small group of patients withdrawing from the treatment prematurely.

- 3.50 The ERG was satisfied with the company's assumption that the utility value was the same for people receiving axitinib and people receiving best supportive care. It agreed that, although people on axitinib may experience utility decreases from adverse events, people receiving best supportive care would experience utility decreases from actively progressing uncontrolled disease. The ERG was concerned that the utility value applied in the progressed disease state remained constant after entry into that state, when it should actually decline as patients near the end of life. It noted that applying declining utility values would increase the ICER slightly if axitinib patients stayed in the progressed disease state for longer than best supportive care patients (prior-sunitinib group), but no impact would be observed if the time spent in the progressed disease state was the same for both treatment arms (prior-cytokine group). The ERG noted from the AXIS clinical trial report that health states were based on the US valuation. It stated that the utilities used in the model appear to be high because studies have shown that US valuations are consistently higher than UK valuations. The ERG stated that it could not reproduce the original utility for the progression-free state; a higher utility value of 0.73 was produced instead using the method described in the company's submission.

Company's additional clinical- and cost-effectiveness evidence before the appeal

- 3.51 The ERG stated that the additional details of the simulated treatment comparison in the prior-sunitinib group provided by the company were clearer than those in the original submission. It also stated that the delta method used to estimate the confidence intervals for the adjustment factors was appropriate.

The ERG stated that the set of confidence intervals that considered uncertainty in the survival estimates for both the axitinib and best supportive care populations was more appropriate (adjustment factors of -1.12 , 95% CI -1.295 to -0.955 using the log-normal distribution and -1.25 , 95% CI -1.418 to -1.1079 using the Weibull distribution, for progression-free survival and adjustment factors of -0.59 , 95% CI -2.01 to 0.82 using the log-normal distribution and -0.68 , 95% CI -2.10 to 0.73 using the Weibull distribution, for overall survival).

- 3.52 The ERG noted that the differences in the median progression-free survival and overall survival for axitinib and best supportive care had been reported as mean values in the company's original submission and then reported as median values in the company's updated analysis. The ERG emphasised the need for consistency in reporting these results, particularly if the progression-free survival and overall survival ratios are being calculated. The ERG also noted that confidence intervals were not provided for these differences in the original and updated analysis. The ERG noted that, in general, the simulated treatment comparison appeared to be well conducted, although it involved some major assumptions, such as the comparability of patients between the trials and that the results of 1 trial would apply in the setting of the other. The ERG stated that the simulated treatment comparison method was a fairly recent method of analysis and that its robustness and reliability are uncertain.
- 3.53 With respect to the plausibility of the survival gains of axitinib compared with best supportive care generated by the simulated treatment comparison, the ERG noted that the results of the meta-analysis of 28 studies presented by the company were based on the earlier published abstract of the Delea et al. (2009) study, and that the updated results based on the full published paper (which includes a larger number of studies) were slightly different from those in the abstract published earlier. The progression-free to overall survival gain relationship based on the subgroup of studies with patients who received prior treatment has been updated from 1 to 1.4 months in the abstract to 1 to 1.04 months in the full publication, whereas the relationship reported for the subgroup of studies in which crossover occurred has been updated from 1 to 1.61 months in the abstract to 1 to 1.29 in the full publication.
- 3.54 The ERG noted the impact of the patient access scheme on the company's base-case ICER. It also noted that the large impact on the ICER made by varying

the post-progression utilities in the prior-cytokine group from approximately £40,000 per QALY gained to over £100,000 per QALY gained (see section 3.30) was a result of the company's use of specific subgroup utilities in the updated analysis, which have a wider confidence interval. The ERG stated that the inclusion of the statistical uncertainties in the updated simulated treatment comparison analysis increased the impact on the ICER by varying the parameters of the parametric survival curves for the prior-sunitinib group. The ERG agreed with the company that the difference in the probabilistic sensitivity analysis results for the prior-sunitinib group (ranging between 65% and 90% probability of being cost effective at a maximum acceptable ICER of £50,000 per QALY gained, see section 3.35) showed that most of the cost-effectiveness uncertainty is because of uncertainty around the median crossover-adjusted (with the RPSFT method) overall survival for best supportive care in the RECORD-1 trial.

Company's submission addendum for the prior-cytokine group after the appeal

- 3.55 The ERG commented that the company had not updated the sunitinib searches, which were last performed in 2007. The ERG agreed with the company that a reliable indirect comparison between axitinib and sunitinib in the prior-cytokine population was not possible.
- 3.56 For the comparison of axitinib with pazopanib, the ERG commented that the ITT populations in the AXIS and VEG105192 trials were reasonably comparable, but that data in the prior-cytokine population were not presented. The ERG conducted additional analyses for an indirect comparison of overall survival between axitinib and pazopanib, using the inverse probability of censoring weighted (IPCW) and RPSFT methods to adjust for crossover in the placebo arm after progression. In the ITT population, the HR was 0.77, in favour of longer overall survival with axitinib than with pazopanib (95% CrI 0.44 to 1.38). In the IPCW analysis, the HR was 1.197 (95% CrI 0.55 to 2.61), and in the RPSFT analysis, the HR was 1.208 (95% CrI 0.30 to 4.82), both in favour of longer overall survival with pazopanib than with axitinib. The ERG noted that none of these analyses gave statistically significantly different results. The ERG stated that none of the overall survival indirect comparison analyses were likely to be reliable because the common treatment effect assumption was unlikely to apply for the RPSFT analysis, the no unmeasured confounder assumption was unlikely to apply to the IPCW assumption, and that all the confidence intervals were

likely to be biased. The progression-free survival analysis was the most likely to be reliable, because it was unaffected by crossover, and there was no clear evidence that any treatment was superior.

- 3.57 The ERG noted that for the company's naive cost-effectiveness analysis there was multiple use of trial single arms, all the results used median values, there were no estimations of uncertainty, and all the comparisons were pairwise and not incremental. The ERG commented that the company's cost-effectiveness analysis can only be seen as indicative, and that it does not provide an estimate of the cost effectiveness of axitinib compared with sunitinib or pazopanib respectively, but only a possible upper limit. However, the ERG acknowledged that, given the evidence base, no good options were available to robustly estimate an ICER for axitinib compared with sunitinib or pazopanib. The ERG also noted there was either a typographical error or a rounding error in the company's submission addendum after appeal, and that using the lower 95% confidence interval for the overall survival hazard ratio of 0.41 for axitinib compared with best supportive care resulted in an overall survival of 17.46 months for best supportive care, rather than 17.6 months as stated in the company's submission addendum after appeal. The ERG further noted that the selective use of this relationship led to an ICER of £36,493 per QALY gained, and not £33,000 per QALY gained, as stated in the company's submission addendum after appeal.

Company's comments and analysis based on Grunwald et al. for the post-sunitinib subgroup after the appeal

- 3.58 The ERG commented that, because there were no trial data, the real overall survival for the best supportive care group was not known, so the surrogate end point of tumour shrinkage could not be validated (using the Prentice criteria developed for validating surrogate end points). The ERG also noted that no patients receiving best supportive care were included in the Grunwald et al. analyses. The ERG commented that it was not clear how tumour shrinkage was assessed in the different trials in the analysis, whether there were any other factors correlated with either tumour shrinkage or overall survival or both, and whether crossover between treatments was permitted after treatment failure.
- 3.59 Full details of all the evidence are in the [committee papers](#).

4 Consideration of the evidence

The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of axitinib, having considered evidence on the nature of advanced renal cell carcinoma and the value placed on the benefits of axitinib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

- 4.1 The Committee considered the clinical need for treatment in people with advanced renal cell carcinoma in whom previous treatments with tyrosine kinase inhibitors or cytokines have failed. The Committee heard from the clinical experts that there was a need for more drugs for people whose disease has become resistant to first-line treatment. It noted the comment from the patient experts that there was an unmet clinical need in this group of people because there are currently no second-line drugs recommended by NICE. The patient experts also stated that availability of another treatment would offer a sense of hope to patients and their families or carers and also reduce the mental burden associated with the lack of treatment options. The patient experts indicated that patients were aware of the adverse events associated with axitinib and were prepared to cope with them.
- 4.2 The Committee further noted the emphasis placed by the consultees on the unmet clinical need for treatment along with the impact, mental burden and uncertainty that limited treatment choice has on people affected by advanced renal cell carcinoma. It took this into full consideration when making its decisions. The Committee heard from the clinical experts that the use of cytokines is rapidly decreasing in clinical practice and only a few people currently receive them because most patients begin treatment with sunitinib or pazopanib. It also noted the consultee comments on a potential breach of article 2 (the right to life) of the Human Rights Act (1998). The Committee exercised due regard to NICE's commitment to promote equality, eliminate unlawful discrimination and actively consider the implications of its guidance for human rights, as stated in section 1.4 of the [guide to the methods of technology appraisal 2013](#).
- 4.3 The Committee noted the marketing authorisation for axitinib (that is, for treating adults with advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine) and discussed the population for whom treatment with axitinib would be appropriate in clinical practice. It kept in mind

that of the 2 antivasular endothelial growth factor first-line treatments recommended by NICE (sunitinib and pazopanib), only sunitinib had been specified in the marketing authorisation for axitinib. The clinical experts further stated that, although both sunitinib and pazopanib are used interchangeably in clinical practice, patients are increasingly initially treated with pazopanib. The Committee noted this and was concerned that the exclusion of a prior-pazopanib group from the AXIS trial and the axitinib marketing authorisation could affect choice of first-line therapy in clinical practice, given that a large number of people currently receive pazopanib. It heard from the clinical experts that, in practice, axitinib would be used in the prior-pazopanib group as well, because pazopanib and sunitinib are both tyrosine kinase inhibitors with similar biochemical activities. This was reflected in the updated scope after appeal for the prior-cytokine group, with sunitinib, pazopanib and best supportive care as comparators. The Committee also noted comments from the second consultation that any NICE recommendation for the use of axitinib as a second-line therapy should not discriminate against people who have already received pazopanib. The Committee agreed that axitinib would be positioned in the treatment pathway for patients with advanced renal cell carcinoma as a second-line treatment for patients who received treatment with a tyrosine kinase inhibitor (either sunitinib or pazopanib).

Clinical effectiveness

- 4.4 The Committee examined the clinical evidence from the AXIS trial, which compared axitinib with sorafenib. The Committee noted that the trial was well conducted and the relevant outcomes were assessed in line with the scope of the appraisal. However, it noted the difficulties in interpreting the AXIS trial results in this appraisal because of the lack of comparisons with any of the scope comparators. The Committee noted that the better progression-free survival results for axitinib (6.7 months for the axitinib group compared with 4.7 months for the sorafenib group [HR 0.67, 95% CI 0.54 to 0.81, $p < 0.0001$]) did not translate into statistically significant overall survival benefits (20.1 months for the axitinib group compared with 19.2 months for the sorafenib group [HR 0.97, 95% CI 0.80 to 1.17, $p = 0.37$]) for the full trial population. The Committee heard the company's explanation that this could be a result of the use of subsequent cancer treatments after progression. It was satisfied with the health-related quality-of-life data collected and assessed in the AXIS trial using both generic and disease-specific instruments. The Committee concluded that AXIS was a

well-conducted trial, which showed that axitinib provided clinical benefit to people who have been treated previously with sunitinib or a cytokine. Because there was no relevant comparator in the AXIS trial, the Committee concluded that its discussion of the efficacy of axitinib would need to be based on the results of the indirect and the simulated treatment comparisons performed by the company. It also concluded that it was reasonable to separate out the results for patients who had received only prior cytokines from people who had received prior tyrosine kinase inhibitors.

- 4.5 The Committee heard from the clinical experts and the company that approximately 1% of patients would receive only prior cytokines. Acknowledging the clinical experts' views (see section 4.2), the Committee noted that the prior-cytokine population has been diminishing since the introduction of sunitinib and pazopanib and NICE's approval of these as first-line treatments. It considered that 'prior-cytokine patients' would, in practice, be given sunitinib or pazopanib, despite previous treatment with cytokines. The Committee examined the analyses performed to generate treatment comparisons of axitinib with best supportive care, sunitinib and pazopanib in the prior-cytokine group.
- 4.6 The Committee discussed the analysis performed to generate a comparison of axitinib with best supportive care in the prior-cytokine group. It noted that the evidence for the indirect comparison was based on the AXIS trial (which compared axitinib with sorafenib) and the TARGET trial (which compared sorafenib with placebo). The Committee accepted the company's use of placebo as a proxy for best supportive care in the indirect and simulated treatment comparisons. It was aware that patient baseline characteristics were not presented separately for the prior-cytokine subgroups in the 2 trials. It noted that the 2 trials were not fully comparable in terms of Memorial Sloan-Kettering Cancer Centre (MSKCC) scores, prior treatments and number of metastatic sites reported. The Committee noted that crossover in the TARGET trial was adjusted by censoring the patients who crossed over and considered that this could have resulted in bias and ultimately affected the robustness of the results of the indirect comparison (progression-free survival of 11 months for the axitinib group compared with 3.5 months for the best supportive care group, a 7.5-month difference [HR 0.25, 95% CrI 0.17 to 0.38] and overall survival of 33.5 months for the axitinib group compared with 23.5 months for the best supportive care group, a 10-month difference [HR 0.63, 95% CrI 0.41 to 0.99]).

It also noted that an assumption of proportional hazards, which assumes a constant treatment effect over a lifetime, had been used to derive the survival estimates and had not been tested. The Committee agreed that, although the results might not be robust, the indirect comparisons were adequately performed. The Committee concluded that axitinib was more clinically effective than best supportive care in the prior-cytokine population.

- 4.7 The Committee considered the naive comparison performed to compare axitinib with sunitinib in the prior-cytokine population. It noted that the little evidence available was from single-arm trials, and that the Evidence Review Group (ERG) agreed with the company that an indirect comparison was not appropriate given the lack of data. The Committee noted that axitinib provided a 5.5-month extension to overall survival compared with sunitinib in the naive comparison. The Committee concluded that, although the naive comparison was the best option given the available evidence, the results were not robust and were subject to uncertainty.
- 4.8 The Committee discussed the evidence used in the indirect comparison of axitinib with pazopanib in the prior-cytokine subgroup, which was based on the AXIS trial (axitinib compared with sorafenib), the TARGET trial (sorafenib compared with placebo) and the VEG105192 trial (pazopanib compared with placebo). The Committee noted that, as a result of the crossover between treatment arms in the VEG105192 trial, the company had only performed an indirect comparison using progression-free survival as an end point and had performed a naive comparison for the overall survival data. The Committee noted that the progression-free survival comparison favoured axitinib, and that the naive overall survival comparison suggested that axitinib provided an additional 6.7 months overall survival benefit compared with pazopanib (see section 3.41). The comparison also suggested that best supportive care provided an additional 1.3 months overall survival over pazopanib (24 months for best supportive care compared with 22.7 months for pazopanib, see section 3.42). The Committee heard from the clinical experts that it was not clinically plausible that best supportive care would have a median overall survival of 24 months, or that best supportive care would have a survival benefit over sunitinib or pazopanib. The Committee then considered the exploratory indirect comparison carried out by the ERG for overall survival. It noted that the hazard ratios for overall survival varied from 0.77 (suggesting that axitinib is better than pazopanib) to 1.21 (suggesting that pazopanib is better than

axitinib) depending on the approach used to adjust for crossover and that all the hazard ratios were associated with wide confidence intervals (see section 3.56). The Committee agreed that, although evidence in favour of a relative advantage for axitinib was available from the progression-free survival comparison, the ERG's indirect comparisons for overall survival data were more appropriate than the company's naive comparison, and these did not favour axitinib. The Committee concluded that the results generated from the naive and indirect comparisons for overall survival and progression-free survival were all subject to substantial uncertainty. The clinical experts agreed with this and did not consider axitinib to be different in effectiveness from sunitinib or pazopanib after prior-cytokine treatment. The Committee concluded that axitinib was likely to have clinical effectiveness comparable to pazopanib and sunitinib.

4.9 The Committee considered the simulated treatment comparison of axitinib with best supportive care (in line with the NICE scope) performed for the prior-sunitinib subgroup using evidence from the AXIS trial (which compared axitinib with sorafenib) and the RECORD-1 trial (which compared everolimus with placebo). It noted that this method of comparison was used to create an adjusted indirect comparison of axitinib with best supportive care in the prior-sunitinib group. The Committee discussed whether the use of the simulated treatment comparison method could be considered reliable and valid given that it is a relatively new method of treatment comparison. It noted the ERG's comment that it was based on a comparison of 2 single treatment arms without random allocations to treatment. The Committee was aware that crossover also occurred in the RECORD-1 trial and, although this was adjusted for using the rank-preserving structural failure time (RPSFT) method, it noted that this method may not be appropriate for subgroups because it assumes the same treatment effect applies across the whole trial population, as well as there being no unobserved factors that should have been controlled for in the analysis. It was also aware that there were key differences between the trial populations in RECORD-1 and AXIS, which could bias the results of the simulated treatment comparison, such as:

- the higher number of prior therapies allowed in RECORD-1
- the small number of people in the prior-sunitinib group
- the inclusion of sunitinib-intolerant patients who had discontinued sunitinib treatment and

- the use of the intention-to-treat (ITT) population (rather than the prior-sunitinib population) to estimate overall survival in the placebo arm of the RECORD-1 trial.

The Committee was therefore concerned about the validity of the simulated treatment comparison analysis. However, it also noted that the company performed an alternative indirect comparison for the prior-sunitinib group using evidence from AXIS and the Swedish database (Renal Comparison; RENCOMP) analyses of sorafenib compared with best supportive care, but noted that the RENCOMP analysis was based on observational data without random allocation to treatments and also needed cautious interpretation. The Committee additionally noted that an assumption of proportional hazards had again been used in the simulated treatment and RENCOMP analyses to derive the survival estimates and had not been tested. The Committee concluded that there were serious limitations with the indirect comparisons performed for the prior-sunitinib group, and that the outcomes from the simulated treatment comparison (progression-free survival [5.8 months for axitinib compared with 1.7 months for placebo], overall survival [15.2 months for axitinib compared with 8.3 months for placebo]) and indirect comparison (overall survival [HR 0.62, 95% CrI 0.38 to 0.997]) should be interpreted with caution. The Committee noted that the company provided confidence intervals for the prior-sunitinib group to account for uncertainty in the results, and it was aware that the simulated treatment comparison was an unconnected comparison of 2 arms from separate studies. The Committee concluded that the robustness and reliability of the estimates from the simulated treatment comparison remained unclear, given the number of uncertainties highlighted.

- 4.10 The Committee examined the plausibility of a post-progression survival gain with axitinib in the context of the progression-free and overall survival relationship presented by the company (see section 3.26). It compared the relationship between progression-free survival and overall survival gain estimated from the company's simulated treatment comparison (1 to 1.6) and that originally modelled by the ERG (1 to 1). It noted that the relationship had been weakened by the inclusion of more studies in which crossover occurred in the updated meta-analysis (1 to 1.04 for the subgroup of trials with prior treatment on the basis of updated RECORD-1 analyses), but that this analysis was not robust because it did not properly take into account crossover between treatment arms (the relationship rose to 1 to 1.29 when adjustments for crossover were made). The Committee also heard from the company that active targeted treatments are associated with higher response rates and tumour shrinkage compared with best supportive care, based on Grunwald et al. The

Committee agreed that the evidence from Grunwald et al. gave some support to the company's simulated treatment comparison results on the post-progression survival benefits of axitinib over best supportive care.

- 4.11 The Committee considered the adverse event profile associated with axitinib that was observed in the AXIS trial. The Committee noted that diarrhoea, which was the most common adverse event, occurred with similar frequency in the axitinib and sorafenib groups. It was aware that hypertension, dysphonia, nausea and hypothyroidism occurred more frequently in the axitinib group, although hand-foot syndrome, rash and alopecia occurred more frequently in the sorafenib group. The Committee also noted the comment from the clinical experts that axitinib was a well-tolerated drug except for the high occurrence of hypertension, which is common with all tyrosine kinase inhibitors. The patient experts commented that people would be willing to accept these adverse events, and so the Committee concluded that axitinib has a manageable adverse event profile compared with other treatments for advanced renal cell carcinoma.

Cost effectiveness

- 4.12 The Committee considered the company's economic model and the ERG's critique of the model. It was satisfied that the outlined economic analysis was acceptable for assessing the cost effectiveness of axitinib. The Committee concluded that the appropriate populations and comparators for the economic evaluation had been captured in the model.
- 4.13 The Committee discussed the assumptions made by the company in developing the economic model. It noted that when alternative survival distributions for progression-free and overall survival were tested in the scenario analysis, they resulted in sizeable changes to the base-case result for the prior-cytokine population and moderate changes for the prior-sunitinib population (see sections 3.30, 3.34 and 3.54). The Committee concluded that the model results were highly sensitive to the distributions used to extrapolate survival.
- 4.14 The Committee discussed the plausibility of the survival gains estimated for the prior-cytokine group from the economic model. It heard from the clinical experts and the patient expert that the overall survival gain of approximately 24 months in the best supportive care group of the prior-cytokine group is not

seen clinically. It noted the company's comment that the implausibility observed may have resulted from the overall survival of 14 months in the placebo arm of TARGET, which was not properly adjusted for crossover. The Committee considered that this possible over-estimation of the overall survival in TARGET was carried over into the overall survival results in the indirect comparison and ultimately affected the model results for the best supportive care group. The Committee heard from both the clinical experts and the company that the lower 95% confidence interval estimate of 17.46 months for overall survival in the best supportive care group was more clinically plausible than the median of 24 months. The Committee was uncertain whether pazopanib and sunitinib were extendedly dominated by axitinib (that is, a quality-adjusted life year [QALY] is attained at a higher cost with pazopanib or sunitinib than with axitinib because the incremental cost effectiveness ratio (ICER) for pazopanib or sunitinib compared with best supportive care is higher than that for axitinib compared with best supportive care), as in the company's naive economic analysis (see sections 3.42 and 3.57). It also noted that the ICERs were sensitive to some of the parameters and assumptions used in the model (such as the utility values, the value of the survival parameters and the type of distribution used to extrapolate survival). The Committee concluded that the company's base-case ICER of approximately £55,300 per QALY gained (with the patient access scheme applied) may have been over-estimated based on the unlikely overall survival gains with best supportive care in the prior-cytokine population, and that there was evidence that the true ICER for the comparison of axitinib with best supportive care in the prior-cytokine population could be lower if the true overall survival for best supportive care was closer to 17.46 months.

- 4.15 The Committee considered the uncertainty around the company's base-case estimates of £33,500 and £52,900 per QALY gained in the prior-sunitinib group. It recognised that the use of the simulated treatment comparison method to derive a best supportive care comparison for axitinib in the group was the greatest source of uncertainty. The Committee discussed the plausibility of the survival gains estimated for the prior-sunitinib group (figures are commercial in confidence; see section 3.16). It noted that the median survival gain difference between axitinib and best supportive care estimated directly from the trials was increased by 63% when modelled (median overall survival estimated for the placebo group was 8.3 months compared with 15.2 months for axitinib). Furthermore, the Committee noted that an implausibly high proportion of the total QALY gains with axitinib (compared with best supportive care) in the

prior-sunitinib group was observed after progression when active treatment with axitinib had stopped. It noted that this was not a feature in either the prior-cytokine analysis or the AXIS trial results. The Committee examined the exploratory analysis performed by the ERG and company in which it was assumed that there was no QALY difference between axitinib and best supportive care in the prior-sunitinib group after progression. When it was also assumed that there was no cost difference after progression the resultant ICER was approximately £52,900 per QALY gained (with the patient access scheme applied). The Committee concluded that the results from the simulated treatment comparison and the post-progression model outputs for the prior-sunitinib group should be interpreted with caution because they lacked clinical plausibility.

- 4.16 The Committee also noted that use of the RENCAMP indirect comparison of axitinib and best supportive care gave higher ICER values than the company's base-case result. When the RENCAMP method was used rather than the simulated treatment comparison, the ICER increased to over £40,000 per QALY gained (with the patient access scheme applied) using the Weibull and Gompertz distributions, suggesting that the method of obtaining a best supportive care comparison was a key driver of the results in this population. The Committee concluded that the results for the prior-sunitinib group should be interpreted with caution because not all the uncertainties had been fully considered.
- 4.17 The Committee considered the company's comments and the summary of Grunwald et al. that some evidence exists from metastatic renal cell carcinoma trials showing QALY gains in the post-progression period in addition to those gained in the progression-free period when targeted therapies are compared with best supportive care in the prior-tyrosine kinase inhibitor group (see section 4.10). The Committee noted the evidence from Grunwald et al. suggesting that there is plausible post-progression benefit because of tumour shrinkage. The Committee concluded that the relationship between progression-free survival and overall survival gain for the prior-sunitinib group was likely to lie between the company's estimate and the ERG's estimate, and was therefore likely to be larger than 1.04 and less than 1.6.
- 4.18 The Committee discussed the available cost-effectiveness estimates for the prior-cytokine group. It noted that the ICER for axitinib compared with best

supportive care fell below £55,300 per QALY gained with any estimate of the relationship between progression-free survival and overall survival gain greater than 1 to 1. It noted that the company's base-case ICER of approximately £55,300 per QALY gained (with the patient access scheme applied) generated for the prior-cytokine group compared with best supportive care was based on the overall survival for best supportive care of 24 months, but fell to £36,500 per QALY gained if 17.46 months for overall survival for best supportive care was used (see section 4.14). The Committee noted there were uncertainties that might increase or decrease this ICER, and concluded that the most plausible ICER is above the range usually considered to be a cost-effective use of NHS resources in NICE technology appraisals (between £20,000 and £30,000 per QALY gained). Based on the comparable clinical-effectiveness evidence in the prior-cytokine group and the differences in NHS costs, the Committee concluded that axitinib, sunitinib and pazopanib could have comparable cost effectiveness.

4.19 For the prior-sunitinib population, the Committee noted that, although there was uncertainty in the simulated treatment comparison method, it accepted that the Grunwald et al. analysis was supportive. It considered that a more plausible ICER for the prior-sunitinib group was likely to lie between the base-case estimate with a progression-free to overall survival gain relationship of 1 to 1.6 (approximately £33,500 per QALY gained) and the estimate assuming no survival gain with a survival relationship of 1 to 1 (approximately £52,900 per QALY gained). Given the balance of the evidence, the Committee concluded that the ICER would likely be towards the middle of this range.

4.20 Because the ICERs for both populations were above £30,000 per QALY gained, the Committee discussed whether axitinib for advanced renal cell carcinoma fulfilled the criteria for a life-extending, end-of-life treatment, which are that:

- the treatment is indicated for patients with a short life expectancy, normally less than 24 months
- there is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment and
- the treatment is licensed or otherwise indicated for small patient populations.

In addition, when taking these criteria into account, the Committee must be persuaded

- that the estimates of the extension to life are robust and that the assumptions used in the reference case of the economic modelling are plausible, objective and robust.

4.21 The Committee agreed that the life expectancy of people with advanced renal cell carcinoma in whom prior cytokines and tyrosine kinase inhibitors such as sunitinib and pazopanib have failed was less than 24 months. It also noted the company's evidence to indicate that axitinib treatment offers an extension to life of at least an additional 3 months in the case of the prior-sunitinib population, compared with the current NHS treatment of best supportive care (see section 4.9). It noted that the company's estimate of the eligible population for whom axitinib is licensed (most in the prior-sunitinib group), that is, 1580 people in year 1 and up to 1743 people in year 5, represented a small patient population. The Committee concluded that axitinib was shown to be a life-extending, end-of-life treatment for the prior-sunitinib population. It also agreed that it was not reasonable to limit this conclusion to people whose prior tyrosine kinase inhibitor was sunitinib, given the growing, if not majority use, of pazopanib as a first-line treatment. This would leave an unmet need and would not reflect clinical practice. Therefore the Committee concluded that its recommendations should apply to the whole prior-tyrosine kinase inhibitor population.

4.22 With regard to the end-of-life criteria in the prior-cytokine population, the Committee agreed that the overall survival gains with best supportive care were improbable, and that axitinib was likely to provide a greater than 3-month survival benefit compared with best supportive care. The Committee considered the comments received from the company of axitinib on the second consultation, on the extension of life provided by axitinib compared with pazopanib being greater than 3 months. The Committee noted that this was supported only by the company's indirect comparison calculations and for progression-free survival and not for overall survival, for which the ERG had shown the possible superiority of pazopanib (see section 4.8). There was indirect comparison evidence only for axitinib compared with pazopanib, and not with sunitinib. Therefore, the Committee concluded that in the prior-cytokine population, substantial uncertainty remained around the naive comparisons between axitinib, sunitinib and pazopanib, and the end-of-life criteria could only be considered met if best supportive care were the only comparator (see section 4.6).

4.23 The Committee then discussed whether the valuation of the health-related

quality of life necessary for axitinib to be considered a cost-effective use of NHS resources for the prior-sunitinib population was reasonable. It discussed both the range of ICER valuations available and the degree of certainty around the estimates. The range of ICERs was £33,500 to £52,900 per QALY gained, and the most plausible valuations depended on the assumptions around the relationship between progression-free survival and overall survival and were likely to be towards the middle of this range (see sections 4.17, 4.18 and 4.19). The Committee concluded that, although the ICERs were subject to considerable uncertainty and were high, the additional weight from the end-of-life criteria that could be assigned to the original QALY benefits in this patient group led to the cost effectiveness of the drug falling within the range currently considered a cost-effective use of NHS resources. Taking into account both the value of the ICERs and the uncertainty around the ICERs, the Committee concluded that axitinib could be considered a cost-effective use of NHS resources in the prior-tyrosine kinase inhibitor population under the supplementary criteria for appraising life-extending, 'end-of-life' treatments.

- 4.24 The Committee then discussed whether axitinib could be considered a cost-effective use of NHS resources for the prior-cytokine population. Although the Committee did not accept the superiority of axitinib over sunitinib and pazopanib and therefore did not accept that the end-of-life criteria had been met for this population, it was aware of the comments from the clinical experts that axitinib, sunitinib and pazopanib were used interchangeably in clinical practice (see section 4.3). The Committee took both this and the cost-effectiveness uncertainties into account. It concluded, first, that axitinib was comparable to the alternative treatments that had been recommended by NICE that meet the 'end-of-life' criteria (sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma and pazopanib for the first-line treatment of advanced renal cell carcinoma) and, second, that only a very small population was now included in the prior-cytokine group and that more uncertainty could be accepted in these circumstances. The Committee therefore concluded that an ICER compared with best supportive care above but close to the upper limit of the normal range was acceptable, and axitinib could be considered a cost-effective use of NHS resources in the prior-cytokine population.
- 4.25 The Committee further considered its recommendation. It noted that the marketing authorisation of axitinib is for treating adults with advanced renal cell

carcinoma, after failure of prior treatment with sunitinib or a cytokine and does not include previous treatment with pazopanib. However it reiterated that it was not reasonable to limit its recommendation to people whose prior tyrosine kinase inhibitor was sunitinib, given the growing, if not majority use, of pazopanib as a first-line treatment. This would leave an unmet need and would not reflect clinical practice. The Committee recognised that the requirement to provide funding by the relevant health bodies (clinical commissioning groups, NHS England and local authorities) within 3 months of its date of final guidance publication applies only within the marketing authorisation (see [implementation sections 5.1 to 5.3](#)).

4.26 The Committee noted the comments made by the company and patient organisations regarding the 'innovativeness' of axitinib. They stated that axitinib was expected to offer a step-change in the second-line management of advanced renal cell carcinoma by improving survival beyond what is expected with best supportive care, while maintaining health-related quality of life. The Committee understood this, as well as noting the needs of patients for further treatment options, but considered that there were no additional gains in health-related quality of life over those already included in the QALY calculations. Therefore, the Committee concluded that the innovative aspects of axitinib with regard to patient benefits were already incorporated in the economic model and analyses.

4.27 The Committee discussed potential equality issues and gave particular consideration to avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity. The Committee noted the following potential equality issues raised by the patient experts, patient organisations and NHS organisations:

- Older patients with additional health issues may find adverse effects more difficult to tolerate.
- People with rare cancers such as kidney cancer have inequity of access to NHS-funded treatments.
- The scope does not consider axitinib for people for whom first-line immunotherapy is unsuitable.

- The Committee considered that these were not equality issues under the legislation. No further equality issues were raised at the Committee meeting or by Committee members. It therefore concluded that its recommendations did not have a particular impact on any of the groups whose interests are protected by the legislation and that there was no need to alter or add to its recommendations.

Summary of Appraisal Committee's key conclusions

TA333	Appraisal title: Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment	Section
Key conclusion		
Axitinib is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine, only if the company provides axitinib with the discount agreed in the patient access scheme.		1.1
At the time of publication (February 2015), axitinib has a UK marketing authorisation only for use after failure with first-line sunitinib or a cytokine. If it is considered for use after any other first-line treatments, the prescriber should obtain and document informed consent and follow the relevant guidance published by the General Medical Council. ^[a]		1.2
Because the remit referred to NICE by the Department of Health for this technology appraisal only includes adults who have been previously treated with sunitinib, the use of axitinib after treatment with other tyrosine kinase inhibitors is not subject to statutory funding.		1.3
The Committee concluded that the incremental cost effectiveness ratio (ICER) of approximately £55,300 per quality-adjusted life year (QALY) gained (with the patient access scheme applied) may have been over-estimated based on the unlikely overall survival gains with best supportive care in the prior-cytokine population. Based on the comparable clinical-effectiveness evidence in the prior-cytokine group and the differences in NHS costs, the Committee concluded that axitinib, sunitinib and pazopanib could have comparable cost effectiveness.		4.14, 4.18

<p>The Committee considered that a more plausible ICER for the prior-sunitinib group was likely to lie between the base-case estimate with a progression-free to overall survival gain relationship of 1 to 1.6 (approximately £33,500 per QALY gained) and the estimate assuming no survival gain with a survival relationship of 1 to 1 (approximately £52,900 per QALY gained). The Committee concluded that the ICER for the prior-sunitinib group was likely to be towards the middle of the range.</p>	<p>4.19</p>	
<p>The Committee concluded that in the prior-cytokine group, substantial uncertainty remained around the naive comparison, and the end-of-life criteria could only be considered met if best supportive care was the only comparator. The Committee concluded that axitinib could be considered a cost-effective use of NHS resources in the prior-tyrosine kinase inhibitor population under the supplementary criteria for appraising life-extending, 'end-of-life' treatments. The Committee concluded that it was not reasonable to limit this conclusion to people who had received sunitinib as their prior-tyrosine kinase inhibitor, because this would not reflect clinical practice given the growing, if not majority, use of pazopanib. This would leave an unmet need in this population, and so the Committee concluded that its recommendations must apply to the whole prior-tyrosine kinase inhibitor population.</p>	<p>4.21–4.23</p>	
<p>The Committee did not accept that axitinib was superior to sunitinib and pazopanib in the prior-cytokine population, and therefore did not accept that the end-of-life criteria had been met for this population, but it was aware that axitinib, sunitinib and pazopanib are used interchangeably in clinical practice. The Committee concluded that it was comparable to the alternative treatments recommended by NICE that meet the end-of-life criteria, and that there was now only a very small population included in the prior-cytokine group and more uncertainty could be accepted. It therefore concluded that an ICER compared with best supportive care above but close to the upper limit of the normal range was acceptable for the prior-cytokine group.</p>	<p>4.24</p>	
<p>Current practice</p>		
<p>Clinical need of patients, including the availability of alternative treatments</p>	<p>The patient experts stated that there was an unmet clinical need for people whose disease has become resistant to first-line treatment. This is because there are currently no second-line drugs for renal cell carcinoma recommended by NICE.</p>	<p>4.1</p>

	<p>The Committee took into full consideration the impact, mental burden and uncertainty that limited treatment choice has on people affected by advanced renal cell carcinoma, along with the unmet clinical need for treatment, when making its decisions. It also noted the consultee comments on a potential breach of article 2 (the right to life) of the Human Rights Act (1998). The Committee exercised due regard to NICE's commitment to promote equality, eliminate unlawful discrimination and actively consider the implications of its guidance for human rights as stated in section 1.4 of the guide to the methods of technology appraisal 2013.</p>	4.2
The technology		
<p>Proposed benefits of the technology</p> <p>How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?</p>	<p>The Committee understood that axitinib was expected to improve survival beyond what is expected with best supportive care in the second-line management of advanced renal cell carcinoma, but considered that there were no additional gains in health-related quality of life over those already included in the QALY calculations.</p>	4.26
<p>What is the position of the treatment in the pathway of care for the condition?</p>	<p>Axitinib has a marketing authorisation for 'the treatment of adult patients with advanced renal cell carcinoma, after failure of prior treatment with sunitinib or a cytokine'.</p>	2.1
<p>Adverse reactions</p>	<p>The Committee concluded that axitinib has a manageable adverse event profile compared with other treatments for advanced renal cell carcinoma.</p>	4.11
Evidence for clinical effectiveness		

<p>Availability, nature and quality of evidence</p>	<p>The Committee noted that the AXIS trial was well conducted and the relevant outcomes were assessed in line with the scope of the appraisal. However, it noted the difficulties in interpreting the AXIS trial results in this appraisal because of the lack of a best supportive care comparison.</p>	<p>4.4</p>
	<p>The Committee concluded that the indirect comparison used to generate a best supportive care comparison for the prior-cytokine group based on the AXIS trial (axitinib compared with sorafenib) and the TARGET trial (sorafenib compared with placebo) and the VEG105192 trial (pazopanib compared with placebo) was adequately performed and the naive comparison was the best option given the available evidence. It also concluded that there were serious limitations with the simulated treatment comparison performed for the prior-sunitinib group using evidence from the AXIS trial and the RECORD-1 trial (which compared everolimus with placebo), and with the indirect comparison using evidence from AXIS and the Swedish database (Renal Comparison; RENCOMP). The Committee also considered the naive comparison performed to compare axitinib with sunitinib and the indirect comparison performed to compare axitinib with pazopanib in the prior-cytokine group, and concluded that both the naive and indirect comparisons were subject to substantial uncertainty but that axitinib was likely to have clinical effectiveness comparable to pazopanib and sunitinib.</p>	<p>4.6–4.9</p>
<p>Relevance to general clinical practice in the NHS</p>	<p>The Committee heard from the clinical experts that the use of cytokines is rapidly decreasing in clinical practice and only a few people currently receive them because most patients begin treatment with sunitinib or pazopanib.</p>	<p>4.2</p>
<p>Uncertainties generated by the evidence</p>	<p>The Committee noted that crossover in the TARGET trial was adjusted by censoring the patients who crossed over and considered that this could have resulted in bias and ultimately affected the robustness of the indirect comparison.</p>	<p>4.6</p>

	<p>The Committee noted the uncertainty in the naive comparison between axitinib and sunitinib in the prior-cytokine group and concluded that, although it was the best option given the available evidence, the results were not robust.</p>	4.7
	<p>The Committee considered that there was some evidence in favour of a relative progression-free survival advantage for axitinib compared with pazopanib from the company's and Evidence Review Group (ERG)'s indirect comparisons, but these results were subject to substantial uncertainty.</p>	4.8
	<p>The Committee was concerned about the validity and reliability of the simulated treatment comparison because it was an unconnected comparison of 2 arms from separate studies.</p> <p>The RENCOMP analysis was based on observational data without random allocation to treatments and also needed cautious interpretation.</p> <p>An assumption of proportional hazards had been used in the indirect comparisons and simulated treatment comparison to derive the survival estimates and had not been tested.</p>	4.9
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	N/A	
Estimate of the size of the clinical effectiveness including strength of supporting evidence	<p>The Committee noted that the better progression-free survival results for axitinib (6.7 months for the axitinib group compared with 4.7 months for the sorafenib group [HR 0.67, 95% CI 0.54 to 0.81, p<0.0001]) did not translate into statistically significant overall survival benefits (20.1 months for the axitinib group compared with 19.2 months for the sorafenib group [HR 0.97, 95% CI 0.80 to 1.17, p=0.37]) for the full trial population.</p>	4.4

	<p>The Committee noted that crossover in the TARGET trial was adjusted by censoring the patients who crossed over and considered that this could have resulted in bias and ultimately affected the robustness of the results of the indirect comparison (progression-free survival of 11 months for the axitinib group compared with 3.5 months for the best supportive care group [HR 0.25, 95% CrI 0.17 to 0.38] and overall survival of 33.5 months for the axitinib group compared with 23.5 months for the best supportive care group [HR 0.63, 95% CrI 0.41 to 0.99]).</p>	4.6
	<p>The Committee concluded that there were serious limitations with the indirect comparisons performed for the prior-sunitinib group, and that the outcomes from the simulated treatment comparison (progression-free survival [5.8 months for axitinib compared with 1.7 months for placebo], overall survival [15.2 months for axitinib compared with 8.3 months for placebo]) and indirect comparison (overall survival [HR 0.62, 95% CrI 0.38 to 0.997]) should be interpreted with caution.</p>	4.9
	<p>Although there was uncertainty about the relationship between progression-free survival and overall survival, the Committee concluded that the evidence from Grunwald et al. supported the company's simulated treatment comparison results on the survival benefits of axitinib over best supportive care.</p>	4.10
Evidence for cost effectiveness		
Availability and nature of evidence	<p>The economic evaluation was based on the 2 separate populations specified in the marketing authorisation for axitinib (the groups of people in whom treatment with sunitinib or cytokines has failed, also referred to as the prior-sunitinib and the prior-cytokine groups).</p>	3.18
	<p>A 3-state Markov cohort model was developed, based on previous modelling of metastatic cancer using Microsoft Excel.</p>	3.19

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>The Committee noted that when alternative survival distributions were tested in the scenario analysis, they resulted in sizeable changes to the base-case result for the prior-cytokine population and moderate changes for the prior-sunitinib population.</p>	<p>4.13</p>
	<p>The Committee considered that the possible over-estimation of the overall survival in the TARGET trial was carried over into the overall survival results in the indirect comparison and ultimately affected the model results for the best supportive care group. The Committee did not consider that axitinib could be considered to extendedly dominate pazopanib and sunitinib (that is, a QALY is attained at a higher cost with pazopanib or sunitinib than with axitinib because the ICER for pazopanib or sunitinib compared with best supportive care is higher than that for axitinib compared with best supportive care) as in the company's naive economic analysis.</p>	<p>4.14</p>
	<p>The Committee concluded that the results from the simulated treatment comparison method used to derive a best supportive care comparison for axitinib in the prior-sunitinib group should be interpreted with caution because they lacked clinical plausibility.</p>	<p>4.15</p>

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The Committee considered that there were no additional gains in health-related quality of life over those already included in the QALY calculations. Therefore, the Committee concluded that the innovative aspects of axitinib with regard to patient benefits were already incorporated in the economic model and analyses.</p>	<p>4.26</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>None identified.</p>	
<p>What are the key drivers of cost effectiveness?</p>	<p>A key driver for the prior-cytokine group was the plausibility of the survival gains in the best supportive care group. The Committee heard from both the clinical experts and the company that the estimate of 17.46 months for overall survival in the best supportive care group was more clinically plausible than 24 months.</p>	<p>4.14</p>
	<p>When the RENCOMP indirect comparison was used rather than the simulated treatment comparison, the ICER increased to over £40,000 per QALY gained (with the patient access scheme applied) using the Weibull and Gompertz distributions, suggesting that the method of obtaining a best supportive care comparison was a key driver of the results in the prior-sunitinib group.</p>	<p>4.16</p>

	Another key driver in the prior-tyrosine kinase inhibitor group was the assumption around the relationship between progression-free survival and overall survival. The ICER fell below £55,300 per QALY gained if a relationship greater than 1 to 1 was used.	4.17, 4.18
Most likely cost-effectiveness estimate (given as an ICER)	The Committee considered that the more plausible ICER for the prior-sunitinib group was likely to lie between the base-case estimate with a progression-free to overall survival gain relationship of 1 to 1.6 (approximately £33,500 per QALY gained) and the estimate assuming no survival gain with a survival relationship of 1 to 1 (approximately £52,900 per QALY gained) and concluded that the ICER would be likely to be towards the middle of this range.	4.19
	For the prior-cytokine group, the Committee noted that the company's base-case ICER of approximately £55,300 per QALY gained (with the patient access scheme applied) compared with best supportive care was based on the overall survival for best supportive care of 24 months, but fell to £36,500 per QALY gained if 17.46 months for overall survival for best supportive care was used.	4.18
Additional factors taken into account		
Patient access schemes (PPRS)	The company manufacturing axitinib has agreed a patient access scheme with the Department of Health. The size of the discount is commercial in confidence.	2.3

<p>End-of-life considerations</p>	<p>The Committee concluded that axitinib was shown to be a life-extending, end-of-life treatment for the prior-sunitinib population. Taking into account both the value of the ICERs and the uncertainty around the ICERs, the Committee concluded that axitinib could be considered a cost-effective use of NHS resources in the prior-sunitinib population under the supplementary criteria for appraising life-extending, 'end-of-life' treatments. The Committee also agreed that it was not reasonable to limit this conclusion to people whose prior-tyrosine kinase inhibitor was sunitinib, given the growing, if not majority use, of pazopanib as a first-line treatment. This would leave an unmet need and would not reflect clinical practice, and so the Committee concluded that their recommendations must apply to the whole prior-tyrosine kinase inhibitor population.</p>	<p>4.21, 4.23</p>
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	<p>The Committee agreed that in the prior-cytokine group, the overall survival gains for axitinib compared with best supportive care were unlikely and that a greater than 3-month survival benefit was likely, but that the evidence for a greater than 3-month survival benefit for axitinib compared with pazopanib was supported only by the company's indirect comparison calculations for progression-free survival and not overall survival. The Committee concluded that substantial uncertainty remained around the naive comparisons between axitinib, pazopanib and sunitinib, and the end-of-life criteria could only be considered met if best supportive care were the only comparator. For the prior-cytokine group, the Committee did not accept that axitinib was superior to sunitinib and pazopanib, and therefore did not accept that the end-of-life criteria had been met for this population, but it was aware that axitinib, sunitinib and pazopanib were used interchangeably in clinical practice. The Committee concluded that axitinib was comparable to the alternative treatments recommended by NICE that meet the end-of-life criteria, and that there was now only a very small population included in the prior-cytokine group and more uncertainty could be accepted. It therefore concluded that an ICER compared with best supportive care above but close to the upper limit of the normal range, was acceptable, and axitinib could be considered a cost-effective use of NHS resources in the prior-cytokine population.</p>	4.22, 4.24
<p>Equalities considerations and social value judgements</p>	<p>The Committee noted the potential equality issues raised by the patient experts, patient organisations and NHS organisations, but concluded that its recommendations did not have a particular impact on any of the groups whose interests are protected by the legislation and that there was no need to alter or add to its recommendations.</p>	4.27
<p>^[a] For further information see the General Medical Council's Prescribing guidance: prescribing unlicensed medicines.</p>		

5 Implementation

- 5.1 Section 7(6) of the [National Institute for Health and Care Excellence \(Constitution and Functions\) and the Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.
- 5.2 At the time of publication (February 2015), axitinib has a UK marketing authorisation for use only after failure with first-line sunitinib or a cytokine. If it is considered for use after any other first-line treatments, the prescriber should obtain and document informed consent and follow the relevant guidance published by the General Medical Council.^[2]
- 5.3 Because the remit referred to NICE by the Department of Health for this technology appraisal only includes adults who have been previously treated with sunitinib, the use of axitinib after treatment with other tyrosine kinase inhibitors is not subject to statutory funding.
- 5.4 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has advanced renal cell carcinoma and the doctor responsible for their care thinks that axitinib is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.5 The Department of Health and the company have agreed that axitinib will be available to the NHS with a patient access scheme which makes axitinib available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to: [Mr Stephen Skyrme](#), Commercial Strategy Lead – Oncology. His correspondence address is Pfizer Ltd, Walton Oaks, Dorking Road, Walton-on-the-Hill, Tadworth, Surrey KT20 7NS.

^[2] For further information see the [General Medical Council's Prescribing guidance: prescribing unlicensed medicines](#).

6 Review of guidance

- 6.1 The guidance on this technology will be considered for review at the same time as NICE technology appraisal guidance 178 and 219 for the second-line treatment of advanced renal cell carcinoma.

Andrew Dillon
Chief Executive
February 2015

7 Appraisal Committee members and NICE project team

Appraisal Committee members

The Appraisal Committees are standing advisory committees of NICE. Members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. There are 4 Appraisal Committees, each with a chair and vice chair. Each Appraisal Committee meets once a month, except in December when there are no meetings. Each Committee considers its own list of technologies, and ongoing topics are not moved between Committees.

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

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor Andrew Stevens

Chair of Appraisal Committee C, Professor of Public Health, University of Birmingham

Professor Eugene Milne

Vice Chair of Appraisal Committee C, Director of Public Health, City of Newcastle upon Tyne

Professor Kathryn Abel

Director of Centre for Women's Mental Health, University of Manchester

Dr David Black

Medical Director, NHS South Yorkshire and Bassetlaw

Dr Daniele Bryden

Consultant in Intensive Care Medicine and Anaesthesia, Sheffield Teaching Hospitals NHS Trust

Dr Andrew Burnett

Director for Health Improvement and Medical Director, NHS Barnet, London

David Chandler

Lay Member

Dr Mary Cooke

Lecturer, School of Nursing, Midwifery and Social Work, University of Manchester

Gail Coster

Advanced Practice Sonographer, Mid Yorkshire Hospitals NHS Trust

Professor Peter Crome

Honorary Professor, Department of Primary Care and Population Health, University College London

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Greg Fell

Consultant in Public Health, Bradford and Airedale Primary Care Trust

Dr Wasim Hanif

Consultant Physician and Honorary Senior Lecturer, University Hospital Birmingham

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Professor Cathy Jackson

Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Dr Janice Kohler

Formerly Senior Lecturer and Consultant in Paediatric Oncology, Southampton University Hospitals Trust

Emily Lam

Lay Member

Dr Nigel Langford

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Dr Allyson Lipp

Principal Lecturer, University of South Wales

Dr Grant Maclaine

Director, Health Economics & Outcomes Research, BD, Oxford

Dr Andrea Manca

Health Economist and Senior Research Fellow, University of York

Henry Marsh

Consultant Neurosurgeon, St George's Hospital, London

Dr Suzanne Martin

Reader in Health Sciences

Dr Claire McKenna

Research Fellow in Health Economics, University of York

Dr Patrick McKiernan

Consultant Paediatrician, Birmingham Children's Hospital

Professor Gary McVeigh

Professor of Cardiovascular Medicine, Queens University Belfast and Consultant Physician, Belfast City Hospital

Dr Iain Miller

Founder & CEO, Health Strategies Group

Dr Paul Miller

Director, Payer Evidence, AstraZeneca UK Ltd

Professor Stephen O'Brien

Professor of Haematology, Newcastle University

Dr Anna O'Neill

Deputy Head of Nursing & Healthcare School/Senior Clinical University Teacher, University of Glasgow

Professor Katherine Payne

Professor of Health Economics, University of Manchester

Dr Martin Price

Head of Outcomes Research, Janssen-Cilag, Buckinghamshire

Alan Rigby

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Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust

Dr Surinder Sethi

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Dr John Stevens

Lecturer in Bayesian Statistics in Health Economics, School of Health and Related Research, Sheffield

Professor Matt Stevenson

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Dr Paul Tappenden

Reader in Health Economic Modelling, School of Health and Related Research, University of Sheffield

Professor Robert Walton

Clinical Professor of Primary Medical Care, Barts and The London School of Medicine and Dentistry

Dr Judith Wardle

Lay Member

NICE project team

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

Nwamaka Umeweni/Grace Jennings/Boglarka Mikudina

Technical Leads

Bhash Naidoo/ Nicola Hay

Technical Advisers

Lori Farrar/Nicole Fisher

Project Managers

8 Sources of evidence considered by the Committee

A. The Evidence Review Group (ERG) report for this appraisal was prepared by Kleijnen Systematic Reviews:

Riemsma R, Al M, Corro Ramos I, Deshpande S et al. Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systematic treatment: a Single Technology Appraisal. York: Kleijnen Systematic Reviews Ltd (October 2012).

B. The following organisations accepted the invitation to participate in this appraisal as consultees and commentators. They were invited to comment on the draft scope, the ERG report and the appraisal consultation document (ACD). Organisations listed in I were also invited to make written submissions. Organisations listed in II and III had the opportunity to give their expert views. Organisations listed in I, II and III also have the opportunity to appeal against the final appraisal determination.

I. Company/sponsor:

- Pfizer

II. Professional/specialist and patient/carer groups:

- James Whale Fund for Kidney Cancer
- Kidney Cancer UK
- Cancer Research UK
- Royal College of Nursing
- Royal College of Physicians

III. Other consultees:

- Department of Health
- NHS Devon
- NHS Norfolk
- Welsh Government

IV. Commentator organisations (did not provide written evidence and without the right of appeal):

- Commissioning Support Appraisals Service
- Department of Health, Social Services and Public Safety for Northern Ireland
- Healthcare Improvement Scotland
- National Cancer Research Institute
- Kleijnen Systematic Reviews Ltd
- National Institute for Health Research Health Technology Assessment Programme
- National Collaborating Centre for Cancer

C. The following individuals were selected from clinical expert and patient expert nominations from the non-company/sponsor consultees and commentators. They gave their expert personal view on axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment by attending the initial Committee discussion and providing written evidence to the Committee. They were invited to comment on the ACD.

- Dr Janet Brown, Senior Lecturer, Honorary Consultant Medical Oncology, nominated by Royal College of Physicians – clinical expert
- Professor Robert Hawkins, Director of Medical Oncology, nominated by Royal College of Physicians – clinical expert
- Dr Pat Hanlon, nominated by Kidney Cancer UK – patient expert
- Jacqueline Lowe, nominated by Kidney Cancer UK – patient expert

D. Representatives from the following company/sponsor attended Committee meetings. They contributed only when asked by the Committee chair to clarify specific issues and comment on factual accuracy.

- Pfizer

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS.

This guidance was developed using the NICE [single technology appraisal](#) process.

It has been incorporated into the NICE pathway on [renal cancer](#) along with other related guidance and products.

We have produced [information for the public explaining this guidance](#). Tools to help you put the guidance into practice and information about the evidence it is based on are also [available](#).

NICE produces guidance, standards and information on commissioning and providing high-quality healthcare, social care, and public health services. We have agreements to provide certain NICE services to Wales, Scotland and Northern Ireland. Decisions on how NICE guidance and other products apply in those countries are made by ministers in the Welsh government, Scottish government, and Northern Ireland Executive. NICE guidance or other products may include references to organisations or people responsible for commissioning or providing care that may be relevant only to England.

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This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

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