

**NATIONAL INSTITUTE FOR HEALTH AND CLINICAL
EXCELLENCE**

Final appraisal determination

**Everolimus for the second-line treatment of advanced
renal cell carcinoma**

This guidance was developed using the single technology appraisal (STA) process.

1 Guidance

- 1.1 Everolimus is not recommended for the second-line treatment of advanced renal cell carcinoma.
- 1.2 People currently receiving everolimus for the second-line treatment of advanced renal cell carcinoma should have the option to continue treatment until they and their clinician consider it appropriate to stop.

2 The technology

- 2.1 Everolimus (Afinitor, Novartis Pharmaceuticals) is an active inhibitor of the mammalian target of rapamycin (mTOR) protein, a central regulator of tumour cell division and blood vessel growth in cancer cells. Everolimus has a UK marketing authorisation for the treatment of patients with advanced renal cell carcinoma (RCC), whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy.
- 2.2 Everolimus is contraindicated in people who have hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients. The summary of product characteristics (SPC) lists the following as special warnings and precautions for everolimus use: non-infectious pneumonitis, localised and systemic infections

(including pneumonia, other bacterial infections and invasive fungal infections), hypersensitivity reactions and oral ulcerations. For full details of side effects and contraindications, see the SPC.

2.3 Everolimus is administered orally. The recommended dosage is 10 mg once daily and treatment should continue as long as clinical benefit is observed or until there are unacceptable adverse events. Management of severe and/or intolerable adverse events may require dose reduction to a suggested dosage of 5 mg daily or temporary withholding of everolimus. The price for a pack of 10-mg tablets (30 tablets per pack) is £2970 (excluding VAT; 'British national formulary' [BNF] edition 59). The manufacturer of everolimus has agreed a patient access scheme with the Department of Health, in which the first pack of everolimus is free and each subsequent pack costs £2822. The daily cost of everolimus with the patient access scheme is £94, with an 8-week cycle costing £5264. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

3 The manufacturer's submission

The Appraisal Committee (appendix A) considered evidence submitted by the manufacturer of everolimus and a review of this submission by the Evidence Review Group (ERG; appendix B).

3.1 The manufacturer presented evidence on the clinical effectiveness of everolimus used within the marketing authorisation and in line with the appraisal scope. The manufacturer also stated that everolimus is the only mTOR inhibitor available in an oral form for the treatment of advanced RCC. The main evidence came from one phase III, multicentre, double-blind randomised controlled trial (RCT). The RCT, RECORD-1, compared everolimus plus best supportive care (277 participants) with placebo plus best supportive

care (139 participants). Best supportive care consisted of drug and other types of therapy, including symptom control, palliative care and monitoring of progression. Trial participants were adults (18 years or older) with advanced RCC with a clear-cell component confirmed by histology or cytology, whose disease had progressed while on or within 6 months of stopping treatment with sunitinib, sorafenib or both. Previous therapy with a cytokine (for example, interferon-alfa or interleukin-2) or bevacizumab was allowed. The participants had a Karnofsky performance score of 70% or more, and were stratified according to whether they had received prior therapy with sunitinib, sorafenib or both, and Memorial Sloan Kettering Cancer Centre (MSKCC) prognostic category. The baseline characteristics of the patients in the two treatment arms were generally similar. The arms were relatively well balanced in terms of previous therapy.

- 3.2 The primary outcome in the RCT was progression-free survival, which was defined as time from randomisation to disease progression or death. Tumour assessments were performed using RECIST (Response Evaluation Criteria in Solid Tumours) and were confirmed by an independent central radiology review. Once disease progression was confirmed, patients who previously received placebo plus best supportive care could be offered open-label everolimus plus best supportive care if the treating clinician thought this in the best interests of the patient. The median progression-free survival was 4.90 months (95% confidence interval [CI] 3.98 to 5.52) for patients receiving everolimus plus best supportive care and 1.87 months (95% CI 1.84 to 1.94) for patients receiving placebo plus best supportive care (hazard ratio [HR] 0.33, 95% CI 0.25 to 0.43). This meant there was a 67% reduction in risk of disease progression for patients receiving everolimus plus best supportive care compared with those receiving placebo plus best supportive care at the final analysis. The median progression-free

survival was statistically significantly longer in patients receiving everolimus ($p < 0.001$).

- 3.3 Sunitinib is the only first-line treatment for advanced and/or metastatic renal cell carcinoma currently recommended by NICE (NICE technology appraisal guidance 169), therefore the manufacturer undertook a final analysis of progression-free survival according to previous VEGF-targeted therapy. Approximately 44% of patients in each treatment arm had received prior sunitinib treatment, 30% had received sorafenib treatment, and 26% had received both sunitinib and sorafenib. There was a statistically significant improvement in progression-free survival for all subgroups irrespective of prior VEGF-targeted therapy. For people whose disease had failed to respond to sunitinib, there was a 66% reduction in risk of disease progression with everolimus plus best supportive care compared with placebo plus best supportive care.
- 3.4 During the blinded phase of the RCT, a statistically significant difference in median overall survival was not identified for the two treatment arms. At the final analysis (November 2008), the median overall survival was 14.78 months in the everolimus plus best supportive care arm and 14.39 months in the placebo plus best supportive care arm. The resulting hazard ratio was 0.87 (95% CI 0.65 to 1.17), which was not statistically significant ($p = 0.177$).
- 3.5 A total of 76% of patients assigned to receive placebo plus best supportive care had crossed over to receive everolimus plus best supportive care by the time of the February 2008 analysis. Therefore, the manufacturer adjusted the overall survival results for the crossover by using the Inverse Probability of Censoring Weight (IPCW) method in a post-hoc analysis. This method aims to adjust for crossover by recreating the population that would have been evaluated if crossover had not occurred. People who do not cross

over get a greater weighting (in this case a factor of 1.81) in order to correct for the resulting bias. The manufacturer explained that the IPCW method was used to control for crossover because it produces a hazard ratio, it does not require data to be normally distributed, it does not 'borrow' information from crossed over patients and it does not impose a structural model to control for the effect of crossover. The IPCW analysis suggested a statistically significantly longer mean overall survival for people who received everolimus plus best supportive care (mean overall survival 10.1 months) compared with those who received placebo plus best supportive care (mean overall survival 5.1 months) (HR 0.55, 95% CI 0.31 to 0.97).

3.6 The manufacturer reported the results of a meta-analysis of 28 trials of a range of treatments for advanced RCC (8770 patients). The meta-analysis explored the relationship between progression-free survival and overall survival. A subgroup analysis found an overall survival benefit of 1.61 months (95% CI 0.7 to 2.52) per 1 month gain in progression-free survival for the 24 studies without crossover from placebo to active treatment. The overall survival benefit was 1.42 months (95% CI 0.34 to 2.51) per 1 month progression-free survival in the 16 studies in which patients had received prior therapy. The manufacturer stated that the survival benefit of 5 months (for everolimus plus best supportive care versus placebo plus best supportive care) obtained from the IPCW analyses was in line with the survival benefit hypothesised from the meta-analysis.

3.7 In the RCT, health-related quality of life was measured using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire—Core 30 and the Functional Assessment of Cancer Therapy—Kidney Symptom Index, Disease Related Symptoms (FKSI—DRS) score. No generic measures of

health-related quality of life were included. More than 65% of patients completed the questionnaires at each time point. Time to deterioration in functioning/symptoms was delayed with everolimus plus best supportive care by 3.5 months compared with placebo plus best supportive care. The median time to deterioration according to FKSI–DSR score was 7.4 months for everolimus plus best supportive care and 3.9 months for placebo plus best supportive care (HR 0.72, $p = 0.044$).

3.8 The manufacturer used data from the RCT to evaluate the safety profile of everolimus therapy. There were more all grade adverse events in the everolimus plus best supportive care arm (40.1%) than the placebo plus best supportive care arm (22.6%). The most frequent adverse events related to everolimus treatment were anaemia (103 events) and stomatitis (103 events). The manufacturer stated that most adverse events reported were reversible, transient and manageable, and that the greater incidence of adverse events in the everolimus plus best supportive care arm was a result of the longer duration of exposure to everolimus. A total of 13.9% of patients randomised to receive everolimus plus best supportive care and 2.9% of patients randomised to receive placebo plus best supportive care discontinued treatment because of adverse events.

3.9 The manufacturer developed a Markov model to assess the cost effectiveness of everolimus plus best supportive care compared with best supportive care alone. The model used a hypothetical group with advanced RCC whose cancer had progressed on or within 6 months of receiving VEGF-targeted therapy (that is, sunitinib, sorafenib, and/or bevacizumab) and who had demographic characteristics reflecting those of the RECORD-1 trial. The model had four distinct health states: stable disease without adverse events, stable disease with adverse events,

progressed disease and death. All people entered the model in the stable disease without adverse events health state. Everolimus treatment (10 mg once daily) was given until disease progression (defined by the RECIST criteria) or unacceptable adverse events were experienced. In the latter case, the dosage was sometimes reduced to 5 mg daily or everolimus treatment was interrupted. Because of this the manufacturer used a dose intensity of 91.8% in the model. The model had a cycle length of 8 weeks and a time horizon of 144 weeks, which the manufacturer stated reflected the maximum life expectancy of the population in the model. Discounting was applied from the second year onwards and a half-cycle correction was not applied. No subgroup analyses were conducted by the manufacturer.

- 3.10 Rates of adverse events, treatment withdrawal, disease progression, and deaths were taken from the RCT and used to calculate the probabilities that a person would move between health states (transition probabilities). The observed event rates in the RCT were used directly to calculate the number of people entering the 'stable disease with adverse events' health state and the 'progressed disease' health state for both treatment arms. Only grade 3 and 4 adverse events associated with everolimus treatment and best supportive care were included in the model. The rates of grade 3 and 4 adverse events were taken directly from the RCT up to cycle seven of treatment. The trial ended after the seventh cycle and the rates after this cycle were assumed to remain constant.
- 3.11 For health states leading to death, the RCT data were used directly for the everolimus plus best supportive care arm only. For the best supportive care alone arm, the probability of dying was calculated by deriving the IPCW Cox model hazard ratio for mortality (that is, a hazard ratio of 0.55) and then applying this to the transition

probabilities in the everolimus arm. The manufacturer explained that the group of patients receiving best supportive care was therefore at a constantly higher relative risk of mortality at any given cycle. Mean overall survival for everolimus plus best supportive care was estimated to be 10.1 months compared with 5.1 months for best supportive care alone.

3.12 The utility values used in the model were taken from the Assessment Group's estimates for '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' (NICE technology appraisal guidance 178). These were 0.76 for stable disease without adverse events, 0.71 for stable disease with adverse events, 0.68 for progressed disease and 0 for death. The manufacturer did not use individual disutility (that is, loss of utility) estimates for each adverse event associated with treatment with everolimus, but instead applied a single overall disutility estimate of -0.05 for being in the health state 'stable disease with adverse events'. The manufacturer clarified that this disutility was maintained throughout all subsequent cycles. The costs of adverse events were assumed to last only for one cycle.

3.13 The manufacturer has agreed a patient access scheme with the Department of Health in which the first treatment pack of everolimus is free to the NHS and following treatment packs cost £2822 (that is, a 5% discount on the acquisition cost of everolimus). It was assumed by the manufacturer that there would be no additional costs to the NHS associated with administration of the patient access scheme. The costs associated with best supportive care, monitoring and adverse events were taken from the Assessment Group's estimates for NICE technology appraisal 178. No additional costs were assumed to be associated with tests or

special appointments for everolimus administration. Any additional resource use incurred was assumed to be associated with the provision of best supportive care and the underlying cancer. The ongoing cost of resource use was estimated to be £110 for each cycle of everolimus and £182 for a CT scan every three cycles. The estimated cost for best supportive care was £641 per cycle. In addition, 72% of patients in the RCT received other treatments after everolimus treatment had ended (such as sunitinib, sorafenib and bevacizumab). Therefore, an additional cost of £2428.78 per cycle for the other treatments was also incorporated for the 'progressed disease' health state.

- 3.14 Comparison of everolimus plus best supportive care with best supportive care alone produced a base-case incremental cost-effectiveness ratio (ICER) of £51,613 per quality-adjusted life year (QALY) gained. One-way sensitivity analyses showed that the ICER was most sensitive to the estimate of overall survival in the best supportive care arm. When the hazard ratio for overall survival was taken from the intention-to-treat population (that is, a hazard ratio of 0.87), the ICER increased to £91,256 per QALY gained (including the patient access scheme). Probabilistic sensitivity analyses suggested that if the maximum acceptable amount to pay for an additional QALY gained was £50,000 then everolimus had a 40% probability of being cost effective (including the patient access scheme).
- 3.15 The ERG stated that the manufacturer's submission was generally of good quality and appropriate to the decision problem. Although the clinical effectiveness evidence was derived from only one RCT, this was of good quality and demonstrated that everolimus plus best supportive care significantly improved progression-free survival compared with placebo plus best supportive care. The

ERG also stated that the economic model developed by the manufacturer appeared appropriate for the decision problem.

3.16 The ERG highlighted that the main factor affecting cost effectiveness was the estimate of overall survival used in the economic model. The ERG agreed that it was important to correct the data for the confounding caused by the crossover that occurred. However, the ERG stated that the manufacturer had made two key errors in applying the IPCW method in the economic model. Firstly the manufacturer had failed to convert the transition probabilities to rates before applying the hazard ratio multiplier, leading to transition probabilities greater than one. The ERG stated that using the correct approach the base-case ICER was increased from £51,613 to £53,479 per QALY gained. Secondly, the ERG stated that in applying the mortality hazard ratio, the manufacturer overestimated the mortality in the best supportive care arm. This is because there was a higher level of progression in the best supportive care arm and more deaths in the 'progressed disease' state. The ERG stated that this in effect 'double-counted' some of the deaths in the best supportive care arm and in effect improved the overall mortality hazard ratio in favour of the everolimus arm (and therefore improved the cost-effectiveness estimates). The ERG stated that correcting for this, in addition to converting the transition probabilities to rates as described above, the base-case ICER increased further from £53,479 to £64,988 per QALY gained. In addition, the ERG noted that other methods to control for crossover could have been investigated, in particular the Rank Preserving Structural Failure Time (RPSFT) model. This method had been used previously in 'Sunitinib for the treatment of gastrointestinal stromal tumours' (NICE technology appraisal guidance 179).

- 3.17 The ERG stated that the discounting should have been applied from the second cycle (not from the second year as in the model). When the ERG changed the manufacturer's model by discounting costs and benefits (at 3.5%) in this way, the amended ICER (described in section 3.16) increased from £64,988 to £65,231 per QALY gained. The ERG also highlighted concern about the assumption that patients experiencing adverse events were assumed to experience a utility decrement for only one cycle, after which their utility was assumed to return to a level equivalent to the state without adverse events. Costs for treatment of adverse events were, however, assumed to remain. The ERG also considered that the difference in utility between stable disease and progressed disease (0.76 versus 0.68) may understate the benefit demonstrated for everolimus in delaying progression.
- 3.18 In response to the factual check of the ERG report, the manufacturer also produced analyses using the RPSFT method to derive estimates of overall survival. The RPSFT method estimates the overall survival of patients randomised to receive placebo assuming that they had not crossed over (that is, they had remained on placebo for the duration of the trial). This method is therefore based on a comparison of the groups according to the way they were randomised. The RPSFT method proportionally 'shrinks' the estimated amount of additional survival conferred to patients who crossed over to receive everolimus, thereby changing the mortality hazard ratio used in the economic model. This analysis was conducted at a later time point than the IPCW analysis; at this later time point (November 2008), 81% of patients who were allocated to placebo plus best supportive care had crossed over to receive everolimus plus best supportive care.
- 3.19 The RPSFT method estimated that survival was nearly twice as long with everolimus plus best supportive care compared with best

supportive care alone (relative risk 1.93, 95% CI 0.50 to 8.50). Estimates of mean overall survival of 15.18 months with everolimus plus best supportive care and 7.67 months with best supportive care alone were generated by the economic model. The manufacturer also presented updated cost-effectiveness estimates using the RPSFT method to derive estimates of overall survival, with all other base-case assumptions in the model unchanged. The analysis produced an ICER of £53,128 per QALY gained for everolimus plus best supportive care compared with best supportive care alone.

3.20 The ERG expressed concerns about the way the RPSFT method had been applied to the manufacturer's economic model. The ERG stated that the mortality risk in the best supportive care arm had been overestimated. This was because the longer-term extrapolation of the overall survival curve for patients receiving best supportive care only was based on a death rate estimated from the RPSFT analysis based on a single trial data point. The ERG stated that more data should be used when extrapolating overall survival to the long term. It therefore conducted an exploratory analysis using revised transition probabilities for the best supportive care arm of the model. The ERG calculated the new transition probability for cycles 6 to 18 as the mean of the probabilities in cycles 4 and 5 and stated that it provided an example of a more realistic interpretation of the overall survival in the best supportive care arm. All other model transition values were the same as those used in the manufacturer's analysis. The resulting ICER was £75,725 per QALY gained (including discounting from the second cycle) and £74,935 per QALY gained (including discounting from the second year).

3.21 During the consultation period of this appraisal, the manufacturer submitted revised cost-effectiveness estimates using both the

IPCW and RPSFT methods to derive overall survival estimates. The new IPCW analysis considered a treatment duration of 312 weeks (39 cycles) rather than 144 weeks as in the original model. In addition, more recent data from the final analysis in November 2008 were used and discounting at a rate of 3.5% was applied from the second cycle in the model (rather than from the second year). Finally, the transition probabilities were converted to rates before applying the hazard ratio multiplier (rather than applying the hazard ratio multiplier directly to the transition probabilities as in the original analysis). The new IPCW analysis resulted in a mean overall survival of 16.2 months with everolimus plus best supportive care and 9.6 months with best supportive care alone (an incremental overall survival gain of 6.6 months). The revised base-case analysis gave incremental QALYs of 0.398 and incremental costs of £20,949. This resulted in an ICER for everolimus plus best supportive care compared with best supportive care alone of £52,684 per QALY gained. No revised sensitivity analyses were provided.

- 3.22 The revised RPSFT analysis considered treatment duration of 312 weeks (39 cycles) rather than 144 weeks as in the original model. Discounting at a rate of 3.5% was applied from the second cycle in the model (rather than from the second year). In addition, to extrapolate the longer-term overall survival curve for patients receiving best supportive care, the mean of the transition probabilities for cycles 5 and 6 (rather than the value of the transition probability in cycle 6) was applied to cycles 7 to 39. The revised RPSFT analysis resulted in a mean overall survival of 16.1 months with everolimus plus best supportive care and 7.9 months with best supportive care alone (an incremental overall survival gain of 8.2 months). The revised base-case analysis gave incremental QALYs of 0.50 and incremental costs of £24,853. This resulted in an ICER for everolimus plus best supportive care

compared with best supportive care alone of £49,537 per QALY gained. No revised sensitivity analyses were provided.

3.23 The ERG considered the manufacturer's revised IPCW analysis. It agreed that the longer time horizon was appropriate. The ERG judged that the model differed from the one provided in the original submission in terms of the transition probabilities to the states with adverse events, disease progression and death. The ERG stated that no further information had been provided by the manufacturer that explained the differences in the transition probabilities. It therefore judged that it was not possible to fully appraise the cost-effectiveness estimates that were obtained when using the manufacturer's revised IPCW model. The ERG also expressed concern over the wide range of uncertainty associated with the overall survival estimates in the IPCW analysis. The ERG conducted one-way sensitivity analyses that varied the hazard ratio for overall survival at intervals across the 95% confidence limits (0.31 to 0.97) of the overall survival hazard ratio from the IPCW analysis. This resulted in ICERs (with the patient access scheme applied) ranging from £43,071 per QALY gained (with a hazard ratio for overall survival of 0.31) to £253,051 per QALY gained (with a hazard ratio for overall survival of 0.97).

3.24 The ERG then considered the manufacturer's revised RPSFT analysis. It agreed that the longer time horizon was appropriate. The ERG noted that the manufacturer had calculated the mean transition probabilities of two cycles to extrapolate the long-term overall survival associated with best supportive care. It noted that although this approach was preferred to the original method of using only one data point, it still essentially used single trial points to extrapolate data to the longer term. In addition, the ERG noted that the data at cycle 6 were based on a small number of patients and could be unrepresentative of the whole trial population.

Therefore, the ERG stated that a more appropriate approach would be to extrapolate the overall survival using all of the data points in the best supportive care arm. The ERG conducted exploratory analyses and extrapolated the survival curves by fitting a Weibull distribution to both arms of the model. No other changes were made to the manufacturer's revised RPSFT model. A mean overall survival of 16.7 months with everolimus plus best supportive care and 10.8 months with best supportive care alone (an incremental overall survival gain of 5.9 months) was obtained. The revised base-case analysis gave incremental QALYs of 0.33 and incremental costs of £18,986. This resulted in an ICER for everolimus plus best supportive care compared with best supportive care alone of £58,316 per QALY gained.

- 3.25 Full details of all the evidence are in the manufacturer's submission and the ERG report, which are available from www.nice.org.uk/guidance/TAXXX

4 Consideration of the evidence

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

Clinical effectiveness

- 4.2 The Committee heard from clinical specialists and patient experts that there are limited treatment options for people with advanced RCC. The Committee noted that currently sunitinib is the only first-line treatment recommended by NICE and that this recommendation was based on the assumption that no second-line treatments were available. It acknowledged that there are no

second-line treatments recommended by NICE for people whose disease has stopped responding to sunitinib and that everolimus could offer an option for the second-line treatment of advanced RCC in people whose disease has progressed on first-line treatment with sunitinib.

4.3 The Committee heard from the patient experts and clinical specialists that advanced RCC is a relatively rare cancer and noted the views of patient experts and clinical specialists on the severity of the disease. The Committee also heard that people undergoing second-line chemotherapy valued the increased life expectancy offered and were prepared to cope with the adverse effects of these treatments. The Committee noted the increased frequency of all grade adverse events associated with everolimus treatment in the RECORD-1 trial. In particular the Committee noted that the most common grade 3 or 4 adverse events suspected to be related to everolimus treatment were anaemia, hyperglaeceamia, stomatitis, fatigue, hypercholesterolaemia and dyspnoea. However, the Committee was advised by the patient experts and clinical specialists that everolimus would be tolerated by most people with advanced RCC, and that people receiving everolimus would do so after having received sunitinib as a first-line treatment and so would be prepared for the adverse effects associated with everolimus. The Committee discussed the risk of pneumonitis and immunosuppression associated with everolimus. The clinical specialist confirmed that although pneumonitis and immunosuppression had been associated with everolimus in clinical practice, these adverse events would stop on discontinuation of treatment and were therefore considered manageable.

4.4 The Committee discussed the evidence of clinical effectiveness (from the RECORD-1 trial) of everolimus in people with advanced

RCC whose disease had progressed on or within 6 months of stopping VEGF-targeted treatment. The Committee noted that the most of the trial population had a good performance status. The clinical specialist highlighted that in clinical practice only people with a good performance status would be considered for second-line therapy because people with a poorer performance status would be too ill to receive any active treatment. Therefore the Committee accepted that the trial population was likely to be similar to people considered for second-line therapy in UK clinical practice. The Committee also agreed that the RECORD-1 trial was of good methodological quality and therefore the results could be considered robust.

4.5 The Committee discussed the results of the RECORD-1 placebo-controlled trial. The Committee agreed that the results demonstrated that everolimus plus best supportive care had increased progression-free survival by approximately 3 months compared with placebo plus best supportive care. The Committee acknowledged that the relative estimates of overall survival according to the intention-to-treat analyses were biased because 81% of people had crossed over to receive everolimus in the trial. The Committee heard from the clinical specialist that an increase in progression-free survival would be expected to result in an increase in overall survival because gains in overall survival had been observed in clinical practice with the introduction of sequential chemotherapy for advanced RCC. The Committee noted the meta-analysis submitted by the manufacturer (see section 3.6) and accepted that a 1.4-month increase in overall survival per 1 month increase in progression-free survival for patients with advanced RCC who had received prior therapy was plausible.

4.6 The Committee agreed that it was appropriate to adjust the intention-to-treat results (which gave a median overall survival

estimate of 14.8 months for everolimus plus best supportive care and 14.4 months for best supportive care alone) to control for the crossover using statistical modelling techniques. However, the Committee agreed that any estimate of overall survival obtained using statistical modelling would be subject to some uncertainty because a number of assumptions would have to be made.

- 4.7 The Committee acknowledged that the manufacturer had updated both the IPCW and RPSFT analyses in response to comments received during consultation. The Committee noted that the resulting estimates of overall survival were 16.2 and 16.1 months with everolimus plus best supportive care and 9.6 and 7.9 months with best supportive care using the IPCW and RPSFT methods respectively. The ERG conducted exploratory analyses of the manufacturer's estimates derived using the RPSFT method (see section 3.24) and noted that the estimates of overall survival were 16.7 months with everolimus plus best supportive care and 10.8 months with best supportive care. The Committee noted that the overall survival estimates for both everolimus and best supportive care were higher with the ERG's exploratory analyses than the manufacturer's analyses. The Committee concluded that although there was sufficient evidence that everolimus increased progression-free and overall survival compared with best supportive care, the exact magnitude of the overall survival gain was uncertain because it was based on modelled data as opposed to data directly observed in the trial, but accepted that it would be more than 3 months.

Cost effectiveness

- 4.8 The Committee noted that the key factor in determining the cost effectiveness was the estimate of overall survival and discussed the IPCW and the RPSFT methods used to estimate this from the RECORD-1 trial data. It heard from the ERG that it considered the

RPSFT method to be more methodologically robust than the IPCW method because it does not assume that there are no unmeasured confounders. In addition, the Committee understood that the manufacturer's revised IPCW analysis contained a number of unexplained differences between the original and revised models, and so the ERG could not conduct a full critique of the revised IPCW analysis. The Committee also noted that the RPSFT method had been used previously in 'Sunitinib for the treatment of gastrointestinal stromal tumours' (NICE technology appraisal guidance 179). The Committee therefore concluded that, in this instance, it was more appropriate to evaluate the cost effectiveness of everolimus based on the estimates generated using the RPSFT method.

4.9 The Committee discussed the validity of the estimates of overall survival from the manufacturer's and ERG's RPSFT analyses. The Committee noted the ERG's criticism that the manufacturer's extrapolation of long-term survival in the best supportive care arm was still not based on all of the available data (it was based on the mean of cycles 5 and 6 derived from the RPSFT analysis) and that these data may not be representative of the whole trial population. The Committee accepted that the use of a Weibull distribution, which used all available data, was a more appropriate method for estimating overall survival and produced a better fit to the empirical data points.

4.10 The Committee acknowledged comments received that overall survival with best supportive care in the ERG's exploratory analyses using the Weibull distribution (10.8 months) was higher than that was seen in clinical practice, and that the estimate in the manufacturer's analysis (7.9 months) was more likely to reflect clinical practice. The Committee accepted for this appraisal that the costs and utilities associated with living in the 'progressed disease'

health state were similar in patients receiving everolimus and those receiving best supportive care and the incremental difference in overall survival was a key factor in determining the cost effectiveness. The Committee noted that the difference in overall survival between patients receiving everolimus and those receiving best supportive care was 8.2 months in the manufacturer's revised RPSFT analysis and 5.9 months in the ERG's revised RPSFT analysis. It noted the earlier conclusion that an increase in overall survival of 1.4 months per month of increased progression-free survival was plausible. Therefore, the Committee agreed that the incremental overall survival derived using the manufacturer's revised RPSFT analysis (8.2 months) was greater than expected, based on the increase in progression-free survival of 3 months observed in the RECORD-1 trial. The Committee accepted that the ERG's estimate of overall survival for patients receiving best supportive care using the RPSFT analysis was higher than observed in clinical practice, but the incremental difference in overall survival for everolimus versus best supportive care (5.9 months) was more plausible than that derived by the manufacturer and was based on all of the available data.

- 4.11 The Committee then discussed the manufacturer's and ERG's cost-effectiveness estimates derived using the RPSFT method: £49,500 and £58,300 per QALY gained respectively. The Committee understood that these estimates also included a patient access scheme which had been agreed with the Department of Health. The Committee noted its earlier conclusions that the ERG's analysis (which extrapolated the overall survival with best supportive care using all of the available trial data) resulted in the most plausible incremental overall survival for everolimus versus best supportive care. The Committee therefore concluded that the ICER of £58,300 per QALY gained (derived by the ERG) was the most plausible.

4.12 The Committee then discussed other aspects of the manufacturer's model and the critique by the ERG. The Committee considered that the time horizon and discounting in the analyses were appropriate. However, the Committee had concerns about the validity of some of the assumptions used in the economic model. Firstly it noted that all patients entered the economic model in the 'stable disease without adverse events' health state. The Committee heard from the clinical specialist that in practice eligible patients would present with progressed disease and it was likely that some people starting a second-line therapy for advanced RCC experienced adverse events. Secondly, the Committee was concerned about the model assumption that the costs of managing associated adverse events would apply for only one treatment cycle. However, the Committee heard from the clinical specialist that adverse events would be managed by 'drug holidays' or dose reduction and therefore treatment of adverse events would not be expected to incur significant ongoing costs. The Committee also heard from the clinical specialist that the primary ongoing adverse event with everolimus was fatigue, but that this was common to all cancer treatments and there were currently no treatments for its management. Therefore the Committee agreed that the cost estimates used for adverse events in the model were acceptable.

4.13 The Committee noted that the utility estimates in the model were neither directly obtained nor mapped from the RECORD-1 trial. The Committee noted that the estimates of utility for each of the disease states were similar. The Committee accepted that a larger decrement in utility may be plausible when a person moves from a 'stable disease' health state to a 'progressed disease' health state. The Committee noted comments from the ERG and the results of the one-way sensitivity analyses which showed changes in utility estimates had little effect on the ICERs. The Committee agreed

that although the utility estimates were subject to some uncertainty, the utility assumptions in the economic model were acceptable.

4.14 The Committee was aware of the supplementary advice from NICE that should be taken into account when appraising treatments which may extend the life of people with a short life expectancy and which are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- 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.
- 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 the assumptions used in the reference case economic modelling are plausible, objective and robust.

4.15 The Committee then discussed whether everolimus as a second-line treatment for advanced RCC fulfilled the criteria for consideration as a life-extending, end-of-life treatment. It was aware that in England and Wales the total number of people who would be eligible for treatment with everolimus was less than 4000. The Committee heard that the life expectancy for people with advanced RCC receiving best supportive care alone was unlikely to be greater than 24 months and was potentially as low as 5 months according to clinical specialist comments. The Committee also noted that the evidence from the RPSFT analysis suggested that everolimus increased survival by more than 3 months compared

with best supportive care. In summary, the Committee was satisfied that everolimus met the criteria for being a life-extending, end-of-life treatment, and that the evidence presented for this consideration was sufficiently robust.

4.16 The Committee then discussed whether the cost-effectiveness estimate of everolimus of £58,300 per QALY gained was an appropriate use of NHS resources for a life-extending, end-of-life treatment. It considered the impact of giving a greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy person of the same age. The Committee also considered the magnitude of additional weight that would need to be assigned to the original QALY benefits in this patient group for the cost effectiveness of the drug to fall within the range currently considered a cost-effective use of NHS resources. The Committee considered that the additional weight that would need to be assigned to the original QALY benefits would be too great, even when the patient access scheme was incorporated. Therefore the Committee concluded that it could not recommend everolimus for the second-line treatment of advanced RCC as a cost-effective use of NHS resources.

4.17 The Committee considered whether there were any subgroups of patients for whom everolimus would be considered a cost-effective use of NHS resources, and whether NICE's duties under the equalities legislation required it to alter or to add to its recommendations in any way. The Committee noted that no subgroups of patients had been identified and agreed that that there are no specific equality issues relevant to this appraisal.

Summary of Appraisal Committee's key conclusions

TAXXX (STA)	Appraisal title: Everolimus for the second-line treatment of advanced renal cell carcinoma	FAD section
Key conclusion		
Everolimus is not recommended for the second-line treatment of advanced renal cell carcinoma (RCC).		1.1
Current practice		
Clinical need of patients including the availability of alternative treatments	The Committee heard from the patient experts and clinical specialists that advanced RCC is a relatively rare cancer and noted the views of patient experts and clinical specialists on the severity of the disease. The Committee also heard that people undergoing second-line chemotherapy valued the increased life expectancy offered and were prepared to cope with the adverse effects of these treatments.	4.3
The technology		
Proposed benefits of the technology How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The Committee acknowledged that there are no second-line treatments recommended by NICE for people whose disease has stopped responding to sunitinib and that everolimus could offer an option for the second-line treatment of advanced RCC in people whose disease has progressed on first-line treatment with sunitinib.	4.2
What is the position of the treatment in the pathway of care for the condition?	The Committee acknowledged that everolimus could offer an option for the second-line treatment of advanced RCC in people whose disease has progressed on first-line treatment with sunitinib.	4.2
Adverse events	The Committee noted the increased frequency of all grade adverse events associated with everolimus treatment in the RECORD-1 trial...The Committee concluded that although there were adverse events that had been associated with everolimus in clinical practice, these adverse events would stop on discontinuation of treatment and were therefore considered manageable.	4.3

Evidence for clinical effectiveness		
Availability, nature and quality of evidence	<p>The Committee agreed that the RECORD-1 trial was of good methodological quality and therefore the results could be considered robust.</p> <p>The Committee agreed that everolimus plus best supportive care had increased progression-free survival by approximately 3 months compared with placebo plus best supportive care.</p> <p>The Committee acknowledged that the relative estimates of overall survival according to the intention-to-treat analyses were biased because 81% of people had crossed over to receive everolimus in the trial. Therefore the Committee agreed that it was appropriate to adjust the results to control for the crossover using statistical modelling techniques.</p> <p>The Committee noted that the resulting estimates of overall survival were 16.2 and 16.1 months with everolimus plus best supportive care and 9.6 and 7.9 months with best supportive care using the IPCW and RPSFT methods respectively. The ERG conducted exploratory analyses of the manufacturer's estimates derived using the RPSFT method (see section 3.24) and noted that the estimates of overall survival were 16.7 months with everolimus plus best supportive care and 10.8 months with best supportive care.</p> <p>The Committee therefore concluded that although there was sufficient evidence that everolimus increased progression-free and overall survival compared with best supportive care, the exact magnitude of the overall survival gain was uncertain because it was based on modelled data as opposed to data directly observed in the trial, but accepted that it would be more than 3 months.</p>	4.4, 4.5, 4.6 and 4.7
Relevance to general clinical practice in the NHS	The Committee accepted that the trial population was likely to be similar to people considered for second-line therapy in UK clinical practice.	4.4

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Uncertainties generated by the evidence	<p>The Committee agreed that any estimate of overall survival obtained using statistical modelling would be subject to some uncertainty because a number of assumptions would have to be made.</p> <p>However, the Committee concluded that there was sufficient evidence that everolimus increased progression-free and overall survival compared with best supportive care, the exact magnitude of the overall survival gain was uncertain because it was based on modelled data as opposed to data directly observed in the trial, but accepted that it would be more than 3 months.</p>	4.6, 4.7
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The Committee did not identify any specific groups of people for whom the technology was considered particularly effective.	4.17
Estimate of the size of the clinical effectiveness including strength of supporting evidence	The Committee concluded that there was sufficient evidence that everolimus increased progression-free and overall survival compared with best supportive care, the exact magnitude of the overall survival gain was uncertain because it was based on modelled data as opposed to data directly observed in the trial, but accepted that it would be more than 3 months.	4.7

Evidence for cost effectiveness		
Availability and nature of evidence	<p>The manufacturer developed a Markov model to assess the cost effectiveness of everolimus plus best supportive care compared with best supportive care alone.</p>	3.9 to 3.12
	<p>The Committee noted that the key factor in determining the cost effectiveness was the estimate of overall survival and heard from the ERG that it considered the RPSFT method to be more methodologically robust than the IPCW method because it does not assume that there are no unmeasured confounders. In addition, the Committee understood that the manufacturer's revised IPCW analysis contained a number of unexplained differences between the original and revised models, and so the ERG could not conduct a full critique of the revised IPCW analysis. The Committee therefore concluded that, in this instance, it was more appropriate to evaluate the cost effectiveness of everolimus based on the estimates generated using the RPSFT method.</p>	4.8

<p>Uncertainties around and plausibility of assumptions and inputs in the economic model</p>	<p>No revised sensitivity analyses had been undertaken by the manufacturer.</p> <p>The Committee discussed the validity of the estimates of overall survival from the manufacturer's and ERG's RPSFT analyses... The Committee accepted that the use of a Weibull distribution, which used all available data, was a more appropriate method for estimating overall survival and produced a better fit to the empirical data points.</p> <p>The Committee acknowledged comments received that overall survival with best supportive care in the ERG's exploratory analyses using the Weibull distribution (10.8 months) was higher than was seen in clinical practice, and that the estimate in the manufacturer's analysis (7.9 months) was more likely to reflect clinical practice. The Committee noted that the difference in overall survival between patients receiving everolimus and those receiving best supportive care was 8.2 months in the manufacturer's revised RPSFT analysis and 5.9 months in the ERG's revised RPSFT analysis...The Committee accepted that the ERG's estimate of overall survival for patients receiving best supportive care using the RPSFT analysis was higher than observed in clinical practice, but the incremental difference in overall survival for everolimus versus best supportive care (5.9 months) was more plausible than that derived by the manufacturer and it was based on all of the available data.</p>	<p>3.22, 4.9, 4.10</p>
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<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 noted that the utility estimates in the model were neither directly obtained nor mapped from the RECORD-1 trial. The Committee noted that the estimates of utility for each of the disease states were similar. The Committee accepted that a larger decrement in utility may be plausible when a person moves from a 'stable disease' health state to a 'progressed disease' health state... The Committee agreed that although the utility estimates were subject to some uncertainty, the utility assumptions in the economic model were acceptable.</p> <p>No potential health-related benefits have been identified that were not included in the economic model.</p>	<p>4.13</p>
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>The Committee noted that no subgroups of patients had been identified</p>	<p>4.17</p>
<p>What are the key factors in determining cost effectiveness?</p>	<p>The Committee noted that the key factor in determining the cost effectiveness was the estimate of overall survival.</p>	<p>4.8</p>
<p>Most likely cost-effectiveness estimate (given as an ICER)</p>	<p>The Committee therefore concluded that the ICER of £58,300 per QALY gained (derived by the ERG) was the most plausible.</p>	<p>4.11</p>
<p>Additional factors taken into account</p>		
<p>Patient access scheme</p>	<p>The manufacturer has agreed a patient access scheme with the Department of Health in which the first treatment pack of everolimus is free to the NHS and following treatment packs cost £2822 (that is, a 5% discount on the acquisition cost of everolimus).</p>	<p>3.13</p>
<p>End-of-life considerations</p>	<p>The Committee concluded that everolimus for advanced RCC met the criteria for being a life-extending, end-of-life treatment, and that the evidence presented for this consideration was sufficiently robust.</p>	<p>4.15</p>
<p>Equalities considerations, social value judgements</p>	<p>No equality issues relating to population groups protected by equality legislation were highlighted when the scope for this appraisal was developed, or during the appraisal.</p>	<p>4.17</p>

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below). These are available on our website (www.nice.org.uk/guidance/TAXXX). [NICE to amend list as needed at time of publication]

- Slides highlighting key messages for local discussion.
- Costing report and costing template to estimate the savings and costs associated with implementation.
- Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Related NICE guidance

Published

- Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. NICE technology appraisal guidance 169 (2009). Available from www.nice.org.uk/guidance/TA169

- Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of renal cell carcinoma. NICE technology appraisal guidance 178 (2009). Available from www.nice.org.uk/guidance/TA178

Under development

NICE is developing the following guidance (details available from www.nice.org.uk):

- Pazopanib for the first-line treatment of metastatic renal cell carcinoma (earliest anticipated date of publication December 2010).

7 Review of guidance

7.1 The guidance on this technology will be considered for review in February 2013.

Gary McVeigh

Vice Chair, Appraisal Committee

June 2010

Appendix A: Appraisal Committee members and NICE project team

A *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 four 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.

Dr David Black

Director of Public Health, Derbyshire County Primary Care Trust

Dr Daniele Bryden

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

Professor Mike Campbell

Statistician, Institute of Primary Care and General Practice, University of Sheffield

David Chandler

Lay member

Dr Chris Cooper

General Practitioner, St John's Way Medical Centre, London

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R & D Unit

Professor Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Dr Alan Haycox

Reader in Health Economics, University of Liverpool Management School

Professor Catherine Jackson

Professor of Primary Care Medicine, University of St Andrews

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Henry Marsh

Consultant Neurosurgeon, St George's Hospital, London

Professor Gary McVeigh (Vice Chair)

Professor of Cardiovascular Medicine, Queen's University Belfast and
Consultant Physician, Belfast City Hospital

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Neil Myers

General Practitioner

Dr Richard Nakielny

Consultant Radiologist, Sheffield Teaching Hospitals Foundation Trust

Dr Katherine Payne

Health Economics Research Fellow, University of Manchester

Dr Danielle Preedy

Lay member

Dr Martin Price

Head of Outcomes Research, Janssen-Cilag

Miles Scott

Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

Dr Surinder Sethi

Consultant in Public Health Medicine, North West Specialised Services
Commissioning Team

Professor Andrew Stevens

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

Paul Trueman

Health Economics Research Group, Brunel University

Dr Judith Wardle

Lay member

B NICE project team

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

Helen Tucker

Technical Lead

Rebecca Trowman

Technical Adviser

Lori Farrar

Project Manager

Appendix B: Sources of evidence considered by the Committee

- A. The Evidence Review Group (ERG) report for this appraisal was prepared by Peninsula Technology Assessment Group (PenTAG)
- Pitt M, Crathorne L, Moxham T, et al., Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma, November 2009
- 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. Manufacturer/sponsor:
- Novartis Pharmaceuticals
- II. Professional/specialist and patient/carer groups:
- James Whale Fund for Kidney Cancer
 - Kidney Cancer UK
 - Macmillan Cancer Support
 - Rarer Cancers Forum
 - Royal College of Nursing
 - Royal College of Physicians, Medical Oncology Joint Special Committee
 - United Kingdom Oncology Nursing Society
- III. Other consultees:
- Department of Health
 - Welsh Assembly Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- NHS Quality Improvement Scotland
- National Institute for Health Research Health Technology Assessment Programme
- Peninsula Technology Assessment Group, University of Exeter (PenTAG)

C. The following individuals were selected from clinical specialist and patient expert nominations from the non-manufacturer/sponsor consultees and commentators. They gave their expert personal view on everolimus by attending the initial Committee discussion and providing written evidence to the Committee. They were also invited to comment on the ACD.

- Dr Kate Fife, Consultant Clinical Oncologist, nominated by Royal College of Physicians – clinical specialist
- Beryl Roberts, Lead Oncology Nurse, nominated by United Kingdom Oncology Nursing Society – clinical specialist
- Pat Hanlon, nominated by Kidney Cancer UK – patient expert
- Jackie Lowe, nominated by Kidney Cancer UK – patient expert
- Bill Savage, nominated by James Whale Fund – patient expert

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

- Novartis Pharmaceuticals