National Institute for Health and Clinical Excellence

Everolimus for the second-line treatment of metastatic renal cell carcinoma

Evaluation Report

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal

Everolimus for the second-line treatment of metastatic renal cell carcinoma

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Premeeting briefing

Everolimus for the treatment of advanced renal cell carcinoma

This briefing presents the key issues arising from the manufacturer's submission, Evidence Review Group (ERG) report and statements made by consultees and their nominated clinical specialists and patient experts. Please note that this briefing is a summary of the information available and should be read with the full supporting documents.

The manufacturer was asked to provide:

Further details of the results of the RECORD-1 trial by age and ethnic group.

Comment on the transferability of RECORD-1 trial to UK clinical practice.

Clarification of the definition of 'best supportive care' used in the RECORD-1 trial.

Clarification of the methods used to carry out blinding in the RECORD-1 trial.

Provision of a copy of the report by an independent statistician on the Inverse Probability of Censoring Weight (IPCW) method that was used to analyse the data from the RECORD-1 trial.

Clarification of why the IPCW method was used in preference to other available methods.

Provision of a cost-effectiveness analysis using an estimate of overall survival obtained from intention-to-treat data from the RECORD-1 trial (that is, without the use of IPCW or any other statistical method to correct for bias associated with crossover).

Clarification of the method used to calculate transition probabilities in the economic model.

Licensed indication

Everolimus (Afinitor, Novartis) has a UK marketing authorisation for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF)-targeted therapy.

Everolimus is administered orally.

Key issues for consideration

- Does the Committee consider the estimate of mean overall survival used in the base-case of 10.1 months for everolimus and 5.1 months for best supportive care reflective of what would be seen in clinical practice?
- Does the Committee consider the Inverse Probability Censoring Weights (IPCW) method used to generate these survival estimates to be robust?
- Does the committee consider the methodology used to implement the IPCW method in the model robust, in particular:
    - Should the transition probabilities have been converted to rates before applying the hazard rate multiplier as suggested by the ERG?
    - Has the mortality in the BSC arm of the model been overestimated as suggested by the ERG?
- Does the committee consider the IPCW method or the Rank Preserving Structural Failure Time (RPSFT) method to estimate overall survival more appropriate?
    - What are the implications of the wide confidence intervals around the hazard ratio derived from the IPCW and RPSFT analyses in interpreting the clinical and cost effectiveness of everolimus compared with best supportive care?
    - Does the Committee consider the estimate of mean overall survival of 15.2 months for everolimus and 7.7 months for best supportive care generated by the RPSFT method reflective of what would be seen in clinical practice?
- Does the Committee consider the methodology used to implement the RPSFT method in the model robust, in particular:
    - Should the extrapolation of the death state transition probabilities in the best supportive care arm for cycles 6 to 18 have been based on the RPSFT survival estimate from one data time point in the RECORD-1 trial?

- What is the Committee's view on the plausibility of the assumptions about adverse events in the model, in particular that:
    - People would experience a utility decrement for only one cycle after which their utility would return to a level equivalent to the state without adverse events but costs for treatment of adverse events would remain?

Related NICE guidance

- Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. NICE technology appraisal 169 (2009). Available from www.nice.org.uk/TA169
    - Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- 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 178 (2009). Available from www.nice.org.uk/TA178
    - Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic renal cell carcinoma.
    - Sorafenib and sunitinib are not recommended as second-line treatment options for people with advanced and/or metastatic renal cell carcinoma.

1 Decision problem

1.1 Decision problem approach in the manufacturer's submission

Table 1 Decision problem for everolimus

Population	Adults with advanced renal cell carcinoma whose disease has progressed on or after treatment with vascular endothelial growth factor-targeted therapy
Intervention	Everolimus 10 mg/day
Comparators	Best supportive care alone
Outcomes	Progression-free survival Overall survival Tumour response rate Health related quality of life and patient-reported outcomes Adverse effects of treatment
Economic evaluation	Cost–utility of everolimus plus best supportive care versus best supportive care alone in adults with advanced renal cell carcinoma whose disease has progressed on or after treatment with vascular endothelial growth factor--targeted therapy. Analysis to be performed from the perspective of the NHS and personal social services.

1.2 Evidence Review Group comments

1.2.1 Population

The evidence review group (ERG) stated that the population specified was in accordance with the appraisal scope and the licensed indication.

1.2.2 Intervention

The ERG concluded that the intervention in the trial and the economic model, everolimus, reflected the appraisal scope and the marketing authorisation.

1.2.3 Comparators

The ERG stated that the choice of comparator, best supportive care alone, was appropriate and that the definition of best supportive care is in accordance with clinical practice.

1.2.4 Outcomes

The ERG stated that the choice of outcomes was appropriate and in line with the appraisal scope.

1.2.5 Economic evaluation

The ERG concluded that the model was generally well developed and reported, although errors were identified in the way the model was executed. The time horizon of 144 weeks in the manufacturer's model was considered appropriate.

2 Clinical effectiveness evidence

2.1 Clinical effectiveness in the manufacturer's submission

The manufacturer identified one randomised controlled trial (RCT) that met the criteria for inclusion in the review. This was a phase III trial (RECORD-1) that compared a once-daily, oral 10-mg dose of everolimus plus best supportive care (n = 277) with placebo plus best supportive care (n = 139). The primary endpoint was progression-free survival based on tumour assessments performed by the independent central radiology review. Participants were stratified by Memorial Sloan-Kettering Cancer Centre (MSKCC) prognostic score and whether they had received one or two prior treatments (that is, sunitinib and/or sorafenib).

The RCT was a multinational study conducted in 86 centres in Australia, Canada, Europe, Japan and the USA. The study population comprised adults with advanced renal cell carcinoma that showed a clear cell component whose cancer had progressed on or who had stopped vascular endothelial growth factor (VEGF)-targeted therapy (sunitinib, sorafenib or both) within the past 6 months. Previous immunotherapy (interferon-alfa or interleukin-2) or bevacizumab was allowed. The baseline characteristics of the patients in the two treatment arms were generally similar and relatively well balanced in terms of previous therapy. Approximately 44% of patients in each treatment

arm had received prior sunitinib treatment, 30% in each treatment arm had received prior sorafenib treatment, and 26% in each treatment arm had received both sunitinib and sorafenib.

The RCT was designed to be a crossover trial; patients who were receiving placebo plus best supportive care and had disease progression documented radiologically were allowed to receive open-label everolimus treatment if the treating clinician felt that they could benefit. The study was double-blinded up to the point at which disease progression was documented radiologically. The RCT began in December 2006 and the double-blind phase was terminated in February 2008.

Table 2 Progression-free survival results from the double-blind phase of the RECORD-1 trial comparing everolimus plus best supportive care with placebo plus best supportive care

Population	**Median progression-free survival**			
	Everolimus + best supportive care vs. best supportive care (months)	**1st interim analysis hazard ratio (95% confidence interval)**	**Everolimus + best supportive care vs. best supportive care (months)**	**2nd interim analysis hazard ratio (95% confidence interval)**
All (n = 416)	**4.9 vs. 1.9**	0.33 (0.25 to 0.43)	Not reported	0.30 (0.22 to 0.44)
Favourable MSKCC prognosis (n = 120)	5.8 vs. 1.9	0.31 (0.19 to 0.50)	Not reported	0.35 (0.20 to 0.61)
Intermediate MSKCC prognosis (n = 235)	4.5 vs. 1.8	0.32 (0.22 to 0.44)	Not reported	0.29 (0.16 to 0.37)
Poor MSKCC prognosis (n =61)	3.6 vs. 1.8	0.44 (0.22 to 0.85)	Not reported	0.39 (0.19 to 0.81)
MSKCC, Memorial Sloan-Kettering Cancer Centre.				

Table 2 shows that there was a 67% reduction in disease progression at the first analysis time point (70% at the second analysis time point) for people receiving everolimus plus best supportive care compared with people receiving best supportive care only.

A final analysis of progression-free survival was carried out. Based on disease progression events determined by independent central radiology review, the median progression-free survival was 4.90 months (95% confidence interval [CI]: 3.98 to 5.52) for everolimus plus best supportive care and 1.87 months (95% CI: 1.84 to 1.94) for best supportive care only. The resulting hazard ratio was 0.33 (95% CI 0.25 to 0.43) and the difference in median progression-free survival was statistically significant in favour of everolimus ($p < 0.001$).

As current NICE guidance recommends only sunitinib as a first-line treatment for advanced and/or metastatic renal cell carcinoma, a final analysis of progression-free survival according to previous VEGF-targeted therapy was undertaken. Table 3 shows that there were statistically significant improvements in progression-free survival for all of the subgroups by prior VEGF-targeted therapy. For people whose disease had failed to respond to sunitinib, there was 66% less risk of disease progression with everolimus plus best supportive care compared with best supportive care only.

Table 3 Progression-free survival according to prior VEGF-targeted therapy

Prior VEGF-targeted therapy	Number of patients		Median progression-free survival (months) Everolimus +best supportive care vs. best supportive care	Hazard ratio (95% CI)
	Everolimus + best supportive care	Placebo + best supportive care		
Sorafenib only	81	43	Not reported	0.25 (0.16 to 0.42)
Sunitinib only	124	60	Not reported	0.34 (0.23 to 0.51)
Both	72	36	Not reported	0.32 (0.19 to 0.54)
95% CI, 95% confidence interval; VEGF, vascular endothelial growth factor.				

Overall survival

A statistically significant difference in median overall survival was not identified at either the second (hazard ratio [HR] = 0.83, 95% CI 0.50 to 1.37, p = 0.23) or the final analysis (HR = 0.87, 95%CI 0.65 to 1.17, p = 0.177). At

this final analysis, the median overall survival in the everolimus plus best supportive care arm had not been reached and was 13.01 months in the best supportive care only arm.

The manufacturer explained that 76% of patients assigned to receive placebo plus best supportive care crossed over to the everolimus arm at the analysis conducted in February 2008. Therefore, the manufacturer adjusted the overall survival results for the crossover that occurred, by using the Inverse Probability of Censoring Weight (IPCW) method (for details of the how the IPCW method was applied see pages 201–207 of the manufacturer's submission and pages 64–65 of the ERG report). This method aims to adjust for crossover by recreating the population that would have been seen 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. This was a post-hoc analysis (for further details see pages 65–67 of the manufacturer's submission).

The manufacturer explained that the IPCW method was used in preference to other available methods such as the Rank Preserving Structural Failure Time (RPSFT) model (which proportionally 'shrinks' the estimated amount of additional survival conferred to people who cross over). The RPSFT method was used in a previous NICE appraisal of sunitinib for the treatment of gastrointestinal stromal tumours (NICE technology appraisal 179), but the IPCW method was used in the current appraisal for the following reasons:

- it produces a hazard ratio rather than treatment effect in terms of time to event
- the IPCW method does not require data to be normally distributed
- the manufacturer investigated applying parametric distributions to the RECORD-1 data, but did not find goodness of fit for all transitions (progression-free survival to progression, progression-free survival to death, and progression to death)
- the IPCW method does not 'borrow' information from crossed over patients as other methods do

- the IPCW method provides a potentially more powerful estimate of the treatment effect on survival and its significance because it does not 'borrow' information from patients who cross over (as the RPSFT method does)
- the IPCW method does not impose a structural model to control for the effect of crossover and so was anticipated to be more robust than the RPSFT method.

For further details see appendices 2, 3 and 4 of the manufacturer's submission and pages 93–98 of the manufacturer's response to the request for clarification.

The IPCW-adjusted Cox proportional hazards model suggested that treatment with everolimus plus best supportive care reduced the risk of mortality by 45% compared with placebo plus best supportive care (HR = 0.55, 95% CI 0.31 to 0.97). This hazard ratio equated to a difference in overall survival of 4.97 months for everolimus compared with best supportive care alone. Mean overall survival for the everolimus plus best supportive care arm and best supportive care only arm when adjusted with the IPCW method was 10.1 months and 5.1 months, respectively. The suggestion that survival was nearly twice as long with everolimus plus best supportive care compared with best supportive care alone was also reflected in the relative risk (RR) of 1.82.

Health-related quality of life and adverse events

No generic measure of health-related quality of life was collected in the RCT. Patient-reported outcomes were measured using the disease-related symptoms score of the Functional Assessment of Cancer Therapy – Kidney Symptom Index (FKSI–DRS) and the European Organisation for Research and Treatment of Cancer quality of life questionnaire-core 30 (EORTC–QLQ–30). The manufacturer stated that the mean scores over time indicated that the results were similar for everolimus plus best supportive care compared with placebo plus best supportive care. Time to deterioration in functioning/symptoms was stated to be delayed with everolimus plus best supportive care by 3.5 months compared with placebo plus best supportive

care (median time to deterioration according to FKSI–DSR 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).

In the manufacturer's submission, the primary source of data for adverse advents was the RECORD-1 RCT. There were more adverse events and serious 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 everolimus-related adverse events were anaemia and stomatitis (there were 103 anaemia and 103 stomatitis events in the everolimus plus best supportive care arm. For further details, see table 6.10 in the manufacturer's submission.

2.2 Evidence Review Group comments

The ERG did not identify any relevant studies that were not included in the manufacturer's submission. Although only one RCT was included, it was considered to be of high quality. The ERG highlighted concerns about the validity of the estimates of overall survival obtained from the IPCW analysis. However, it stated that this is an area of ongoing academic debate.

The ERG explained that in general it was satisfied that the manufacturer was justified in applying statistical methods to correct for crossover bias and that IPCW is a valid option. However, it was not convinced that IPCW represents the best method in preference to other methods such as the RPSFT approach.

The ERG explained that it believed the RPSFT method would have been more appropriate for the following reasons:

- It is less biased because it is based on comparisons of groups as randomised.
- Assumes that there are no additional confounders in the placebo arm of the trial that have not been included (that is all key characteristics have been included in the analysis).

2.3 Statements from professional/patient groups and nominated experts

Clinical specialists noted that most people with metastatic or locally advanced renal cell carcinoma are well enough to receive a second-line treatment. The specialists agreed that there was a high level of clinical need for this treatment because the only current treatment option is supportive care and that everolimus represented an innovative treatment. The clinical specialists explained that supportive care frequently involves blood transfusions, inpatient stays, radiotherapy and community care.

The patient and professional groups specified that annually there are just less than 7,000 new registrations of renal cell carcinoma, of which about 40 per cent present (or go on to develop) advanced and/or metastatic disease. The clinical specialists viewed everolimus as being an effective second-line treatment for metastatic or locally advanced renal cell carcinoma and thought that everolimus would be tolerated by most people.

3 Cost effectiveness

3.1 Cost effectiveness in the manufacturer's submission

The manufacturer explained that a systematic search was undertaken, but no existing cost-effectiveness studies were identified.

3.1.1 Manufacturer's de novo economic model

The manufacturer submitted a de novo economic model. The model was a Markov-based patient-level model comparing treatment with everolimus plus best supportive care with best supportive care alone. The time horizon of the model was 144 weeks, the cycle length was 8 weeks and a half cycle correction was not applied. The model used a hypothetical cohort of people with advanced renal cell carcinoma whose cancer had progressed on or who had received VEGF-targeted therapy (that is, sunitinib, sorafenib, and/or bevacizumab) and who had demographic characteristics reflecting those of

the RECORD-1 trial. No subgroup analyses were conducted by the manufacturer.

The model had four health states: stable disease without adverse events, stable disease with adverse events, disease progression, and death. All people were assumed to enter the model in the 'stable disease without adverse events' health state.

Treatment with everolimus consisted of 10 mg/day given as monotherapy in addition to best supportive care. Everolimus treatment was given until disease progression or unacceptable adverse events (defined by the RESIST criteria) and was adjusted to 91.8% dose intensity. The rates of adverse events, treatment withdrawal, disease progression, and deaths from the RECORD-1 trial were used to calculate the transition probabilities. The observed event rates 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 RECORD-1 trial up to cycle seven of treatment. The trial ended after the seventh cycle and the rates after this cycle were assumed to remain constant.

For health states leading to death, the RECORD-1 trial 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 transitions in the everolimus arm. The manufacturer explained that the cohort of patients receiving best supportive care was therefore at a constantly higher relative risk of mortality at any given cycle (for further details see page 116 of the manufacturer's submission). See table 5 for a comparison of the transition probabilities for death for people receiving best supportive care in the RECORD-1 trial and those used in the economic evaluation. Mean survival for everolimus plus best supportive care was estimated to be 10.1 months compared with 5.1 months for best

supportive care alone, giving an estimated gain of 4.97 months for everolimus plus best supportive care

Table 5 Transition probabilities for death in the RECORD-1 trial and the economic model for patients receiving best supportive care only

Cycle	1	2	3	4	5	6	7	8–17
PD to death (RCT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
PD to death (model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD to death (RCT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD to death (model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD with adverse events to death (RCT)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
SD with adverse events to death (model)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RCT, randomised controlled trial; PD, progressed disease; SD, stable disease								

The RECORD-1 trial did not include a generic measure of health-related quality of life (such as the EQ–5D) which could be used to estimate utilities. In the model, the utilities used for health states for patients receiving second-line treatment for advanced renal cell carcinoma were obtained from the Assessment Group estimates from a previous NICE technology appraisal, '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 178). These utility values were 0.76 for stable disease without adverse events, 0.71 for stable disease with adverse events and 0.68 for progressed disease.

Table 6 Resources and costs Cost estimates used in the manufacturer's economic model

	Without patient access scheme		With patient access scheme		
	Unit cost (30 x 10-mg tablet pack) £	**Total cost per 8-week cycle £**	**Unit cost (30 x 10-mg tablet pack) £**	**Total cost per 8-week cycle: first cycle [a] £**	**Total cost per 8-week cycle: subsequent cycles £**
Everolimus acquisition (no dose intensity adjustment)	2970	5544.00	2822	2445.30	5266.80
Everolimus acquisition (with dose intensity adjustment)	2970	5089.39	2822	2244.79[c]	4834.92[c]
Monitoring tests [b]	-	-	-	-	-
Diagnostic tests [b]	-	-	-	-	-
Appointments [b]	-	-	-	-	-
Other costs [b]	-	-	-	-	-
Total patient related costs		5089.39		2244.79	4843.92

[a] First cycle cost based on first month of treatment, everolimus provided at no cost to NHS.
[b] No additional costs are anticipated associated with tests.
[c] Assuming a dose intensity of 91.8%.

The manufacturer has agreed a patient access scheme with the Department of Health (table 6) in which the first treatment pack of everolimus is free to the NHS and following treatment packs cost £2822 ((that is, a 5% discount). It was assumed 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 cost of ongoing resource use for each cycle of everolimus was estimated to be £110

and £182 for three cycles. The estimated cost for best supportive care was £641 per cycle (for a summary of resource use, see pages 54–57 of the ERG report). In addition, 72% of patients in the RECORD-1 trial 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 state.

The manufacturer did not use individual disutility estimates for adverse events 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 (for further details see page 121 of the manufacturer's submission). The manufacturer clarified that this disutility was maintained throughout all subsequent cycles. The costs of adverse events were assumed to only last for one cycle.

3.1.2 Results from manufacturer's de novo economic model

The base-case results in the manufacturer's submission are shown in table 7 below. In this analysis the IPCW method was used to derive the survival estimates in the model,

Table 7 . Base case cost-effectiveness results for everolimus plus BSC versus BSC alone (discounted)*

	Everolimus plus BSC	BSC alone	Everolimus plus BSC versus BSC alone
WITH PAS			
Drug costs (everolimus) (£)**	14,045	0	14,045
Other costs (£)***	11,177	9,517	1,660
TOTAL COSTS (£)	25,222	9,517	15,704
Life years	0.841	0.426	0.414
QALYs	0.607	0.302	0.304
Cost/LYG			37,893
Cost/QALY gained			**51,613**
WITHOUT PAS			
Drug costs (everolimus) £**	17,001	0	17,001
TOTAL COSTS (£)	28,178	9,517	18,661
Cost/LYG			45,027

	Everolimus plus BSC	BSC alone	Everolimus plus BSC versus BSC alone
Cost/QALY gained			**61,330**

The manufacturer's analysis found that if the maximum acceptable amount to pay for an additional quality-adjusted life year (QALY) gained was £60,000 then everolimus had an 80% probability of being cost effective, and 40% if the maximum acceptable amount to pay for an additional QALY gained was £50,000. These analyses included the patient access scheme.

The manufacturer also provided an analysis using standard intention-to-treat analysis of overall survival. These results are summarised in table 8 below.

Table 8 Cost effectiveness of everolimus using intention-to-treat analysis of overall survival

Comparison	**QALYS** Everolimus + BSC vs BSC (Incremental QALY)	**Costs £** Everolimus + BSC vs. BSC (Incremental cost)	**Incremental cost-effectiveness ratio**
Everolimus + best supportive care vs best supportive care (with patient access scheme)	0.607 vs. 0.492 (0.115)	25,222 vs. 14,758 (10,463)	91,256
Everolimus + best supportive care vs best supportive care (without patient access scheme)	0.607 vs 0.492 (0.115)	27,328 vs. 14758 (12,570)	109,627
BSC, best supportive care, QALY, quality adjusted life year			

The manufacturer provided sensitivity analyses (for further details see table 21 of the ERG report). The key driver of the cost-effectiveness estimate of everolimus compared with best supportive care was the method used to analyse overall survival

3.2 Evidence Review Group comments

The ERG said that the model structure was generally appropriate and was in agreement that half-cycle correction is not required in the model. However,

the ERG stated that discounting of 3.5% (which was applied after the 1st year in the model) should have been applied after the first cycle.

The ERG agreed with the manufacturer that the main driver of cost effectiveness is the estimate of survival gain used in the model. The ERG explained that the survival estimates used in the model were derived (utilising the IPCW method) in the following way:

- Transition probabilities for mortality in the everolimus arm were multiplied by a factor of 1.818. This value was the IPCW-calculated mortality hazard ratio for best supportive care only versus everolimus (that is, the reciprocal of 0.55, the everolimus versus best supportive care hazard ratio). The mortality hazard ratio was applied in the model to calculate the key transition probabilities for the cohort of patients receiving best supportive care only who are moving from stable disease states to death and from progressed disease to death.

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 is assumed to return to a level equivalent to the state without adverse events. Costs for treatment were however assumed to remain. Therefore only one episode of adverse events for each patient is supported in the model. This was clarified by the manufacturer in response to a factual check of the ERG report. The manufacturer stated that the disutility associated with experiencing an adverse event was assumed to remain, but that the costs of treating adverse events were only present for one cycle.

The ERG also considered that the difference in utility between stable disease and progressive disease (0.76 vs. 0.68) may understate the benefit demonstrated for everolimus in delaying progression.

3.2.1 ERG's exploration of the manufacturer's model

The ERG specified that the IPCW method was incorrectly applied in the economic model. This was for the following reasons:

- The manufacturer failed to convert the transition probabilities to rates before applying the hazard rate multiplier. The ERG said that the correct approach would be to convert each relevant transition probability in the everolimus arm to rates. These rates would then be multiplied by the mortality hazard ratio and then converted back into revised transition probabilities. The ERG stated that these revised transition probabilities should then be applied to the best supportive care only arm. When this conversion is performed correctly the overall effect is to raise the base-case incremental cost-effectiveness ratio (ICER) from £51,613 to £53,479 per QALY (with patient access scheme applied) and from £61,330 to £63,967 per QALY (without patient access scheme applied)
- Secondly, 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 mortality in the best supportive care arm and in effect improved the overall mortality hazard ratio in favour of the everolimus arm.

Table 9 Hazard ratio state occupancies (alive vs. dead) used in each arm of the manufacturers and ERG models

Cycle	BSC vs Everolimus Manufacturer model	Everolimus vs BSC Manufacturer model	BSC vs Everolimus ERG analysis	Everolimus vs BSC ERG analysis
0	-	-	-	-
1	1.818	0.55	1.82	0.55
2	3.231	0.31	1.82	0.55
3	2.889	0.35	1.82	0.55
4	2.150	0.47	1.82	0.55
5	1.881	0.53	1.82	0.55
6	2.654	0.38	1.82	0.55
7	3.500	0.29	1.82	0.55
8	3.519	0.28	1.82	0.55
9	3.534	0.28	1.82	0.55
10	3.546	0.28	1.82	0.55
11	3.555	0.28	1.82	0.55
12	3.562	0.28	1.82	0.55
13	3.568	0.28	1.82	0.55
14	3.572	0.28	1.82	0.55
15	3.576	0.28	1.82	0.55
16	3.579	0.28	1.82	0.55
17	3.581	0.28	1.82	0.55
18	3.583	0.28	1.82	0.55

- The ERG explained that when they corrected for this error, in addition to correcting the rate conversion error described above, the base-case ICER increased further from a value of £53,479 to £64,988 per QALY (with patient access scheme applied) and from £63,967 to £75,599 per QALY (without patient access scheme applied).

The ERG also changed the manufacturer's model by discounting costs and benefits (at 3.5%) from the first cycle of the model rather than after the first year only. This further increased the amended ICERs described above from £64,988 to £65,231 per QALY gained (with patient access scheme) and from £75,599 to £76,070 per QALY gained (without patient access scheme). See table 10 for a summary of the results.

Table 10 Base-case results from the manufacturer's model including the ERG explorations

Cost-effectiveness results per patient	Undiscounted			3.5% discounting (costs and benefits)		
With patient access scheme applied	**Everolimus plus BSC***	**BSC alone**	**Incremental**	**Everolimus plus BSC***	**BSC alone**	**Incremental**
Total costs £	25,335	12,341	12,994	24,701	12,091	12,610
QALYs	0.609	0.408	0.200	0.595	0.402	0.193
Incremental cost per QALY gained £			64,826			65,231
Without patient access scheme applied	**Everolimus plus BSC***	**BSC alone**	**Incremental**	**Everolimus plus BSC***	**BSC alone**	**Incremental**
Total costs £	27,441	12,341	15,101	26,796	12,091	14,705
QALYs	0.609	0.408	0.200	0.595	0.402	0.193
Incremental cost per QALY gained £			75,335			76,070
BSC, best supportive care; QALY, quality-adjusted life-year.						

The ERG also re-ran the one-way sensitivity analyses presented by the manufacturer with the corrected model parameters (as described above). The results are presented in table 24 of the ERG report.

3.3 Further considerations following premeeting briefing teleconference

3.3.1 Additional analyses from the manufacturer

In response to the factual check of the ERG report, the manufacturer produced an overall survival estimate using the Rank Preserving Structural Failure Time (RPSFT) method. This analysis was conducted using updated

data from November 2008, at which point 81% of people who were allocated to best supportive care had crossed over to receive everolimus.

The RPSFT method estimated that survival was nearly twice as long, with everolimus plus best supportive care compared with best supportive care alone (RR = 1.93, 95% CI from 0.50 to 8.50). This equated to a mean overall survival gain of 7.51 months for everolimus compared with BSC alone. However this difference was not statistically significant.

Table 11 below shows a comparison of the overall survival derived using the IPCW method and the RPSFT method. Note the median overall survival using an intention to treat approach for everolimus plus best supportive care was 14.78 months and 14.39 months with best supportive care alone (HR = 0.87, 95% CI: 0.65 to 1.17, RR not reported).

Table 11 Comparison of results for overall survival using different methods to correct for cross-over bias in the RECORD-1 trial

Method	Data collection time point	Mean OS (months) EV+BSC vs. BSC	HR (95% C.I)	RR
RPSFT	Nov 08	15.18 vs. 7.67	0.52 *	1.93
IPCW	Feb 08	10.09 vs. 5.11	0.55 (0.32 to 0.97)	1.81
RPSFT, rank- preserving structural failure time; IPCW, inverse probability censoring weights. * derived by dividing 1by 1.93; formula specified in manufacturer's submission page 206				

The manufacturer also submitted additional cost-effectiveness analyses in response to the factual check of the ERG report. This analysis differed from the original model in the following ways:

- Mean survival estimate for everolimus plus best supportive care was generated using the RPSFT method (see table 11).
- Data collected in November 2008 from the RECORD-1 trial were used as opposed to data collected in February 2008 because more patients treated with everolimus were still alive in the final cycle of the economic model.

- A Kaplan–Meier curve for the RPSFT-corrected overall survival was used to generate the best supportive care transition probabilities to death for the placebo plus best supportive care arm of the study. The manufacturer explained that because the RPSFT results do not allow differentiation of the conditional probability of death by health state it has assumed the same transition probabilities to death in the placebo plus best supportive care arm for each of the states to death.
- All other base-case assumptions in the model remain unchanged.

The cost-effectiveness results using the RPSFT method and the IPCW method to derive the overall survival estimates are summarised in table 12 below (for further details, see page 4 of the additional analysis provided by the manufacturer).

Table 12 Cost-effectiveness results using the IPCW and RPSFT methods to derive overall survival

	Everolimus plus best supportive care QALY	best supportive care alone QALY	Everolimus plus best supportive care LYG (months)	best supportive care alone LYG (months)	Inc LYG (months)	Inc QALY	Everolimus plus best supportive care cost (£)	best supportive care alone cost (£)	Inc cost (£)	ICER for everolimus plus best supportive care versus best supportive care alone (£/QALY)
Base case with PAS[a] (IPCW Feb 2008 cut-off)	0.607	0.302	0.841 (10.09 months)	0.426 (5.11 months)	0.414 (4.97 months)	0.304	£25,222	£9,517	£15,704	£51,613
Base case without PAS [a] (IPCW Feb 2008 cut-off)						0.304			£18,661	£61,330
With PAS: RPSFT (Nov 2008 cut-off)	0.912	0.454	1.265 (15.18 months)	0.639 (7.67 months)	0.626 (7.51 months)	0.458	£36,168	£11,824	£24,344	£53,128
Without PAS: RPSFT (Nov 2008 cut-off)	0.912	0.454	1.265 (15.18 months)	0.639 (7.67 months)	0.626 (7.51 months)	0.458	£38,312	£11,824	£26,488	£57,808

ICER, incremental cost effectiveness ratio; IPCW, Inverse Probability of Censoring Weight; LYG Life Years Gain; PAS, patient access scheme; QALY, quality-adjusted life-year; RPSFT, Rank Preserving Structural Failure Time.

3.3.2 ERG comments on the additional analysis from the manufacturer

The ERG stated that in this additional analysis there was an over-estimation of the mortality risk in the best supportive care arm. This was because the extrapolation of the overall survival curve for the best supportive care only population was based on a single trial data point.

The ERG conducted an exploratory analysis using a value of 0.157 for the mortality transitions for cycles 6 to 18 in the model (this value in the manufacturer's model was 0.5). The ERG calculated the new transition probability as the mean of the probabilities in cycles 4 and 5 and stated that it provided a more realistic interpretation of the overall survival of best supportive care arm (see figures 1 and 2 in the ERG response to the additional analysis for further details). All other model transition values were same as those used in the manufacturer's analysis. See table 13 for the ERG exploration of the cost effectiveness estimates based on the manufacturers RPSFT analysis.

Table 13 - ERG exploratory cost effectiveness analysis using the RPSFT method to derive estimates of overall survival

	Incremental Costs £s	Incremental Benefit QALYs	ICER £s/QALY
Without PAS (discounted @ 3.5%)	21,471	0.255	**84,079**
Without PAS (undiscounted)	22,228	0.268	82,938
With PAS (discounted @ 3.5%)	19,338	0.255	**75,725**
With PAS (undiscounted)	20,083	0.268	74,935
PAS, Patient Access Scheme			

4 Authors

Helen Tucker and Rebecca Trowman, with input from the Lead Team (Kathryn Abel, Eugene Milne and Judith Wardle).

Appendix A: Sources of evidence considered in the preparation of the premeeting briefing

A The Evidence Review Group (ERG) report for this appraisal was prepared by Peninsula Technology Assessment Group:

- 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 Submissions or statements were received from the following organisations:

I Manufacturer/sponsor:

- Novartis

II Professional/specialist, patient/carer and other groups:

- Kidney Cancer UK
- Royal College of Physicians

Professional organisation statement template

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted] [redacted] on behalf of

Name of your organisation

NCRI/RCP/RCR/ACP/JCCO

Comments coordinated by our nomination for clinical expert Dr Kate Fife

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology?
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?
- other? (please specify)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Metastatic or locally advanced renal carcinoma in England is currently treated first line with sunitinib. There is an error in the 'final scope' that NICE have issued for this appraisal of everolimus for renal cancer. It states that 'current standard treatment of metastatic RCC is immunotherapy with IL-2 or Interferon-alpha'. This has not been the case since the NICE approval of sunitinib (March 2009).

Sunitinib has been the accepted standard treatment in most European countries since 2006, and the recommended first line treatment by all UK experts. It is a tyrosine kinase inhibitor and reduces the growth of tumours by impairing angiogenesis. There has been great inequity in access to sunitinib across the UK during the last three years because some Primary Care Trusts have been prepared to fund 'exceptional cases' whereas many have not. Fortunately this situation has finally been resolved by the NICE appraisal in March 2009. There is universal backing of sunitinib by experts in the UK and worldwide as it is the first effective palliative treatment for metastatic renal cancer in the majority of patients. Immunotherapy was only effective in the small proportion of patients who fell into the 'good prognosis' metastatic disease category.

However, following treatment with sunitinib, many patients are sufficiently well to receive second line treatment. In most other cancers, second line treatments are

routine and many are NICE approved. In breast and colorectal cancers for example, third and subsequent lines of therapy are frequently prescribed. Currently the only option for second line treatment in a patient with renal cancer in England, is supportive care. This is frequently involves blood transfusions, in-patient stays, radiotherapy and high community care costs. The only other option is to enter into a clinical trial. This leads to inequity as such trials are only available in some major cancer centres and are therefore out of reach of the majority of patients. NICE recently rejected the use of sorafenib as second line therapy following interferon.

Everolimus is the first treatment to be licensed for the second line treatment of renal cancer that has randomised phase III trial evidence that it prolongs progression free survival compared to placebo in patients who have received tyrosine kinase inhibitor therapy (RECORD-1 trial). It has a different action to the tyrosine inhibitor class of drugs, and is an inhibitor of mTOR, a cytosolic kinase, resulting in both angiogenesis inhibition and direct effects on tumour cell growth and proliferation. Everolimus showed a significant improvement in progression free survival when compared with placebo (4.0 vs 1.9 months, Hazard ratio 0.3, 95%CI 0.22-0.4, $p<0.0001$). It should be remembered that most of the patients in this trial had had more than one previous therapy and were being treated third or subsequent line. The PFS would be expected to be longer in patients who have only had one previous therapy.

Everolimus demonstrated the same efficacy in all subgroups assessed, including patients younger or older than 65, and patients in the good, intermediate and poor risk prognostic categories (Memorial Sloane Kettering Cancer Center critera). It has the advantage of being a once-daily oral preparation with acceptable side effects. As such it will be used in the out-patient setting of secondary or tertiary care, by consultant oncologists with expertise in renal cancer, and specialist nurse support.

The technology is not currently readily available in the UK, although several centres have entered patients into the everolimus expanded access programme.
There are several clinical guidelines recommending everolimus as second line therapy authored by experts and based on the level I evidence of the RECORD-1 trial for example:
‘UK Guidelines for the systemic treatment of renal cell carcinoma’, Nathan et al, British Journal of Hospital Medicine May 2009 Vol70; 284-6
‘Kidney Cancer; Clinical practice Guidelines in Oncology, Motzer et al, Journal of the National Comprehensive Cancer Network June 2009, Vol 7;618-30.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The current alternative (outside of clinical trials) is supportive care. Everolimus is relatively easy to use by oncologists supported by specialist nurses. As an oral medication it has excellent patient and carer acceptability. Hospital visits need only be monthly once therapy is established. Apart from routine CT scans no additional tests are required, although some patients will need chest X-Rays to monitor pneumonitis.

A patient would be started on everolimus once they had tumour progression on sunitinib. Everolimus causes mainly stable disease (67% in RECORD-1) rather than major tumour shrinkage; for this reason it is advised to continue treatment until unequivocal progression.

The RECORD-1 trial population was performed in patients with a Karnofsky performance status of 70 or greater (ie cares for self but unable to carry on normal activity or do any work). Patients may have had treated brain metastases, and be in either good, intermediate or poor prognostic categories. This trial population reflects our UK population of patients suitable for second line therapy very well. The trial excluded patients with non-clear cell cancer; however the current expanded access programme includes this group of patients, and temsirolimus (an intravenous mTOR inhibitor) showed efficacy in patients with non-clear cell renal cancer. We would therefore advise approval for second line treatment in all histological subtypes of renal cell cancer.

The most important outcome in this trial is an improvement in progression free survival. Because of the efficacy of the new generation of treatments, it is unethical not to permit cross-over to active treatment from the placebo arm. This of course obscures any overall survival benefit (although a statistical analysis of the RECORD-1 trial corrected for crossover showed that a benefit in overall survival was likely; Wiederkehr et all, ECCO-ESMO 2009). There was a clinically meaningful difference in proportion of patients free of progression at 6 months (26% everolimus vs 2% placebo).

Adverse events led to a treatment discontinuation of 10% in the everolimus arm (4% in placebo). The commonest adverse events were stomatitis, rash and fatigue. Pneumonitis and dyspnoea occur in approximately 8% of patients but do not necessarily cause discontinuation of treatment. Overall, tolerability of everolimus is good compared with the tyrosine kinase inhibitor drugs. It also shows an improvement in quality of life and delay in deterioration of physical function (Beaumont et al, ECCO-ESMO 2009).

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

Phase II trial of RAD001 in patients with metastatic renal carcinoma. Jac et al J Clinical Oncology 2007 25 (18suppl) 261S

International Expanded Access Program of RAD 001; this is ongoing until 30/9/09. Early toxicity results have been presented (ECCO-ESMO 2009) and are consistent with results of the RECORD-1 trial.

Temsirolimus is an intravenous mTOR inhibitor that showed an overall survival advantage in first line treatment of patients in the poor prognostic category when compared with interferon.
Temsirolimus, interferon alpha or both for advanced renal cell carcinoma
Hudes et al New Engl J Med 2007 356;2271-81

There are several ongoing phase III trials of second line therapy for renal cancer which will be reporting over the next 2-3 years as this is a new era of therapy for this previously virtually untreatable cancer.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

NICE guidance on this technology would not affect the delivery of care for these patients. No new staff training, facilities or equipment would be required as this is an out-patient based oral therapy.

Everolimus for the second line treatment of advanced and/or metastatic renal cell carcinoma.

Personal Statement;

Current NICE guidance recommends Sunitinib as a first-line treatment for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an ECOG performance status of 0 or 1. It is therefore reasonable for NICE to approve an appropriate second-line treatment for this small group of patients who have an ECOG performance status of 0 or 1 and could benefit from this therapy. In my experience as a senior nurse working within the field of Oncology there are some patients who progress on first-line treatment and become understandably distressed when there is no alternative treatment approved for use when they are well enough to receive further treatment. Some patients are unable to tolerate Sunitinib and it may be contraindicated in some cases, having an alternative therapy could be beneficial for the patient. From personal experience having a licensed but unfunded drug is very frustrating for all concerned including the clinician, nurses, patient and relatives.

Beryl Roberts
UKONS
04/01/10

Patient/carer organisation statement template

Thank you for agreeing to give us your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

About you

Your name: Bill Savage

Name of your organisation: The James Whale Fund

Are you (tick all that apply):

Xa patient with the condition for which NICE is considering this technology?

- a carer of a patient with the condition for which NICE is considering this technology?
- an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)
- other? (please specify)

What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?

1. **Advantages**
(a) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make.

1) 3 months of progression free survival compared to placebo/best supportive care (Record-1 study)

(b) Please list any short-term and/or long-term benefits that patients expect to gain from using the technology. These might include the effect of the technology on:

- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example family, friends, employers)
- other issues not listed above.

- 3 months of extra life
- Enormous emotional benefits to patients, carers friends and families arising from extended survival
- Patient Quotes : " It is a basic human instinct to want to stay alive as long as possible . This drug can offer vital good quality months to spend with my family "
- Patient Quotes " Every day is special . Every day is precious "
- Patient Quotes : " Afinitor works . In 11 days the lumps in my abdomen virtually disappeared, the pain in my back and my left flank abated and my cough vanished . For this I must put up with a slight sore throat and 2 naps a day

What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition? (continued)

2. **Disadvantages**
Please list any problems with or concerns you have about the technology. Disadvantages might include:

- aspects of the condition that the technology cannot help with or might make worse.
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or their family (for example cost of travel needed to access the technology, or the cost of paying a carer).

Afinitor is not a cure for RCC

There are side effects but they are tolerable

Patient Quotes : “the side effects have been gradual . At first there was some fatigue and a few mouth sores but nothing compared to Sutent or IL2

Patient Quotes : “ I’ve had no side effects like I had with Sutent

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

Patients recognise that Afinitor is not a cure for RCC but the vast majority are willing to accept the side –effects for the benefit of extra time with their families

4. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

None

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.
There is no other standard second line treatment available on the NHS in the UK

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement in the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc.)

3 months of progression free survival compared to best supportive care
Ease of use by oral tablet at home
Tolerable side effects

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:

- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

Afinitor has reported side –effects but there are no tolerability issues reported by patients who are overwhelmingly prepared to accept these side effects for the benefits gained

Research evidence on patient or carer views of the technology

If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine NHS care reflects that observed under clinical trial conditions.

This section is not applicable as Afinitor is not available in the UK on the NHS

Experience in the USA indicates acceptable toleration of side -effects

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?

Not Applicable

Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.

Not applicable

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

3 months of progression free survival

Huge emotional benefits in maximising the last months of life with friends and families

Freedom from financial hardship in either buying the drug privately or raising charitable funds to do so.

Patient Quotes : “ Absolute despair was exacerbated by the knowledge that effective drugs were available to me but were denied “

“ There is actually something worse than being given a terminal diagnosis . It’s being given a terminal diagnosis in the knowledge that there are drugs available to prolong your life but you are denied them because you are not considered worth the treatment “

What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

Earlier death than necessary

Emotional trauma arising from being denied effective drugs

Financial hardship if drugs are acquired privately

Are there groups of patients that have difficulties using the technology?

None

Other Issues

Please include here any other issues you would like the Appraisal Committee to consider when appraising this technology.

Afinitor meets all the criteria for the end of life drugs rule change of January 2009 :

- Patients with short life expectancy
- Evidence of life extension of at least 3 months
- Cost effectiveness ratio higher than £ 30K p.a.
- No alternative treatments with similar benefits available on the NHS

Andrew Dillon , Chief Executive of NICE is quoted as follows :
" The Institute is conscious of its responsibilities to support the development of novel treatments for smaller patient groups that provide innovative benefits over and above existing NHS care "

Afinitor is a classic example of this class of drug

There is no second line treatment available on the NHS in the UK beyond best supportive care . This compares very badly to the USA and Europe where up to 4 drugs can be used either in combination or in sequence to limit the progress of metastatic RCC . This is a situation which NICE should address

Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma

Report commissioned by: NIHR HTA Programme

On behalf of: The National Institute for Health and Clinical Excellence (NICE)

Produced by: Peninsula Technology Assessment Group (PenTAG)
Peninsula Medical School, University of Exeter.

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Date completed: 30 November 2009

ABOUT THE PENINSULA TECHNOLOGY ASSESSMENT GROUP (PenTAG)

The Peninsula Technology Assessment Group is part of the Institute of Health and Social Care Research at the Peninsula Medical School. PenTAG was established in 2000 and carries out independent Health Technology Assessments for the UK HTA Programme and other local and national decision-makers. The group is multi-disciplinary and draws on individuals' backgrounds in public health, health services research, computing and decision analysis, systematic reviewing, statistics and health economics. The Peninsula Medical School is a school within the Universities of Plymouth and Exeter. The Institute of Health and Social Care Research is made up of discrete but methodologically related research groups, among which Health Technology Assessment is a strong and recurring theme.

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Competing interests of authors

- None.

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The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme. Any errors are the responsibility of the authors.

Contributions of authors

Mary Bond	Contributed to project management, critiqued the effectiveness evaluation provided by the manufacturers, and contributed to the writing of the report
Louise Crathorne	Contributed to project management, critiqued the effectiveness evaluation provided by the manufacturers, report writing and editing
Chris Hyde	Contributed to the critique of the industry submission, and report writing and editing. He is the guarantor for this report
Tiffany Moxham	Undertook literature searches for the report, and commented on the searches provided by industry
Martin Pitt	Critiqued the model provided by industry and contributed to the writing of the report

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Tables

Figures

Abbreviations and Acronyms

AEs	Adverse Events
aRCC	Advanced Renal Cell Carcinoma
ASCO	American Society of Clinical Oncology
BSC	Best Supportive Care
CCTR	Cochrane Controlled Trials Register
CEAC	Cost-effectiveness Acceptability Curve
CI	Confidence Interval
CR	Complete Response
CRD	Centre for Reviews and Dissemination
CRF	Clinical Record Form
CSR	Clinical Study Report
CT	Computerised Tomography
DARE	Database of Abstracts of Review of Effects
ECOG	Eastern Cooperative Oncology Group
ECCO	European CanCer Organisation
EORTC	European Organisation for Research and Treatment of Cancer
ESMO	European Society of Medical Oncology
EQ-5D	EuroQoL-5 Dimension
ERG	Evidence Review Group
EUA	European Urology Association
FAD	Final Appraisal Determination
FKSI–DRS	Functional Assessment of Cancer Therapy-Kidney Symptom Index Disease Related Symptoms
HR	Hazard Ratio
HRQoL	Health Related Quality of Life
HTA	Health Technology Appraisal
ICER	Incremental Cost Effectiveness Ratio
IDMC	Independent Data Monitoring Committee
IFN-α	Interferon-alpha
IL-2	Interleukin-2
IPCW	Inverse Probability of Censoring Weight
ISPOR	International Society of Pharmacoeconomics and Outcomes
ITT	Intention To Treat
IV	Intravenous
IVRS	Interactive Voice Response System
K-M	Kaplan-Meier
KPS	Karnofsky Performance Scale
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloane-Kettering Cancer Center
mRCC	Metastatic Renal Cell Cancer
MTA	Multiple Technology Appraisal
mTOR	Mammalian Target Of Rapamycin
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Clinical Excellence
NIHR	National Institute for Health Research
NHS EED	NHS Economic Evaluation Database

ORR	Overall Response Rate
OS	Overall Survival
PAS	Patient Access Scheme
PD	Progressive Disease
PenTAG	Peninsula Technology Assessment Group
PF	Physical Function
PFS	Progression Free Survival
PP	Per Protocol
PR	Partial Response
PRO	Patient Reported Outcome
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Year
QL	Equity of Life
QoL	Quality of Life
RCC	Renal Cell Cancer
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
RECORD-1	REnal Cell cancer treatment with Oral RAD001 given Daily-1
RPFST	Rank Preserving Structural Failure Time
RPFSTM	Rank Preserving Structural Failure Time Model
SD	Stable Disease Without Adverse Events
SD+AE	Stable Disease With Adverse Events
STA	Single Technology Appraisal
TKI	Tyrosine Kinase Inhibitor
VEGF	Vascular Endothelial Growth Factor
VEGFr	Vascular Endothelial Growth Factor Receptor

1. Summary

Indented, italicised, single-line spaced text, tables or figures have been copied from the submission by Novartis, hereafter referred to as 'the submission'. References which appear within this text within square brackets refer to those cited in the Novartis submission, the evidence review group (ERG) have also added a note of first author and year.

1.1. Scope of the submission

This is the summary of the ERG report on the manufacturer's submission: Single Technology Appraisal (STA) For Everolimus (Afinitor®) in advanced renal cell carcinoma (aRCC). The objective of this STA as defined by the final scope is:

> *To appraise the clinical and cost effectiveness of everolimus, within its licensed indication, for the treatment of advanced and/or metastatic renal cell carcinoma.* [1]

The scope of the manufacturer's submission is consistent with the components of the question and approach outlined in NICE's final scope. The authorised use of everolimus, an oral drug, is for the treatment of adult patients with aRCC whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF-) targeted therapy.

1.2. Summary of submitted clinical effectiveness evidence

A systematic review of the effectiveness of everolimus was submitted. It focused on the RECORD-1 study. This was a randomised, double-blind, placebo-controlled trial of 416 participants. 277 were randomised to 10mg everolimus once a day, in addition to best supportive care (BSC), and 139 to an identical placebo tablet in addition to BSC. The manufacturer submission summarised the identified benefits as:

- 67% reduction in the risk of disease progression or death (HR=0.33, 95% CI 0.25-0.43), equating to a mean progression free survival of 4.90 months for everolimus plus BSC, versus 1.87 months for placebo plus BSC, a difference which was highly statistically significant (p<0.001)
- A non-statistically significant treatment related difference in overall survival (OS) (HR=0.82; 95%CI 0.57-1.17; p=0.137), but a result which was highly likely to have been influenced by a very high level of patients in the placebo arm swapping to everolimus treatment after progression had been detected.

- Partial or stable tumour response in 69% of patients with everolimus against 32% in the placebo arm.
- Stable quality of life (QoL)/patient reported outcomes (PROs) in everolimus compared to placebo.

The ERG appraisal indicates that the evidence identified is relevant and complete. The interpretation is reasonable, although the ERG would place greater emphasis on the much higher frequency of adverse events (AEs), of a severity likely to have an impact on patient QoL, in the everolimus arm of the trial relative to the placebo arm. The trial data available indicate that patient health-related quality of life (HRQoL) was identical in the early stage of the trial, despite there being response to treatment in the everolimus arm.

Although the OS results from the RECORD-1 randomised, controlled trial (RCT) are clear and uncontroversial indicating an improvement which could have resulted from chance alone, the adjustment of the results for switching placebo patients to everolimus following disease progression is an area of genuine academic debate, particularly concerning the most appropriate analytical method.

1.3. Summary of submitted cost effectiveness evidence

The ERG confirmed that there was no existing estimation of cost-effectiveness, and that it was appropriate for the manufacturer submission to focus on a new cost-effectiveness model.

This was a Markov state-transition cost-utility model implemented in Microsoft Excel© which compared treatment with everolimus and BSC with BSC alone, mirroring the question addressed in the RECORD-1 RCT. The four states were stable disease, stable disease with AEs, progressive disease (PD) and death, and the outputs expressed as cost per quality-adjusted life year (QALY). The base-case incremental cost-effectiveness ratio (ICER) was £61,330; this estimate was somewhat reduced when a patient access scheme (PAS) was modelled, but this estimate was still substantially greater than £30,000.

The ERG appraisal indicated that the model was generally well developed and reported. However, a number of important issues were identified:

- Model errors: The manufacturer incorrectly applied the mortality hazard ratio (HR) in their model resulting in a serious bias in favour of everolimus. We attempted to re-calibrate the model to correct for this and the result was an ICER of £76,070

(this is without the PAS and includes discounting in the first year of the model, omitted from the base-case in the manufacturer submission).

- The statistical approach used to adjust for cross-over bias in the trial data. While this is a recognised approach, several questions have been raised about its underlying assumptions and use in preference to other approaches. Use of some sort of adjusted analysis was generally felt reasonable by the ERG and its advisers, but the impact of using it needs to be appreciated. The ICER using the unadjusted OS estimate from RECORD-1 produces was £109,627 (again without PAS and not incorporating correction for the model errors above).

- QoL data are not based on EQ-5D sources. The resulting lack of confidence in the utility parameters in models dealing with aRCC and metastatic renal cell cancer (mRCC) has been commented on in NICE appraisals before.

1.4. Commentary on the robustness of submitted evidence

1.4.1. Strengths

These are as indicated in Section 1.3 of the Executive Summary of this report (see above). Overall, the main strength of the manufacturer submission was a well constructed and presented case on the clinical and cost-effectiveness of everolimus.

1.4.2. Weaknesses

Not withstanding the generally good quality of the manufacturer submission, the model errors identified constitute a weakness.

1.4.3. Areas of uncertainty

Further uncertainty in the stated estimates of cost-effectiveness is introduced by academic debate over the appropriateness and method of any adjustment for switching in RCT which provided evidence on clinical effectiveness and continuing lack of data on the utilities associated with health states experienced during renal cell carcinoma (RCC), particularly its later stages.

1.5. Key issues

The manufacturer's submission offers a clear presentation of its case on the effectiveness and cost-effectiveness of everolimus for people with aRCC whose disease has progressed on or after treatment with VEGF-targeted therapy. The case for clinical effectiveness is generally clear but judgements need to be made on the effect that the model errors, approach to adjustment for switching and uncertainty about utilities have on the proffered estimate of cost-effectiveness.

A further issue, beyond the direct scope of this report, is the impact of end-of life considerations by NICE, which may apply.

2. Background

2.1. Critique of manufacturer's description of underlying health problem

In Section 4.1 of the manufacturer's submission (Source: Novartis Submission, Section 4.1, p19) Novartis provided a summary of incidence and prevalence in England and Wales based on credible sources. Brief evidence was also given of the characteristics of advanced renal cell cancer (aRCC), its aetiology, treatment, prognosis and survival, as well as a brief description of the economic burden of aRCC in the UK.

A description of prognosis and survival is given in Section 4.1.6 (Source: Novartis Submission, Section 4.1.6, p22). aRCC patients with a clear cell component tend to have a relatively poor prognosis compared to non-clear cell histology.[2] The manufacturer notes that performance status in aRCC clinical trials, and in clinical practice, is commonly measured using the Memorial Sloan Kettering Cancer Centre (MSKCC) prognostic risk score. This is a system that combines independent prognostic risk factors and categorises patients into three risk groups according to the number of pre-treatment risk factors (low Karnofsky performance status; haemoglobin level below the lower limit of normal; high corrected serum calcium level (>10mg/dL or 2.5 mmol/L); prior nephrectomy; and high blood lactate dehydrogenase level) present in aRCC patients: Favourable = none; Intermediate = one or two; Poor = three or more. The submission refers to the 2004 version of the MSKCC prognostic risk score which:

> *… categorises patients into three risk groups according to the number of pre-treatment risk factors present in aRCC patient: Favourable = none; Intermediate = one; Poor = two or three. The pre-treatment risk factors are: low Karnofsky performance status; haemoglobin level below the lower limit of normal; and high corrected serum calcium level (>10mg/dL or 2.5 mmol/L. (Source: Novartis Submission, Section 4.1.6, p22)*

The submission highlights that aRCC patients with a clear cell component tend to have a median survival of six to 12 months and 90% of people diagnosed with stage IV renal cell cancer (RCC) die within five years of initial diagnosis (Source: Novartis Submission, Section 4.1.6, p 22). It should be noted that the median survival of six to 12 months cited in the submission is correct for the cytokine era; however, approved first-line treatments used in current clinical practice give longer median survival.

Overall, the evidence presented in this section of the submission is consistent with the background information given in the final scope.[1] This is consistent with the ERG's understanding of the problem.

2.2. Critique of manufacturer's overview of current service provision

Section 4.5 of the submission (Source: Novartis Submission, Section 4.5, page 32) states that:

> *historically there have been limited treatment options for aRCC patients hence the prognosis has been very poor for these patients for many years. Newer targeted therapies have increased the number of treatment options and the potential for clinical benefit. The introduction of new NICE guidance is intended to reduce the potential for variability in clinical practice. (Source: Novartis Submission, Section 4.5, p32)*

The submission acknowledges that the development of targeted therapies; e.g. VEGF, has been the main advance in the treatment of aRCC in recent years.

> *While VEGF is the predominant mediator in angiogenesis with over-expression of VEGF resulting in tumour growth and angiogenesis), there are different strategies for inhibiting its pathway. Anti-VEGF strategies that target the receptor, such as tyrosine kinase inhibitors (TKIs) (sunitinib [Sutent®] and sorafenib [Nexavar®]) have a wider range of inhibitory effects and may disrupt other secondary pathways that are also mediated through receptor kinases (Jain, 2006). Anti-VEGF strategies that specifically target the ligand, such as VEGF antibodies (bevacizumab [Avastin®]) inhibit only the VEGF pathway, and therefore may inhibit angiogenesis without disrupting other 'off target' pathways (Jain, 2006). (Source: Novartis Submission, Section 4.4.3, p29)*

The manufacturer's submission notes that in 2009 NICE approved sunitinib for the first-line treatment of aRCC and/or metastatic renal cell cancer (mRCC).[3] Bevacizumab, sorafenib and temsirolimus have recently undergone a NICE assessment in the form of a multiple technology appraisal (MTA) with the final guidance issued in August 2009. These agents were not recommended as treatment options for people with aRCC. In addition, sunitinib was not considered clinically effective in the second-line setting.[4] This confirms that BSC is an appropriate comparator.

Table 4.5 of the submission (Table 1, below) refers to EMEA approved aRCC therapies, their specific indications, and their NICE guidance recommendations.

Table 1: Summary of approved indications for leading aRCC treatments

Agent	*Description and mechanism of action*	*Approved EU indication*	*NICE Guidance*
Everolimus (Afinitor®)	*Oral drug that selectively inhibits mTOR, thereby reducing angiogenesis and inhibiting tumour growth*	*Treatment of patients with aRCC, whose disease has progressed on or after treatment with VEGF-targeted therapy [5]*	*Everolimus for the second-line treatment of mRCC. Expected date of FAD April 2010 with full guidance June 2010 [6]*
Sunitinib (Sutent®)	*Oral, small-molecule, multi-targeted TKI resulting in anti-cancer and anti-angiogenesis effects*	*Advanced and/or metastatic renal cell carcinoma (mRCC) [7]*	*Recommended as a first-line treatment option for people with aRCC who are suitable for immunotherapy and have an (ECOG) performance status of 0 or 1 [8]* *Not recommended second-line for the treatment of advanced and/or mRCC [9]*
Sorafenib (Nexavar®)	*Oral, multikinase inhibitor that decreases tumour cell proliferation in vitro*	*Advanced RCC who have failed prior IFN-α or IL-2 based therapy or are considered unsuitable for such therapy [10]*	*Not recommended first- or second-line for the treatment of advanced and/or mRCC [11]*
Temsirolimus (Torisel®)	*IV drug that inhibits mTOR kinase activity, resulting in cell death*	*Advanced renal cell carcinoma who have at least three of six prognostic risk factors [12]*	*Not recommended first-line for the treatment of advanced and/or mRCC [13]*
Bevacizumab (Avastin®)	*Monoclonal antibody preventing angiogenesis by targeting VEGF*	*First-line advanced and/or metastatic renal cell cancer, in combination with IFN-α-2a [14]*	*Not recommended first-line for the treatment of advanced and/or mRCC [15]*

(Source: Novartis Submission, Section 4.4.3, Table 4.5, p30))

Reference is also made to other relevant guidelines for clinical practice – evidence-based consensus guidelines of Nathan *et al.* European guidelines from the European Urology Association (EUA), and the European Organisation for Research and Treatment of Cancer (EORTC); and, US guidelines from the National Comprehensive Cancer Network (NCCN) for kidney cancer recommend the use of surgery first, with drug therapy for those in whom surgery is unsuccessful or not appropriate.

In contrast to the VEGF targeted therapies, everolimus is an oral, once-daily inhibitor of mammalian target of rapamycin (mTOR) that acts on central regulation of cellular processes. Guidelines indicate the potential use of everolimus after VEGF-targeted therapy (including bevacizumab therapy).[16]

3. Critique of manufacturer's definition of decision problem

3.1. Population

The population considered by the submission is:

> *Adults aged ≥18 years with aRCC who had progressed on or within six months of stopping treatment with sunitinib, sorafenib, or both drugs. Previous therapy with a cytokine (IFN-α or IL-2) or bevacizumab was permitted. Prior vaccine therapy in the adjuvant setting was also permitted. Women of childbearing potential must have had a negative serum or urine pregnancy test within seven days prior to the administration of the first study treatment. (Source: Novartis Submission, Section 6.3.1.5, p51)*

This is an adequate description of the population under consideration, and concurs with that defined in the NICE Scope.[1] Overall, the ERG agree that the population considered is reflective of the actual clinical population. With regard to differences in baseline characteristics between the trial and clinical populations the ERG would like to note the following:

- age is not a prognostic factor for advanced renal cell cancer (aRCC) hence the difference in average age between the trial and clinical population was not indicative of anything significant.
- the eligibility criteria are considered standard for a Phase III oncology trial hence fewer patients with co-morbid conditions in the trial population was also not considered indicative of anything significant.

3.2. Intervention

The intervention is everolimus (Afinitor®, Novartis Pharmaceuticles). Everolimus gained marketing authorisation, for the treatment of adult patients whose disease has progressed on or after treatment with vascular endothelial growth factor (VEGF) targeted therapy on 3 August 2009.

> *The recommended dose of everolimus is 10mg/day. Treatment is to be considered for as long as a clinical benefit is observed or until discontinuation for toxicity reasons. Dose interruption or reduction to 5mg/day may be required to manage suspected adverse reactions… The duration of treatment for everolimus will vary from one individual to another. (Source: Novartis Submission, Section 3, p12)*

3.3. Comparators

The single comparator was placebo plus best supportive care (BSC), where BSC was taken to:

> *…represent current clinical practice in the UK for patients who have failed on previous active therapy. In the RECORD-1 trial BSC consisted of the use of both drug and non-drug therapy including the following: ongoing bisphosphanate therapy for treatment of bone metastases, pain medication, localised radiotherapy, nutritional support, oxygen therapy and blood transfusions, use of leukocyte growth factors, and megestrol acetate as an appetite stimulant (except for Japanese patients). The use of other investigational agents was not permitted, nor was the use of other anti-cancer agents whilst the patient was on study drug.([40] Novartis, Full Clinical Study Report-Addendum) (Source: Novartis Submission, Section 6.3.1.4, p51)*

The choice of comparator is in line with the scope which lists the comparator as BSC. In the ERG opinion Novartis' description of BSC fits well with current clinical practice.

The scope also states that 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, sorafenib and/or sunitinib may be included as comparators. The submission acknowledges that these agents have recently undergone a NICE assessment in the form of a multiple technology appraisal (MTA). Sorafenib, temsirolimus, and bevacizumab have not been recommended for use in any of their licensed aRCC settings.[4] Sunitinib was approved for first-line treatment of aRCC and/or mRCC but not deemed clinically effective second-line.[3] This supports the choice of BSC as comparator for this study.

The ERG also commented that for the UK patient population BSC was an appropriate comparator as there is no access to another funded second-line treatment.

3.4. Outcomes

> *The primary outcome considered for assessing **clinical effectiveness** was progression free survival (PFS). The secondary outcome measures included in the trial were: objective tumour response rate, duration of response, overall survival, HRQoL and related patient reports outcomes (PROs), safety outcomes (frequency of adverse events, laboratory summaries and central radiology assessments of pneumonitis). (Source: Novartis Submission, Section 6.3.3.1, p57 [emphasis added])*

The outcome measures are in line with the scope and are discussed in detail in Section 6.3.3 (pp57–62) of the manufacturer's submission.

The outcomes for the **economic analysis** were, incremental cost per quality-adjusted-life-year (QALY), and incremental cost per life-year gained.

3.5. Time Frame

> *The time horizon was patient life-time. Due to the short life expectancy of aRCC patients who have failed on first-line drug therapy, this was a relatively short duration of 144 weeks in the economic model. By this time 100% of the BSC cohort patients and 98.5% of the everolimus cohort patients in the model were predicted to have died. (Source: Novartis Submission, Section 7.2.4.1, p104)*

The ERG agrees that this is an appropriate time frame.

3.6. Other relevant factors

The submission states that:

> *Dosing consisted of a continuous, once-daily, oral dose of 10mg/day everolimus administered at the same time each day with or without food… The dose could be reduced to 5mg/day if patients experienced clinically significant haematological or other AEs that according to a nomogram were felt by the site investigator to be related to the drug. ([40] Novartis, Full Clinical Study Report-Addendum) (Source: Novartis Submission, Section 3, p50)*

This is in accordance with the marketing authorisation (Submission, p12).

4. Clinical effectiveness

4.1. Critique of manufacturer's approach

4.1.1. ERG approach

The ERG re-ran the searches, critically appraised the systematic review under-pinning the manufacturer submission (Source: Novartis Submission, Section 10.2, pages 191–200), and critically appraised the study providing the main source of evidence on clinical effectiveness – the RECORD-1 study.[17] The power calculations for the main included RCT were also re-checked. The work was undertaken between 1 October and 30 November 2009.

4.1.2. Description of manufacturers search strategy and comment on whether the search strategy was appropriate.

The manufacturer provided information both within the manufacturer's submission and from a systematic review commissioned by the manufacturer.[18] Manufacturer searches were performed in the following databases on the 16 June, 2009:

- MEDLINE and MEDLINE IN PROCESS [MEZZ] Dialog DataStar 1950–June 2009
- EMBASE [EMZZ] Dialog DataStar 1980–June 2009
- BIOSIS [BIZZ] Dialog DataStar 1985–June 2009

Separate search strategies were provided for EMBASE, Medline with Medline in-process, and BIOSIS by the manufacturer. All search strategies are based on a conjunction of terms identifying renal cell carcinoma (RCC) and terms identifying everolimus as an intervention. For each term, a combination of thesaurus headings (where possible) and free-text search-words was used. All searches were limited to humans and excluded editorials and letters. No additional limitations or study design filters were utilised. No comparators or outcomes were specified to limit the searches in any of these databases.

Searches were also carried out for conference abstracts on the following websites:

- ASCO Website 2005–2009 Search date: 16 June, 2009

- ECCO Website 2006, 2008 Search date: 16 June, 2009
- ESMO Website 2005, 2007 Search date: 16 June, 2009

The terms used for the conference site reports were everolimus, RAD001, Afinitor, AND (metastatic) renal cell carcinoma, kidney cancer.

Additionally the manufacturer states the following resources were reviewed for additional published or unpublished data on the clinical effectiveness and safety of everolimus although no individual search strategies were provided:

- HTA database (CRD) website
- Database of abstracts of review of effects (DARE) (CRD website)
- NHS Economic Evaluation Database (NHS EED) (CRD website)
- Cochrane Database of Systematic Reviews (CCTR)
- Clinical Trials.gov
- Current Controlled Trials (www.controlled-trials.com)
- NICE and NIHR Health Technology Assessment website
- Hand searching of selected primary study references

According to the accompanying review the hand searches were of abstracts from the International Society of Pharmacoeconomics and Outcomes (ISPOR) Journal and Value in Health between 2005 and January 2009.

In addition the manufacturer provided unpublished clinical study reports and supplementary internal reports for the RECORD-1 trial.

All the combination of terms within the search strategies to define the renal cell carcinoma population and/or the intervention and resources used were appropriate, replicable, and the resulting hits appear correct given the search date and database/interface used. The ERG re-ran all the provided search strategies and checked for on-going trials in the Meta Register of Controlled Trials and in the ClinicalTrials.gov online database. Where citations of potential interest were found they were checked against the excluded studies list in the accompanying systematic review and the reasons for exclusion confirmed. As a result of this no additional trials were found.

4.1.3. Statement of the inclusion/exclusion criteria used in the study selection and comment on whether they were appropriate.

The submission included the following kinds of studies of clinical effectiveness:

> *Study design for primary data extraction was randomised controlled trials (RCTs). Primary outcomes of interest were related to efficacy (overall survival, progression free survival, and tumour response rate), HRQoL/PRO, and safety (Grade III or IV adverse events (AEs) or high volume Grade I/II AEs). Outcomes of interest were to be extracted from systematic reviews of Phase II or III RCTs and single RCTs (both parallel, cross-over designs, and studies comparing different doses or schedules of the drugs of interest) that may either be blinded or un-blinded and published (with additional unpublished material from clinical study reports if available). The systematic review protocol also allowed for data from secondary level designs to be considered, which included single-arm trials and observational studies, and expanded access programmes, if in the opinion of the reviewers this source provided valuable supplementary evidence to the primary RCT evidence. Only English language publications and abstracts were considered. Specific exclusion criteria covered: pre-clinical and biological studies; animal studies; Phase I clinical trials; editorials, opinions, commentaries, reviews (other than systematic reviews); non-English language studies; reports/abstracts where there were insufficient methodological details to judge study quality. (Source: Novartis Submission, Section6.2.2, p40)*

These inclusion and exclusion criteria are appropriate. The submission explains the processes used in study selection and data extraction which is in line with the standard review process – see also Appendix 1, page 89 of this report.

4.1.4. Table of identified studies. What studies were included in the submission and what were excluded.

The search results presented by the manufacturer identified one randomised, controlled trial (RCT) in the relevant population, the Phase III RECORD-1 study. The search also identified one full peer-reviewed publication relating to this second interim analysis, published by Motzer et al, in the *Lancet* in 2008.[19]

Publications relating to the Phase III RECORD-1 study were included. This includes: an abstract and slide presentation of the key final analysis results at the 2008 European Society for Medical Oncology (ESMO) meeting (Escudier *et al*, 2008),[20] a further abstract reporting the same results at an American Society of Clinical Oncology (ASCO) Genitourinary Cancers Symposium (Kay *et al*, 2009),[21] and an ASCO abstract reporting patient reported outcomes (PROs) results from the RECORD-1 trial final analysis (Beaumont *et al*, 2009).[22]

Publications relating to the Motzer *et al* publication were included.[19] This includes: two 2008 ASCO meeting presentations, one a slide presentation (Motzer *et al*, 2008)[23] and the other a poster presentation relating to the same abstract (Motzer *et al*, 2008).[19]

In addition to the Phase III RCT, the systematic review identified two supportive Phase II non-RCT studies considered by the reviewers to be relevant to the decision problem. This included: a Phase II single arm study of everolimus in patients with progressive measurable aRCC whose disease had progressed following no more than one prior therapy (Amato *et al*);[24] and, a Phase II single arm study of everolimus in patients with aRCC whose disease has progressed after no more than two previous therapies, supported by a 2008 ASCO abstract and poster (Jac *et al*, 2008).[25]

We did not identify any relevant studies that were not included in the submission.

There do not appear to be any directly relevant ongoing studies, but there do appear to be studies in progress investigating the role of everolimus in the earlier management of metastatic renal cell cancer (mRCC) in comparison with other vascular endothelial growth factor (VEGF)-targeted therapies.

4.1.5. Description and critique of manufacturers approach to validity assessment

Details of Novartis' critical appraisal of study RECORD-1 randomised, controlled trial (RCT), alongside our critique, can be seen in Table 2 below. Please note that italicised text has been cited directly from the submission (cross references are given).

Table 2: Critical appraisal of relevant RCTs

Assessment question	Novartis response	ERG comment
Study design [Jadad score 1 = 0/1]	*RCT*	The study is well-designed. *The trial was an international, multi-centre, double-blind, randomised, placebo-controlled, phase III trial designed to investigate the efficacy and safety of continuous daily treatment with everolimus (10mg/day plus BSC versus placebo plus BSC in patients with aRCC with a clear cell component which has progressed following or on VEGF-targeted therapy. The RECORD-1 study was designed to be a cross-over trial; hence patients receiving placebo plus BSC with documented radiological disease progression were allowed to cross-over to receive open-label everolimus treatment if the treating clinician felt that the patient could benefit from this treatment. (Source: Novartis Submission, Section 6.3.1.2, p47)*
Is a power calculation provided?	*Yes*	Yes. *Power calculations to identify the number of patients required to achieve a clinically meaningful 33% reduction in risk of disease progression for everolimus plus BSC versus placebo plus BSC were performed and reported. (Source: Novartis Submission, Section 6.3.5, p69)*
Is the sample size adequate?	*Yes*	Yes, the sample size is adequate re-calculated in StatsDirect. Considering a recruitment time of 16 months and an additional follow-up of five months a total of 362 patients had to be included. This number included the assumption that about 10% of patients are lost to follow-up during the study. The total patient population at the time of data cut-off was 410 patients. [CSR RECORD-1]
Was ethical approval obtained?	*Yes*	Yes, ethical approval was obtained. The original study protocol and all amendments issued prior or during the study were reviewed by the local Independent Ethics Committee or Institutional Review Board for each centre. The study

Assessment question	Novartis response	ERG comment
		was conducted according to the ethical principles of the Declaration of Helsinki. Informed consent was obtained from each patient in writing before any screening procedures were initiated.[17]
Were the study eligibility criteria specified?	*Yes*	Yes, the study eligibility criteria are specified. *Eligible patients were adults aged ≥18 years with aRCC who had progressed on or within six months of stopping treatment with sunitinib, sorafenib, or both drugs. Previous therapy with a cytokine (IFN-α or IL-2) or bevacizumab was permitted. Prior vaccine therapy in the adjuvant setting was also permitted. Women of childbearing potential must have had a negative serum or urine pregnancy test within seven days prior to the administration of the first study treatment. (Source: Novartis Submission, Section 6.3.1.5, p51)*
Were the eligibility criteria appropriate?	*Yes*	The eligibility criteria specified in the RECORD-1 study match those outlined in the final scope. The eligible population in the study is younger than in actual clinical practice (average age ≥65 years vs ≥71 years). In addition, the exclusion criteria also rule out a number of co-morbid conditions associated with this age. The ERG agrees that the eligibility criteria are appropriate and inline with other oncology trials.
Were patients recruited prospectively?	*Yes*	Patients were recruited prospectively.
Was assignment to the treatment groups really random? [Jadad score 2 = 0/1, -1 if inappropriate]	*Partial Yes**	*Patients were randomised on enrolment into the study. Patients were assigned 2:1 to the everolimus plus BSC and placebo plus BSC arms, respectively. This was achieved by the investigator calling an automated, interactive voice response system to assign a unique randomisation number to each patient. A block randomisation was applied to ensure 2:1 randomisation (4 blocks for everolimus plus BSC, 2 for placebo plus BSC).(Source: Novartis Submission, Section 6.3.1.3, p47)* Concealment of randomisation was adequate; patients were randomised using a computer-based system. An Interactive Voice Response System (IVRS) assigned a unique randomisation number to each patient which was used to link the patient to one of the two available treatments.[17]
Was the treatment allocation concealed?	*Yes*	To ensure that treatment assignment was unbiased: *The study was double-blinded up to the point of documented radiological disease progression by central radiological review. The randomisation data was kept confidential to all bar the independent data monitoring committee (IDMC) until time of unblinding with the randomisation list kept under lock within Novartis. (Source: Novartis Submission,*

Assessment question	Novartis response	ERG comment
		Section 6.3.1.3; pp47–48) Concealment of treatment allocation was adequate; treatment was assigned using a computer-based system. The treatment randomisation list was generated by Covance IVRS using a validated system that automated the random assignment of patient numbers to randomisation numbers.[17] After final database lock, when the study data were cleaned and verified, the blinded drug codes were revealed and made available to the study team for the analysis of the data.[17]
Were adequate baseline details presented?	*Yes*	The baseline characteristics are reported (Source: Novartis Submission, Section 6.3.2 and Table 6.3, pp53–54) and were similar to the renal cell cancer (RCC) population in England and Wales.
Were the participant's representative of the population in question?	*Yes*	The characteristics of patients recruited to the trial were similar to the RCC population in England and Wales. However, study participants were younger (average age ≥61 years) and fitter Eastern Cooperative Oncology Group (ECOG) 0–1. In addition, the exclusion criteria rule out other severe/uncontrolled medical conditions (e.g. symptomatic congestive heart failure, unstable angina pectoris, recent MI and cardiac arrhythmia). The ERG advised that the participants were representative of the RCC population in England and Wales. It was noted that the difference in mean age between the trial population and clinical population was not clinically significant; and, the mean age (range) was comparable with the clinical population. The exclusion of patient with co-morbid conditions is standard procedure for oncology trials and also not significant.
Were the groups similar at baseline?	*Yes*	The two patient groups had similar baseline characteristics (Source: Novartis Submission, Section 6.3.2, Table 6.3, p53). *There were more patients aged ≥65 in the placebo group, although the mean age and range was similar. All patients bar one in placebo had the kidney as the primary site of cancer, all patients across both arms had received prior drug therapy, most had undergone prior surgery (primarily nephrectomy), and all had received prior medication for their cancer. Only a few patients did not demonstrate a clear cell component. The majority of patients in both arms were Caucasian. The prognosis of most patients in both arms was classified using MSKCC criteria as intermediate, although patients entering the trial still had relatively good performance scores (entry criteria). (Source: Novartis Submission, Section 6.3.2, p53)* The ERG advised that there was nothing of clinical significance between the two groups at baseline. The difference in the number of patients between the two treatment arms (40.4% [everolimus + BSC]

Assessment question	Novartis response	ERG comment
		vs 70.5% [placebo + BSC]) was noted but on further investigation this was found to be a transcription error. The clinical study report notes the figures as (40.4% [everolimus + BSC] vs 29.5% [placebo + BSC]).[17]
Were baseline differences adequately adjusted for in the analysis?	*NA***	There were no adjustments in the analysis as baseline characteristics reported were very similar.
Was the study described as double blind? [Jadad score 3=0/1]	*Partial Yes****	Yes. The study was double-blinded up to the point of documented radiological disease progression by central radiological review.
Were the outcome assessors blind?	*Partial Yes****	Assessment of outcomes was performed by an independent central review which was also blinded.
Was the care provider blind?	*Partial Yes****	The allocated treatment arm was not revealed to the centre investigator or the patient until the point of documented disease progression by central radiological review.
Were participants blinded?	*Partial Yes****	The allocated treatment arm was not revealed to the patient until the point of documented disease progression by central radiological review.
Was the method of blinding described and appropriate? [Jadad score 4=0/1, -1 if inappropriate [7]]	*Yes*	Yes. *The study was double-blinded up to the point of documented radiological disease progression by central radiological review. The allocated treatment arm was not revealed to the centre investigator or the patient until this point. In addition, the independent central review investigators who performed the selection of target lesions for tumour assessments and outcome assessments were also blinded. The randomisation data were kept confidential to all bar the independent data monitoring committee (IDMC) until time of un-blinding with the randomisation list kept under lock within Novartis. Disclosure was only allowed once patients experienced disease progression, so that those receiving placebo could potentially be switched to everolimus or during a medical emergency when disclosure was necessary to provide optimum treatment. (Source: Novartis Submission, Section 6.3.1.3, pp47–48)* The method of blinding described above is appropriate. Patients, physicians, and outcome assessors were all blinded as to assigned treatment until the point of disease progression; control treatment was described as indistinguishable (identical in packaging, appearance [tablet size, colour,

Assessment question	Novartis response	ERG comment
		unit dose]) and scheduled of administration;[17] no mention is made of whether the blinding of patients and assessors was tested.
Are the outcome measures relevant to the research question?	*Yes*	The range of primary and secondary outcome outcomes were in line with the final scope and relevant to the research question, with progression free survival (PFS) as the primary outcome, supported by assessment of overall survival, (tumour) response rate and HRQoL and related patient reported outcomes (PROs). The RECORD-1 study also considers duration of response as a secondary outcome measure. (see also Novartis Submission, p57)
Is compliance with treatment adequate?	*Yes*	*Treatment compliance was assessed by the investigator or his/her designee at each office visit as follows:* ▪ *Patients were requested to bring their unused medication including empty packaging to the clinic at each visit* ▪ *All doses taken by the patient and all dose changes during the study were recorded on the Dosage Administration CRF* ▪ *The investigator maintained drug accountability records for each patient including tablets administered, tablets used , dose changes, dates dispensed and intervals between visits* ▪ *Drug accountability was routinely monitored by the Novartis monitor* *At the end of the study or when feasible, the Novartis monitor performed a final drug accountability review. In all participating sites bar the US, all used or unused study medication was destroyed according to the sites local regulatory procedures. (Source: Novartis Submission, Section 6.3.3.6, pp59–60)* Treatment compliance is described (above) but no other measurements are made.
Are withdrawals/dropouts adequately described? [Jadad score 5=0/1]	*Yes*	The reasons for patient withdrawal and discontinuation at the final and second interim analysis timepoints are stated – including disease progression, adverse events, withdrew consent, lost to follow-up, and death (see also Novartis Submission, Figure 3, p56).
Are all patients accounted for?	*Yes*	All patients are accounted for *Of 554 patients screened, 416 patients were randomly allocated to treatment: 277 patients assigned to everolimus 10mg/day and 139 patients assigned to placebo plus BSC. Only five randomised patients did not receive everolimus plus BSC or placebo plus BSC treatment for various reasons primarily including use of prohibited medications, and one placebo patient had no baseline safety*

Assessment question	Novartis response	ERG comment
		assessment so was excluded from further safety analysis. *By the final analysis cut-off date, 75 (27%) everolimus plus BSC patients and 6 (4%) placebo plus BSC patients were still continuing treatment. The reasons for patient discontinuation at the final and second interim analysis timepoints are stated – including disease progression, adverse events, withdrew consent, lost to follow-up, and death (Source: Novartis Submission, Figure 3, p56).* *At the time of the end of double-blind analyses, 106 of 121 patients in the placebo plus BSC group had crossed over. At the time of the second interim analysis, 79 of 98 (81%) placebo-treated patients who had locally assessed radiological progression were unblinded and crossed over to receive open-label everolimus. Sixty of the 79 placebo-treated patients (80%) had progressed within eight weeks of enrolment. (Source: Novartis Submission, Section 6.3.2, p54-55)*
Is the number randomised reported?	*Yes*	Yes. The 416 patients randomised to everolimus plus BSC or placebo plus BSC represented the final full analysis dataset.
Are protocol violations specified?	*No*	None specified.
Are data analyses appropriate?	*Yes*	*All efficacy analyses were performed using ITT methods, with appropriate and standard statistical analysis. Point estimates and measures of variability (HRs estimated using stratified Cox proportional hazards model with 95% confidence intervals) were presented for the primary outcome measure of PFS for both the whole trial population and sub-groups analysed. Hazard ratios were also generated for survival outcomes. In addition, p values using stratified log rank tests for the difference in effect of everolimus plus BSC and placebo plus BSC were measured and presented for these variables. Standard statistical tests were also performed for differences in Grade 3 or 4 AEs between everolimus plus BSC and BSC and placebo plus BSC. (Source: Novartis Submission, Section 6.3.5, p70)* ITT and 'on-drug' are both normal approaches when analysing efficacy and safety. An Inverse Probability of Censoring Weight (IPCW) model was used to address the issue of cross-over from placebo plus BSC after disease progression. This is discussed in further detail in Section 5.2.3.3 of this report.
Is analysis conducted on an ITT basis?	*Yes*	An ITT population was used for all efficacy analyses in the RECORD-1 study. However, an IPCW model was used to address the issue of cross-over from placebo plus BSC after disease progression (post-hoc analysis). This is discussed in further detail in Section 5.2.3.3 of this report.

Assessment question	Novartis response	ERG comment
Are missing data appropriately accounted for?	*Yes*	No description found as to how missing data were accounted for. However, Figure 6.3 of the Novartis submission (Source: Novartis Submission, Figure 3, p56) shows that the loss to follow-up was extremely small (n=2).
Were any sub-group analyses justified?	*Yes*	Sub-group analyses specified in original protocol (i.e. before starting the trial): *Predefined sub-group analysis was performed on differences in PFS based on Memorial Sloane-Kettering Cancer Centre (MSKCC) prognostic score category. (Source: Novartis Submission, Section 6.3.4.4, p64)* Additional post-hoc, exploratory sub-group analyses were performed as follows: *median PFS by gender, prior VEGFr-TKI therapy (sorafenib, sunitinib or both), age (<65 years, ≥65 years), geographical region (US and Canada, Europe, Australia and Japan). (Source: Novartis Submission, Section 6.3.4.4, p64)*
Are the conclusions supported by the results?	*Yes*	The conclusion that: *everolimus represents a clinically-effective treatment for a population of aRCC patients who do not have any NICE recommended or licensed treatment options* is justified by the results (in brief above).
Jadad score	4.00	The RECORD-1 study was funded by Novartis Oncology, and was registered (NCT00410124). The information provided is consistent with the protocol recorded in the NCT archive.[26] The trial design is typical of that used to investigate the efficacy and safety of new cancer drugs. There are missing data which aren't accounted for; however, Figure 6.3 of the Novartis submission *(Source: Novartis Submission, Figure 3, p56)* shows that the loss to follow-up was extremely small (n=2) so this was not considered problematic. The submission acknowledges that it is difficult not to crossover patients when they demonstrate progression and subsequent extrapolation of trial data to estimate survival benefit for the economic analysis is not straightforward, and discusses the IPCW method used to correct for this. This is discussed in further detail in Section 5.2.3.3 (page 64). The trial was in line with the ERG's understanding of the other phase III oncology trials, and consistent with characteristics of aRCC patient population: demographic, baseline characteristics, and choice of comparator.
Supplementary questions to those used in the PenTAG HTA report are in red/bold *True randomisation for primary endpoint of PFS, but cross-over design enabled patients progressing on placebo to receive everolimus **No strong need to adjust due to very similar baseline characteristics ***Partial Yes - blinding was the case for the primary endpoint of PFS, but was lifted on disease progression when placebo patients could cross over to		

Assessment question	Novartis response	ERG comment
everolimus (for ethical reasons)		

4.1.6. Description and critique of manufacturers outcome selection

The primary outcome measure in the trial was progression free survival (PFS). The secondary outcome measures included in the trial were: objective tumour response rate; duration of response; overall survival; health related quality of life (HRQoL) and related patient reported outcomes (PROs) and safety outcomes (frequency of adverse events, laboratory summaries and central radiology assessments of pneumonitis) (Source: Novartis Submission, Section 6.3.3.1, p57).

The manufacturer uses outcome measures in accordance with those used in the RECORD-1 trial[17] which concurs with the outcome measures specified in the final scope.[1]

4.1.7. Description and critique of the statistical approach used

4.1.7.1. RECORD-1: Planned statistical analysis

The 416 patients randomised to everolimus plus BSC or placebo plus BSC represented the final full analysis dataset. These patients were eligible for efficacy assessment by ITT analysis according to the treatment and strata they were assigned to at randomisation. A per protocol population was not defined for analysis. In addition, a safety population consisted of all patients who received at least one study drug dose and had at least one pose-baseline safety assessment (274 and 137 patients in the everolimus plus BSC and placebo plus BSC arms, respectively) ([40] Novartis, Full Clinical Study Report – Addendum]).

Pre-specified statistical analysis for the primary endpoint consisted of the following ([40] Novartis, Full Clinical Study Report – Addendum]):

Median PFS with 95% confidence intervals was measure using Kaplan-Meier time to event of interest methods, with the statistical significance of the difference between treatment arms assessed using the stratified log-rank test, adjusting for strata defined by MSKCC prognostic score.

Hazard ratios of the treatment effect were estimated using a stratified Cox proportional hazards model for the difference between the treatment arms in PFS outcomes, with two-sided 95% confidence intervals.

Analysis was based on tumour assessments performed by the independent central radiology review. However, PFS comparisons based on site investigator review were also performed ([40] Novartis, Full Clinical Study Report – Addendum]).

In terms of secondary endpoints, overall survival (OS) was analysed using the same statistical methods. Overall response rate (ORR) was defined as the proportion of patients who attained a CR (complete response) or PR (partial response) during the trial. ORR was compared between treatment arms using exact Mantel-Haenszel test, stratified by MSKCC criteria. Duration of response (defined as CR or PR) was analysed descriptively as no responders were expected in the placebo plus BSC arm ([40] Novartis, Full Clinical Study Report – Addendum]).

For PRO outcomes, mean FKSI-DRS and EORTC QLQ-C30 global health/QoL scores were evaluated over time from baseline to patient disease progression). An assessment of median time to deterioration in PRO was performed. Time to clinically meaningful deterioration was defined as a decrease from baseline of at least 3 points for FKSI-DRS, at least 10% for EORTC physical function (PF) and global equity of life (QL) scales, and at least 10 points for KPS. Comparisons were made using Cox proportional hazards ratios and stratified log rank tests ([40] Novartis, Full Clinical Study Report – Addendum]).

Patients who were still alive and had not experienced disease progression as of the analysis cut-off dates were censored at the last date of adequate tumour evaluation prior to the cut-off. Other reasons for PFS analysis censoring were patient lost to follow-up, consent withdrawn, adequate assessment no longer available, receiving new anti-cancer treatment or event documented after missing >2 tumour assessments ([40] Novartis, Full Clinical Study Report – Addendum]).

Differences in the incidence of grade 3 and 4 AEs between treatment groups were assessed using the Fisher's exact test ([40] Novartis, Full Clinical Study Report – Addendum]). (Source: Novartis Submission, Section 6.3.4.3, pp62–64)

4.1.7.2. RECORD-1: Sub-group analysis/secondary analysis

Predefined sub-group analysis was performed on differences in PFS based on MSKCC prognostic score category.

Additional exploratory sub-group analyses were performed for median PFS by gender, prior VEGF-r TKI therapy (sorafenib, sunitinib or both), age (<65 years, ≥65 years), geographic region (US and Canada, Europe, Australia and Japan).

Statistical analysis for the sub-groups consisted of hazard ratios using an unstratified Cos proportional hazards model and p values generated by the unstratified log-rank test ([40] Novartis, Full Clinical Study Report – Addendum]) (Source: Novartis Submission, Section, 6.3.4.4, p64)

4.1.7.3. RECORD-1: Interim and final analysis

In recent years more rigorous requirements for data monitoring in cancer trials have been implemented, specifying the need for formal interim analyses ([104] National Cancer Institute, 2001). Hence, for the RECORD-1 trial, first and second interim analyses were planned in the study protocol after approximately 30% (about 87 events) and 60% (about 174 events); respectively of the targeted 290 PFS events had been observed. The aim of the interim analyses were to enable the study to be stopped due to safety issues (at first interim analysis) or if the efficacy objectives were met, or due to lack of efficacy ('futility') (at the second interim analysis) ([44] Motzer, 2008).

A cut-off date was set for October 15th 2007 for the second interim analysis, by which time 191 PFS events had been observed (66% of the target 290 events) ([44] Motzer, 2008). After analysis of this data the independent data monitoring committee recommended early termination of the study on PFS efficacy grounds due to the pre-specified efficacy stopping boundary of p≤0.057 being reached (according to the Lan and DeMets method (1983) ([105] Lan, 1983). With O'Brien Fleming type stopping rules (1979) ([106] O'Brien, 1979). At the second interim analysis cut-off, 272 patients

had been recruited to the everolimus plus BSC arm and 138 to the placebo plus BSC arm. This data was the basis of the Motzer et al., 2008 publication in the Lancet ([44] Motzer, 2008).

Notification to terminate the trial was received on 28th February 2008, with this marking the end of the double-blind phase. Hence, as recruitment and data collection had continued beyond the second interim analysis cut-off date of 15th October 2007, a further final analysis of the primary and secondary endpoints within the double-blind RCT conducted including the additional patients and follow-up to the 28th February 2008. This is the primary data reported in the Clinical Study Report (CSR)-addendum and in this submission ([40] Novartis, Full Clinical Study Report-Addendum). By this time, 266 progression free events had been observed in 416 patients recruited – an additional five in the everolimus plus BSC arm and an additional 1 placebo plus BSC patient (see Figure 6.3). The statistical analysis plan was constructed in order to test the statistical significance of differences in outcomes between the treatment arms when the defined efficacy or futility boundary was crossed. As this was crossed early at the second interim analysis stage, and the null hypothesis rejected, this means that test of statistical significance (p values) performed for the final analysis are essentially descriptive in nature. (Source: Novartis Submission, Section 6.3.4.5, pp64–65, and Figure 6.3, p56)

General approach

The approach to the statistical analysis of RECORD-1 data was generally sound. The only contentious issue relates to attempts after the main trial analysis to adjust for switching placebo patients to the active treatment (everolimus) after the primary end-point (progression free survival) had been reached. This critical issue is discussed in detail in Section 5.2.3.3 of this report (see p 64)

4.1.8. Summary statement

The submission contains all the relevant studies and the relevant data within those studies. The submitted evidence also adequately reflects the decision problem defined in the submission.

The main source of evidence on effectiveness is the RECORD-1 study. In terms of small patient numbers and openness to bias, the two other non-randomised studies referred to were of minimal importance to the arguments on clinical effectiveness and, as such, are not considered in detail in this ERG report on the manufacturer's submission.

Initial concerns about a marked imbalance in the RECORD-1 baseline characteristic ≥65 years as reported in the manufacturer's submission were traced to an error in transcription of information from the clinical trial report – reported n=98 (70.5%) placebo + BSC group when it should be n=41 (29.5%) (see also Novartis Submission, Table 6.3, p53)

The validity of the main body of clinical effectiveness was good. The only issue of possible concern for the RECORD-1 study is its early termination. There is growing evidence that early termination of trials is associated with a systematic overestimation of effect size.[27] However, closer examination of the development of the results suggests that it may be inappropriate to consider the trial as terminated early – the final analysis was based on 266 PFS events; the target suggested by the power calculation was 290.

There are issues of concern about subsequent re-analysis of the OS data from the RECORD-1 trial which are critiqued in depth Section 5.2.3.3 of this report (see, p 64).

4.2. Summary of submitted evidence

4.2.1. Summary of results

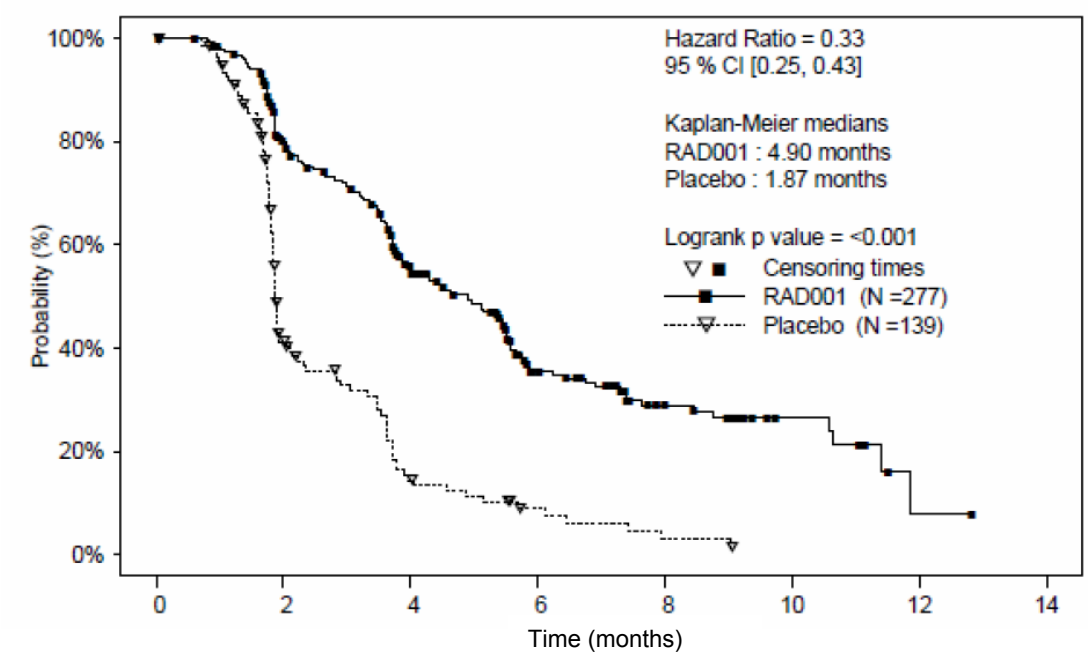
4.2.1.1. Primary endpoint results

4.2.1.1.1. Progression-free survival

Progression free survival in the overall population

Based on the independent central radiology review, there was a 67% reduction in risk of progression associated with everolimus plus BSC compared to placebo plus BSC (HR=0.33, 95% CI: 0.25-0.43) at final analysis cut-off. The everolimus plus BSC arm showed a statistically significant difference in median PFS of 3.03 months compared to placebo plus BSC (p<0.001). Median PFS for everolimus plus BSC was 4.90 months (95% CI: 3.98-5.52) and for placebo plus BSC was 1.87 months (95% CI: 1.84-1.94) ([40] Novartis, Full Clinical Study Report - Addendum; [74] Escudier, 2008). The Kaplan-Meier plot for median PFS is presented in Figure 6.4 [Figure 1 below. (Source: Novartis Submission, Section 6.4.3, pp71–73)

Figure 1: Progression free survival everolimus plus BSC versus placebo plus BSC: Final analysis



[40] Novartis, Full Clinical Study Report-Addendum, [74] Escudier et al., 2008) (Source: Novartis Submission, Figure 6.4, p72*)*

The K-M plot was based on 266 PFS events defined by the time each patient experienced progression or death (prior to progression). In the everolimus plus BSC arm there were 155 PFS events (56% of patients) consisting of 134 disease progression events and 21 deaths. In the placebo plus BSC arm there were 111 PFS events (80% of patients) consisting of 103 progression and 8 death events. Therefore, 122 patients (44%) and 28 patients (20%) in the everolimus plus BSC and placebo plus BSC groups, respectively, had not progressed or [40] Novartis, Full Clinical Study Report-Addendum).

The disease progression events determined by local site investigators were similar (N=152, 55% of patients, and N=121, 87% of patients, for everolimus plus BSC and placebo plus BSC, respectively). The results based on local site investigation were consistent with those from the central radiological review with a 68% reduction in risk of disease progression or death (HR=0.32 with 95% CI: 0.25-0.41) and the difference in median PFS statistically significant in favour of everolimus (p<0.001). Median PFS was 5.49 months in the everolimus plus BSC group and 1.87 in the placebo plus BSC group ([40] Novartis, Full Clinical Study Report-Addendum).

A pre-defined analysis of PFS based on central radiology review using a multivariate Cox model stratified by MSKCC risk criteria and adjusted for age, gender and prior therapy, and all other multivariate analyses using stratified or unstratified Cox models, produced very similar PFS hazard ratio results as the main analysis ([40] Novartis, Full Clinical Study Report-Addendum).

The second interim analysis cut-off also demonstrated a clear reduction in risk of disease progression or death and a statistically significant difference in median PFS between everolimus plus BSC and placebo plus BSC (HR=0.30; 95%CI: 0.22 to 0.40, p<0.001), supporting the outcomes demonstrated at the final analysis ([44] Motzer, 2008).

Progression Free Survival by sub-groups (Source; Novartis Submission, Section 6.4.4, p73)

PFS by MSKCC prognostic category: Sub-group analysis by MSKCC prognostic category was pre-specified. This demonstrated a statistically significant difference in PFS for all three categories. There was a 69%, 68% and 56% reduction in disease progression or death risk for the everolimus plus BSC group versus placebo plus BSC for favourable, intermediate and poor risk categories, respectively (Table 6.7 [Table 3, below]). A statistically significant difference was found for the poor risk patients despite small patient numbers. (Source: Novartis Submission, Section 6.4.4.1, p73)

Table 3: Progression free survival by MSKCC prognostic category

MSKCC category	*Everolimus plus BSC*	*Placebo plus BSC*	*hazard ratio* (95%CI)*	*p-value***
Favourable risk (N)	81	39		
Median PFS (months)	5.8	1.9	0.31 (0.19-0.50)	<0.001
Intermediate risk (N)	156	79		
Median PFS (months)	4.5	1.8	0.32 (0.22-0.44)	<0.001
Poor risk (N)	40	21		
Median PFS (months)	3.6	1.8	0.44 (0.22-0.85)	0.007

*N = number of patients; * Unstratified Cox proportional hazards model; ** Stratified 1 sided log-rank test*

([40] Novartis, Full Clinical Study Report-Addendum)

(Source: Novartis Submission, Table 6.7, p74)

Table 6.8 (Table 4, below) presents the hazard ratios for other sub-groups at final analysis based on central radiology review. For all sub-groups the differences in median PFS between everolimus plus BSC) and placebo plus BSC) were statistically significant at the p<0.001 level.

Table 4: Everolimus plus BSC versus placebo plus BSC treatment effect by sub-group

Sub-group	*No. of patients*		*HR (95%CI)* everolimus plus BSC versus placebo plus BSC*	*Log-rank p value***
	Everolimus plus BSC	*Placebo plus BSC*		
Age				
<65 years	*165*	*98*	*0.34 [0.25, 0.47]*	*<0.001*
≥65 years	*112*	*41*	*0.33 [0.21, 0.51]*	*<0.001*
Gender				
Male	*216*	*106*	*0.32 [0.24, 0.42]*	*<0.001*
Female	*61*	*33*	*0.39 [0.23, 0.67]*	*<0.001*
Prior VEGFr-TKIs				
Sorafenib only	*81*	*43*	*0.25 [0.16, 0.42]*	*<0.001*
Sunitinib only	*124*	*60*	*0.34 [0.23, 0.51]*	*<0.001*
Both	*72*	*36*	*0.32 [0.19, 0.54]*	*<0.001*
Region				
US and Canada	*77*	*53*	*0.29 [0.19, 0.46]*	*<0.001*
Europe	*180*	*71*	*0.38 [0.27, 0.53]*	*<0.001*

Australia and Japan	*20*	*15*	*0.18 [0.07, 0.49]*	*<0.001*

Unstratified Cox proportional hazards model; **Unstratified 1 sided log- rank test

([40] Novartis, Full Clinical Study Report-Addendum)

(Source: Novartis Submission, Figure 6.8, p74)[28]

In particular, type of prior therapy was not associated with any differences in outcomes. The reduction in risk of progression or death for prior treatment with sunitinib (recommended by NICE for first-line use in aRCC) was 66% for the everolimus plus BSC patients versus placebo plus BSC (HR=0.34, 0.23, 0.51, p<0.001), which is almost the same as the overall risk reduction of 67%.

This generally faithfully represents the results as obtained in the RECORD-1 study.

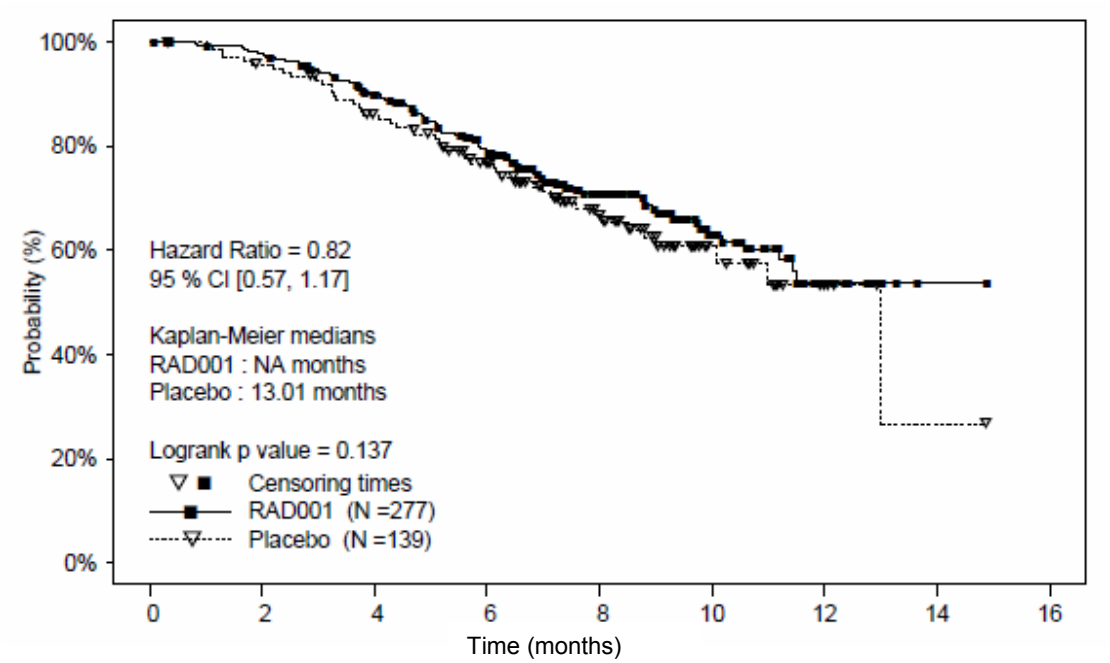
4.2.1.2. Secondary endpoint results

4.2.1.2.1. Overall survival

Overall survival results in RECORD-1 (Source: Novartis Submission, Section 6.4.5.1, p77)

Due to the cross-over trial design, overall survival (OS) was not a primary endpoint in the trial, as it is highly likely that the placebo plus BSC group will have inflated survival estimates as they were allowed to receive open-label everolimus upon disease progression. Median overall survival had not been reached for the everolimus plus BSC patients at either the second interim or final analysis cut-off points, ([44] Motzer, 2008; [74] Escudier 2008), and was 8.8 months and 13.01 months for placebo plus BSC at the two time points, respectively. However, the median survival for the placebo plus BSC arm is an overestimate as 76% of placebo plus BSC patients crossed-over. Hence a statistically significant difference in median survival was not found by the final analysis stage (HR=0.82, 95% CI: 0.57-1.17, p=0.137) (Novartis, Full CSR) This was consistent with the HR found for the second interim analysis (HR=0.83, 95% CI: 0.50-1.37, p=0.23) ([44] Motzer, 2008). The Kaplan-Meier plot for OS by treatment group for the final analysis is presented in Figure 6.7 (Figure 2, below). Overall, in the everolimus plus BSC group there were 85 OS events (31%) and 48 (35%) in the placebo plus BSC arm, 1ith 192 patients (69%) and 91 patients (65.5%) still alive or lost to follow up in each arm, respectively ([40] Novartis, Full Clinical Study Report-Addendum).

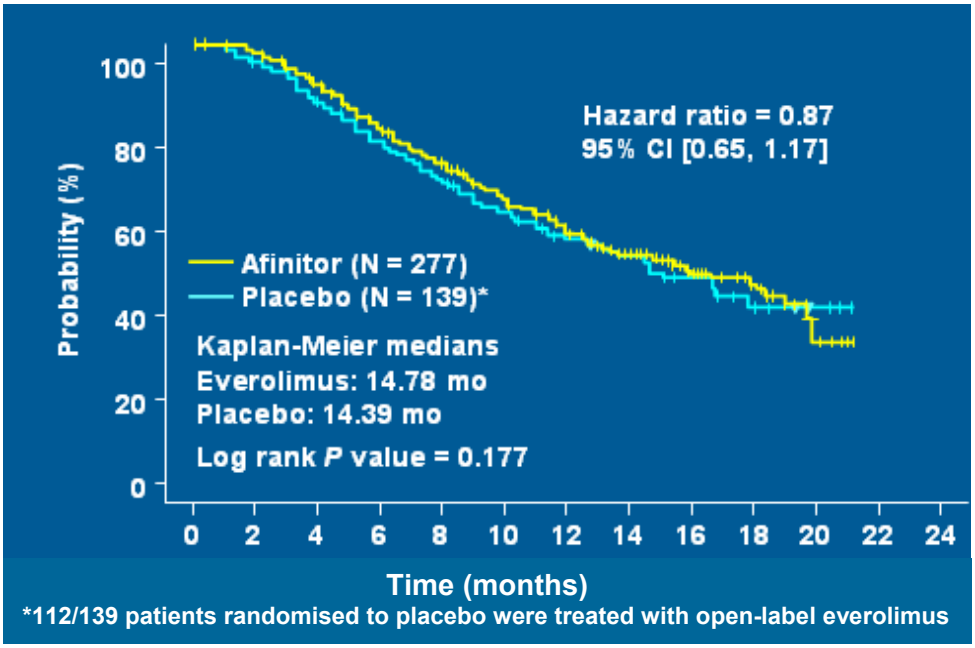
Figure 2: Overall survival outcomes by treatment at final analysis



([40] Novartis, Full Clinical Study Report-Addendum)
***(Source: Novartis* Submission, Figure 6.7, p77)**

A further analysis of OS was performed at a November 2008 cut-off date ([112] Motzer 2009). The median survival for the placebo plus BSC arm was 14.39 months – a statistically significant difference in OS was not observed (HR=0.87, 95% CI: 0.65-1.17, p=0.177). The K-M curves were similar for both treatment groups (Figure 6.8 [Figure 3, below). The lack of significant difference by this stage, based on ITT analysis, was not surprising due to the high cross-over of placebo plus BSC patients (112 out of 139 (81%) by November 2008) to receive everolimus plus BSC ([112] Motzer, 2009).

Figure 3: Overall survival outcomes (Nov 2008 cut-off)



([112] Motzer, 2009)

(Source: Novartis **Submission, Figure 6.8, p78)**

The results show no statistically significant treatment-related difference between the two arms. However, there was a high level of switching of placebo plus BSC patients to treatment with everolimus plus BSC following disease progression, which is highly likely to have biased the OS result due to three-quarters of patients going on to receive everolimus. The Inverse Probability of Censoring Weight (IPCW) method was used to correct for this. It is important to note that the actual result was a hazard ratio of 0.82, and the hazard ratio of 0.55 used in the health economic base case is an adjusted result. This suggests that HR=0.82 should have been used in the base case, and 0.55 used in the sensitivity analysis. This is discussed in greater detail in Section 5.2.3.3 (page 64).

4.2.1.2.2. Objective tumour response rate

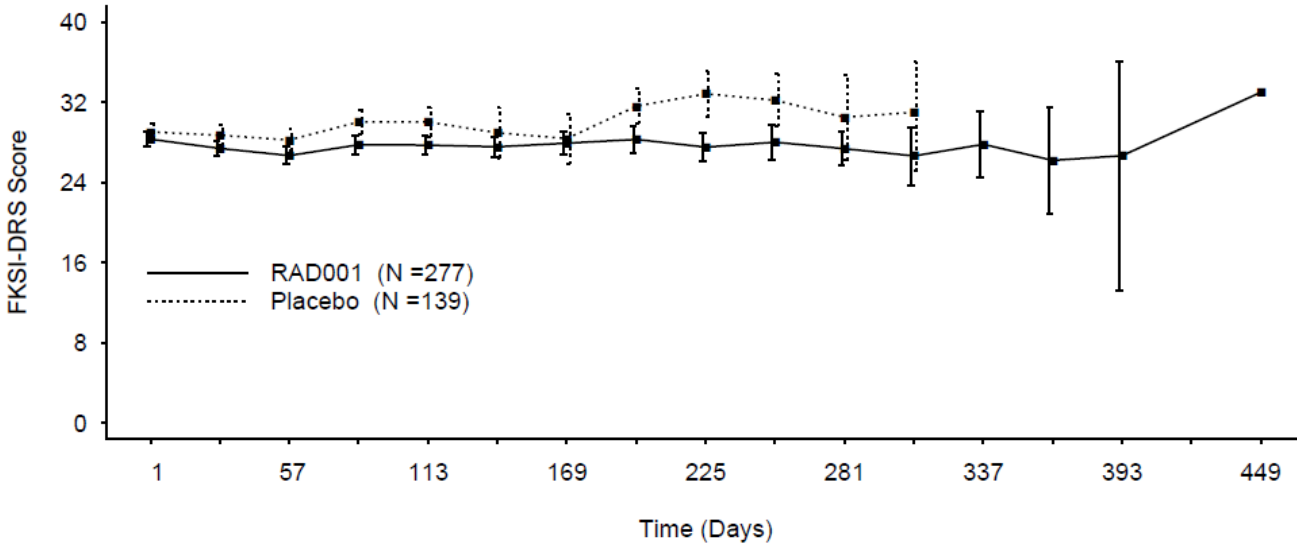
> *Based on RECIST criteria, everolimus plus BSC demonstrated a greater proportion of target lesion response rates that were classified as partial or stable disease, and lower rates of progressive disease as compared to placebo plus BSC. At the final analysis there were 190 patients whose best overall response was classified as partial or stable (69%) compared to only 45 (32%) placebo plus BSC patients. (Source: Novartis Submission, Section 6.4.6, p80)*

4.2.1.2.3. Patient Reported Outcomes and HRQoL

Patient reported outcomes deserve greater emphasis than accorded in the Executive Summary provided in the submission. We would therefore draw attention to some of the additional detail reported in the main text of the submission.

> *Data from the full analysis set for the mean scores over time for each of the PRO instruments in the RECORD-1 trial revealed similar HRQoL/PRO and functioning/symptom results for everolimus plus BSC and placebo plus SBC patients ([40] Novartis, Full Clinical Study Report-Addendum) – see Figures 6.10 and 6.11 (Figure 4 [below] and Figure 5 [below]. This indicates that there were no tolerability issues associated with everolimus that had an adverse impact on patient health related quality of life. This low HRQoL impact may also be related to the convenience of everolimus oral once daily administration. (Source: Novartis Submission, Section 6.4.7, p82)*

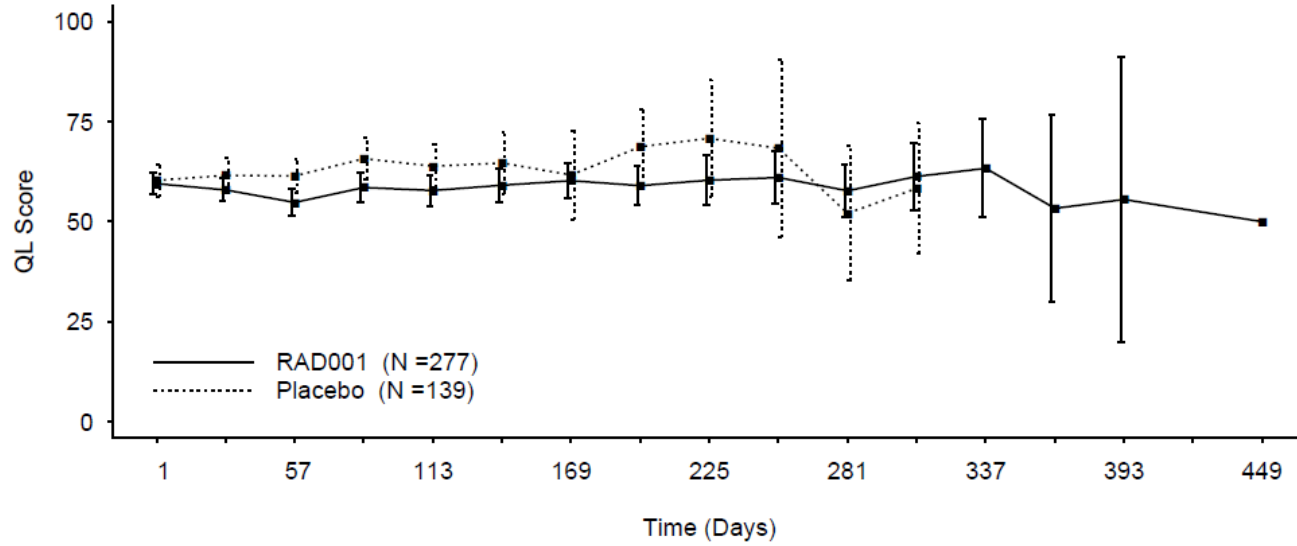
Figure 4: Longitudinal mean FKSI-DRS scores by treatment: Full Analysis Set



([40] Novartis, Full Clinical Study Report-Addendum)

(Source: Novartis Submission, Figure 6.10, p83)

Figure 5: Longitudinal mean scores of the Global health status/HRQoL scale (QL) of the EORTC QLQ-C30 questionnaire by treatment: full Analysis Set



([40] Novartis, Full Clinical Study Report-Addendum)

(Source: Novartis Submission, Figure 6.11, p83)

PRO/HRQoL questionnaires are often reported in cancer clinical trials as being poorly completed with many missing questionnaires and missing data ([102] Bernhard, 1998; [113] Hahn 1998). However, in RECORD-1 compliance was reasonably good given the advanced nature of the RCC. Compliance at baseline was between 86% and 92% for the FKSI-DRS and EORTC QLQ-C30 instruments in both treatment arms and despite the requirement to be completed monthly there was still at least 65% compliance by Day 113 (post-baseline Visit 4). Hence, sufficient data was available to assess the health related quality of life impact associated with treatment ([40] Novartis, Full-Clinical Study Report-Addendum). (Source: Novartis Submission, Section 6.4.7, p84)

Figure 4 and Figure 5 show clearly that despite lack of response to everolimus, patient quality of life appears to be similar in the BSC alone arm. In addition response rates to the questionnaires were 60% or above in both arms until Day 113. In the manufacturer's submission the interpretation that maintenance of HRQoL with everolimus is reassuring, might also be regarded as disappointing, given that some additional benefit might also be expected to arise from tumour response in the everolimus arm of the study.

4.2.1.2.4. Safety

Safety also deserves greater emphasis than accorded in the Executive Summary provided in the submission. We would therefore draw attention to some of the additional detail reported in the main text of the submission.

> *Safety of everolimus in conjunction with best supportive care (BSC) (Source: Novartis Submission, Section 6.7.2, p85)*
>
> *The pivotal phase III RECORD-1 trial ([40] Novartis, Full Clinical Study Report-Addendum; [44] Motzer, 2008) is the only study that allows direct comparison with placebo plus BSC and hence has an ability to discriminate between drug and disease related toxicities. In the final analysis, 274 and 137 patients with aRCC received at least one dose of everolimus (10mg/day) or placebo, respectively, in conjunction with BSC. In total, 165 patients were exposed to everolimus (10mg/day) for ≥4 months (Novartis, Full-CSR; Escudier, 2008). In the everolimus plus BSC group there were 21 (7.6%) on-treatment deaths versus 7 (5.1%) deaths in the placebo plus BSC arm. Three of the everolimus group deaths were due to infectious causes and deemed drug related. ([40] Novartis, Full Clinical Study Report-Addendum).*
>
> *… The greater incidence of AEs and (SAEs) in the everolimus plus BSC arm, reported in 40.1% of everolimus plus BSC patients versus 22.6% for placebo plus BSC patients, is related to the much longer duration of exposure for the former ([40] Novartis, Full Clinical Study Report-Addendum).*
>
> *Everolimus was generally well-tolerated and safety findings were consistent with the smaller phase II studies. The most frequent treatment-related AEs of any grade (incidence ≥5%) were anaemia, stomatitis, asthenia, fatigue, cough, diarrhoea, rash, nausea, anorexia and peripheral oedema, hypercholesterolemia, pyrexia, headache, mucosal inflammation, epistaxis, hypertryglyceridaemia, pruritis, dry skin, hyperglycaemia, pnemonitis, asthenia,, and blood creatinine increase ([40] Novartis, Full Clinical Study Report-Addendum).*
>
> *The severity reports with everolimus were predominantly Grade 1 and Grade 2 events. Grade 3 and Grade 4 events were often reversible, transient and manageable. The most common Grade 3 or 4 adverse events suspected to be related to treatment (incidence ≥3%) were anaemia, hyperglycaemia, stomatitis, fatigue, hypercholesterolaemia, and dyspnoea. The majority of these events resolved either spontaneously or following appropriate medical management.*
>
> *Non-infectious pneumonitis which is a known risk for all mTOR inhibitors was identified early in the program and management guidelines (including CT scans and pulmonary function tests) were implemented. Grade 3 pneumonitis was reported in*

only 2.5% of the patients receiving everolimus plus BSC treatment in the RECORD-1 study and there were no cases of Grade 4 penumonitis reported ([40] Novartis, Full Clinical Study Report-Addendum).

There is consistent evidence that adverse events of all grades are experienced to a greater degree in the everolimus arm of the study. Many of these have an impact on HRQoL, but the excess applies to major events which are likely to have an impact. This is captured in the Clinical Study Report: [redacted] In general, the ERG states that the manufacturer submission understates the nature and likely impact of the observed AEs on patient quality of life.

4.2.2. Critique of submitted evidence syntheses

No meta-analysis was required. The effectiveness summary in the manufacturer submission generally faithfully represents the results as obtained in the RECORD-1 study. The submitted evidence also adequately reflects the decision problem defined in the submission.

4.2.3. Summary of clinical effectiveness

A systematic review of the effectiveness of everolimus was submitted. It focused on the RECORD-1 study. This was a randomised, double-blind, placebo-controlled controlled trial of 416 participants. 277 were randomised to 10mg everolimus once a day, in addition to best supportive care (BSC), and 139 to an identical placebo tablet in addition to BSC. The manufacturer submission summarised the identified benefits as:

- 67% reduction in the risk of disease progression or death (HR=0.33, 95% CI 0.25-0.43), equating to a mean progression free survival of 4.90 months for everolimus plus BSC, versus 1.87 months for placebo plus BSC, a difference which was highly statistically significant (p<0.001).
- A non-statistically significant treatment related difference in overall survival (HR=0.82; 95%CI 0.57-1.17; p=0.137), but a result which was highly likely to have been influenced by a very high level of patients in the placebo arm swapping to everolimus treatment after progression had been detected.
- Improved rate of partial or stable tumour response in 69% of patients with everolimus against 32% in the placebo arm.

- Stable quality of life/patient reported outcomes in everolimus compared to placebo.

The ERG appraisal indicates that the evidence identified is relevant and complete. The interpretation is reasonable, although the ERG would place greater emphasis on the much higher frequency of AEs, of a severity likely to have an impact on patient QoL, in the everolimus arm of the trial relative to the placebo arm. The trial data available indicate that patient HRQoL was identical in the early stage of the trial, despite there being response to treatment in the everolimus arm.

Although the overall survival results from the RECORD-1 RCT are clear and uncontroversial indicating an improvement which could have been accounted for by chance alone, the adjustment of the results for switching of placebo patients to everolimus after progression is an area of genuine academic debate, particularly concerning the most appropriate analytical method. This is discussed in greater detail in Section 5.2.3.3 (page 64).

5. Economic evaluation

In this chapter, we assess the cost-effectiveness analysis submitted by Novartis. Firstly we review the search strategy adopted by Novartis and provide an overview of the economic model used (Section 5.1). There follows an examination of the cost-effectiveness analysis using standard approaches for critical appraisal of economic evaluation (Section 5.2). Finally the model results as provided by Novartis are analysed (Section 5.3).

5.1. Overview of manufacturer's economic evaluation

5.1.1. Description of manufacturer's search strategy and comment of whether the search strategy was appropriate

Searches were performed in the following databases on the 16th and 17th June, 2009 (not stated which applies to which database):

- MEDLINE and MEDLINE IN PROCESS [MEZZ] Dialog DataStar 1950–June 2009
- EMBASE [EMZZ] Dialog DataStar 1980–June 2009
- BIOSIS [BIZZ] Dialog DataStar 1985–June 2009
- NHS Economic Evaluation Database (NHS EED) 2000-2009

Separate search strategies were provided for EMBASE, Medline with Medline in-process, and BIOSIS by the manufacturer. All database searches are based on thesaurus (where possible) and free-text words for the renal cell carcinoma population combined with the intervention (everolimus), terms and those for finding economic evaluations [renal cell terms AND everolimus terms AND economic/cost terms]. None of the database searches use a filter specifically for finding individual utility or quality of life information. Editorials and letters have been excluded from the searches but there are no additional limits or filters on any of the search strategies.

Searches were also carried out for conference abstracts on the following websites:

- ASCO Website 2005–2009 Search date: 16 June 2009
- ECCO Website 2006, 2008 Search date: 16 June 2009

- ESMO Website 2005, 2007 Search date: 16 June 2009

The terms used for searching the conference site reports were “everolimus, RAD001, Afinitor, AND cost-effectiveness, cost-utility, cost-benefit, cost, (metastic) renal cell carcinoma, kidney cancer.”

Additionally the manufacturer states the following resources were accessed for relevant economic evaluations:

- HTA database (CRD) website
- Database of abstracts of review of effects (DARE) (CRD website)
- NHS Economic Evaluation Database (NHS EED) (CRD website)
- Cochrane Database of Systematic Reviews (CCTR)
- Clinical Trials.gov
- Current Controlled Trials (www.controlled-trials.com)
- NICE and NIHR Health Technology Assessment website
- Hand searching of selected primary study references

According to the accompanying review the hand searches were of abstracts from the International Society of Pharmaeconomics and Outcomes (ISPOR) Journal and Value in Health between 2005 and January 2009.

The databases and search strategies reported are appropriate for identifying specific economic evaluations for renal cell carcinoma where everolimus is the intervention. The ERG re-ran all the provided search strategies, no additional economic evaluations were found.

5.1.2. Overview of Model

The Novartis model was developed as a Markov state-transition cost-utility model and implemented in Microsoft Excel©. In general, we found the model to be well presented and coded appropriately. We did however discover two significant errors in the implementation of a key hazard ratio for overall survival (OS) in the model. These errors are summarised below and outlined in more detail in Section 5.2.3.3.4:

- The hazard ratio (HR) multiplier was incorrectly applied to the transition probabilities in the placebo (i.e. BSC only) arm of the model. This multiplier had been applied directly to the transition probabilities, rather than first converting these probabilities to rates before multiplying and then converting the revised rates back into transition probabilities. Since these probabilities in the model are relatively high, this error is significant.

- In applying the HR multiplier to mortality probabilities in the BSC only arm, the model fails to account for increased death caused by greater progression in this arm. This leads to a bias which exaggerates the death rate for patients in the BSC only arm (i.e. under-estimates the hazard ratio for overall survival of everolimus versus BSC only).

In our analysis, we corrected for these errors and re-ran the Novartis model. A full account of our outputs is presented in Section 6.2. In the recalculated results, the base-case model incremental cost effectiveness ratio (ICER) values are £65,231 with patient access scheme (PAS) applied, and £76,070 without PAS applied (increased from values of £51,613 and £61,330 respectively presented in Novartis' analysis).

A key component of Novartis' cost effectiveness analysis is the use of the statistical method of inverse probability of censoring weights (IPCW) to adjust the proportional hazard for overall survival between arms. This approach is justified in the Novartis submission by reference to the large proportion of patents in the trial placebo arm (76%) that cross-over to open-label everolimus on disease progression.

In view of the critical part played by the use of IPCW in the cost-effectiveness analysis presented by Novartis, we have included an extensive examination of its application in Section 5.2.3.3. This section describes the rational and application of IPCW in the analysis and examines both the appropriateness of its use in the context of the RECORD-1 trial data and also how the outputs from the IPCW analysis are integrated in the economic model.

5.1.3. Model Structure

Novartis' cost effectiveness analysis is based on a simple Markov state-transition model for advanced renal cell carcinoma (RCC). The model, illustrated in Figure 6, is based on the following four discrete health states:

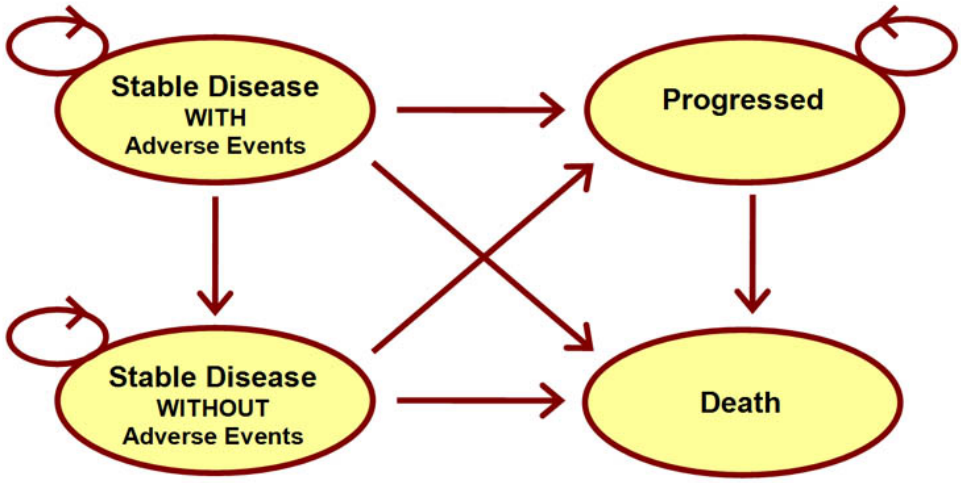
1. Stable Disease without adverse events (SD),

2. Stable Disease with adverse events (SD+AE)

3. Progressive disease (PD)

4. Death

Figure 6 : Structure of Novartis Model



Source: Adapted from Novartis submission Figure 7.1, p.105

All patients enter the model in the SD state. They remain in this state until they experience adverse events, disease progression or death. Once patients enter the SD+AE state they stay in this state until entering either the PD state or death. It was assumed that once AEs were experienced they would be resolved within one cycle, after which patients would be assigned the utility and costs associated with SD. Patients in the PD state remain there until death. Death is the absorbing state of the model.

The model cycle length is eight weeks and a time horizon of 144 weeks (18 cycles) is used. After 144 weeks virtually all the patients in the model have died, effectively therefore the model covers the lifetime horizon of the patient cohort. A half-cycle correction is not applied in the model since it is argued that it is unnecessary given the relatively short cycle duration.

5.1.4. Natural history

The model submitted by Novartis follows an established and simple structure for the modelling of cancer treatments. This structure distinguishes the progression of the illness into: stable states, progressed state and death. Patients enter the model in stable state (without AEs) and then progress according to the transition probabilities specified for each arm of the model. The natural history of patients in the model is essentially in one direction

only as the disease progresses. There is therefore no provision in the model for patients to move from the progressed state back to stable states. Adverse events are represented in the model using a separate state, and the effects of adverse events in terms of reduced utility and increased treatment costs are assumed to persist for one cycle only.

5.1.5. Treatment effectiveness within submission

Treatment effectiveness within the model is represented primarily by the transition probabilities between states (represented by the arrows in Figure 6). For this, data from the RECORD-1 trial were used to develop time-dependent transition probabilities for each of the model arms. 'Time-dependent' transition probabilities entail that a specific transition probability is applied for *each successive cycle* of the model rather than each transition probability remaining constant throughout the time horizon of the model (i.e. all cycles).

For the both treatment and comparator arms, observed patient data from RECORD-1 trial were used directly to calculate the following transition probabilities in the model:

- SD to SD+AE state: observed trial data for rates of occurrence of grade 3 and 4 adverse events were used to calculate this transition separately for each model arm. Rates of AE were lower in the BSC only patients resulting in a lower transition probability in this arm (see Table 5 below)

- Stable states (SD and SD+AE) to progressed disease (PD): the transition probability from stable states to the progressed state in the model was derived directly from the data in the RECORD-1 trial. This varied between the two compared arms of the model since patients progressed at a faster rate in the BSC only arm of the trial. For each arm of the model the probability of disease progression from stable state was assumed to be equivalent for patients both with adverse events (SD) and without adverse events (SD+AE).

- Stable states (SD & SD+AE) to death: The probability of transition from stable states to death for the everolimus treatment arm in the model was calculated based on the RECORD-1 trial outputs. For the BSC only arm of the model, the probability of transition from stable states to death was calculated by first deriving a hazard ratio using the IPCW statistical method (described in Section 5.2.3.3) and then using this mortality hazard ratio to multiply the transitions in the everolimus arm. The product of this calculation was then used as the transition probabilities for the BSC only arm.

- For each cohort the probability of moving from both the SD and SD+AE health states to the PD health state were the same in each arm. In addition, the probability of moving form both SD and SD+AE health states to death were also assumed to be the same within each arm. The purpose of the SD+AE state was simply to assign to this state additional costs and disutility to recognise both the cost and quality of life impact of in treatment.

- Cycles 8-18 of the model represent time points beyond the period of trial data collected from the RECORD-1 trial. For these transition probabilities values were assumed in the model to be the same as used in cycle 7. Therefore the transition probabilities in the model from cycle 7 to 18 remain constant.

The transition probabilities used in the Novartis model base case are shown in Table 5

Table 5 : Transition Probabilities used in the Novartis Base case Model

BSC ONLY		Model Cycle							
From State	To State	0	1	2	3	4	5	6	7-18
Stable	Stable + AE	[redacted]							
Stable	Progressed								
Stable +AE	Progressed								
Progressed	Death								
Stable	Death								
Stable + AE	Death								
EVEROLIMUS + BSC		Model Cycle							
From State	To State	0	1	2	3	4	5	6	7-18
Stable	Stable + AE	[redacted]							
Stable	Progressed								
Stable +AE	Progressed								
Progressed	Death								
Stable	Death								
Stable + AE	Death								

Source:Adapted from Novartis Submission. Table 7.3, p.117

It is instructive to compare the mortality transition probabilities used in the base case model which have been derived using the hazard ratio calculated from the IPCW statistical approach, with the values that are directly reflect the intention to treat trial data for the BSC only arm. These comparative values for the affected transition probabilities are shown in Table 6.

Table 6 : Base case model values for mortality transition probabilities base case values compared to intention to treat data for the BSC arm.

BSC ONLY – base case values from IPCW method		Model Cycle							
From State	To State	0	1	2	3	4	5	6	7-18
Progressed	Death	[redacted]							
Stable	Death								
Stable + AE	Death								
BSC ONLY –trial data (ITT values)		0	1	2	3	4	5	6	7-18
Progressed	Death	[redacted]							

Stable	Death	[redacted]							
Stable + AE	Death	[redacted]							

5.1.6. Health related quality of life

Utility values used for the four states in the model are shown below in Table 7

Table 7 : Utility values for Modelled States

Disease State	Mean value	(St. Dev.) [95%CI]	Source
Stable disease (SD) without adverse events	0.76	0.03 [0.70, 0.81]	Peninsula Technology Assessment Group (2008).[29].
Stable disease (SD) with adverse events	0.71	0.04	(-0.05) disutility associated with dyspnea Health state utility scores in advanced non-small cell lung cancer. (Doyle et al 2008).[30]
Progressive disease (PD)	0.68	(0.04) [0.61, 0.76]	Peninsula Technology Assessment Group (2008).[29].
Death	0	0	Accepted by definition

Source: Novartis Submission. Table 7.4 p.122

The RECORD-1 trial did not use EQ-5D or any other generic preference based measure to estimate utilities. Rather, utility values for health states for patients receiving second-line aRCC treatment were taken from the PenTAG Report for the NICE technology appraisal of aRCC drug interventions.[29] These values used in the Assessment Group economic model were based on a manufacturer submission reporting trial based EQ-5D utilities.

In their report Novartis highlight the following limitations in the available utility data:

- utilities for health states were not directly derived from patients who had failed first-line treatment,
- insufficient detail to assess the methods used, and the numbers of patients in the trial they were derived from was low.[29]

However, Novartis point out that there are no utility values available for health states for aRCC patients who have experienced disease progression following treatment with VEGF-targeted therapies. The PenTAG model values were therefore applied in the everolimus economic model as the most appropriate and best currently available.

The difference in mean utility between the stable/PFS and PD states of 0.08 is likely to be on the conservative side, as recognised by NICE Appraisal Committee reported in the guidance

for sunitinib.[3] Due to uncertainty in the state utility values sensitivity and scenario analysis has been performed on mean utilities.

5.1.7. Resources and costs

The model uses costs based on the NHS and PSS perspective as specified by the NICE reference case. Costs included were drug cost, disease management costs (such as appointments, scans and tests), some adverse event costs and palliative care costs associated with death.

Table 8 summarises for each arm of the model the base case values used for costs in each state of the model, for scenarios where PAS is applied and without PAS.

Table 8 : Summary of costs per cycle by health state: everolimus and BSC cohorts – including Patient Access Scheme (PAS)

Health state	Everolimus plus BSC cost per cycle £	Cost coverage	BSC Cost per cycle £	Cost coverage
Stable Disease without AEs* [without PAS]	4,944.92** † [5,199.39]	Everolimus cost plus healthcare resource use	110	Healthcare resource use
Stable Disease with AEs* [without PAS]	5,485.27** † [5,739.74]	Everolimus cost, healthcare resource use and AE cost	294.01	Healthcare resource use and AE cost
Progressive disease	3,069.78	Healthcare resource use and supportive therapy	3,069.78	Healthcare resource use and supportive therapy
Death	3,923.00	One off end of life palliative care cost	3,923.00	One off end of life palliative care cost

**In addition, there is a baseline cost of £237 for both everolimus plus BSC and BSC cohorts, and the cost of a CT scan every 3 cycles at £182*

***The cost per cycle with PAS is after the first month in which everolimus is provided at zero cost to the NHS*

†Cost incorporates 91.8% everolimus dose intensity adjustment

Source: Novartis Submission. Table 7.10, p.131

5.1.7.1. Costs : Everolimus drug acquisition cost

Within their analysis, Novartis base the cost of everolimus on patients receiving the standard daily dose of 10mg per day until disease progression. The majority of patients in the RECORD-1 trial received the full dose of everolimus (10mg per day), however there were some dose adjustments and interruptions primarily due to adverse events so that the adjusted average dose was 9.18mg/day (i.e. a dose intensity of 91.8%). This value of dose

intensity was therefore applied in the model base case. The list price for everolimus (10mg) is £2,970 per pack of 30 tablets (1 month supply) Everolimus drug cost per 8 week cycle adjusted for 91.8% dose intensity was included in the economic model.

A patient access scheme (PAS) has been discussed with the Department of Health and is pending Ministerial approval. This scheme offers the first months supply (10mg or 5mg tablets x 30) of everolimus at zero cost to the NHS. Subsequent one month packs (30 x 10mg tablets) will be offered to the NHS at a cost £2,822. This equates to 5% discount on the list price. N.B. This 5% discount applies to packs of the 10mg tablets only. There are no operational costs assumed for the PAS, as it involves the completion of a short form by the hospital pharmacist regarding the first month at zero cost. Novartis present details of the PAS scheme in Section 1 of their report.

The acquisition cost of everolimus with and without the PAS applied is presented in Table 9. Dose intensity estimate was explored in sensitivity analysis for the model outputs, including an estimate of cost-effectiveness based on 80% and 100% dose intensity.

Table 9 : Everolimus drug and patient costs with and without patient access scheme

	Intervention without PAS		Intervention with PAS		
	Unit cost (30 x 10mg tablet pack)£	Total cost per 8 week cycle £	Unit cost (30 x 10mg tablet pack) £	Total cost per 8 week cycle– first cycle* £	Total cost per 8 week cycle – subsequent cycles £
Everolimus acquisition (no dose intensity adjustment)	2,970	5,544.00	2,822	2,445.30	5,266.80
Everolimus acquisition (with dose intensity adjustment)	2,970	5,089.39	2,822	2,244.79†	4,834.92†
Monitoring tests**	-	-	-	-	-
Diagnostic tests**	-	-	-	-	-
Appointments**	-	-	-	-	-
Other costs**	-	-	-	-	-
Total patient related costs		5,089.39		2,244.79	4,843.92

**First cycle cost based on first month of treatment provided at no cost to NHS.*

***No additional costs are anticipated associated with tests or special appointments for everolimus administration. Any additional resource use incurred is routine and associated with the provision of best supportive care and the underlying cancer.*

†The 8 week cycle costs are calculated assuming the 91.8% dose intensity adjustment. The unit costs are not DI adjusted in the table.

Source: Novartis Submission. Table 7.5, p.124

5.1.7.2. Costs : Resource use and costs associated with aRCC

Within their economic model, Novartis base their estimates of ongoing resource use for the stable and progressive disease states on those assumed in the previous PenTAG economic

model for NICE on BSC resource use.[29] As the PenTAG estimates were estimated per 6 week cycle, these were adjusted to reflect the 8 week cycles in the everolimus economic model.

The resource use was primarily associated with patient monitoring (assumed to be GP led), tumour scans, and blood tests. In the economic model patients are assumed to incur initial resource use post VEGF-targeted therapy disease progression consisting of a GP appointment, a CT scan, and a blood test. This is applied for patients in stable disease at baseline (cycle 0). Subsequently, as part of patient monitoring, patients are assumed to visit a GP twice and have two blood tests during every 8 week cycle. A CT scan is assumed to be performed less frequently – once every 3 cycles.

The resource use estimates and unit costs applied are presented in Table 10, resulting in an initial cost of £237, an ongoing cost of £110 per cycle and a CT scan cost of £182 per 3 cycles in stable disease. As BSC was common to the everolimus and BSC only cohorts these costs were applied to time spent in stable disease to both arms of the model.

Table 10 : Resource use estimates and costs for stable disease states

	Resource	Mean Frequency or duration	Unit cost £	Total Cost £
Baseline (initial resource use)	GP visit	1 visit	52[a]	52
	CT scan	1 scan	182[b]	182
	Blood test	1 test	3[c]	3
Cost of baseline resource use				237
Follow-up resource use	GP visit	2 visits per 8 weeks	52[a]	104
	Blood test	2 tests per 8 weeks	3[c]	6
	CT scan	1 scan per 3 cycles	182[b]	182
Cost of ongoing resource use – per cycle				110
Additional cost of CT scan – per 3 cycles				182

Sources for unit costs:

a: Curtis, 2008 [31]. PSSRU costs, Table 8.8b – GP visit 17.2 minutes

b: Code RA14Z (CT scan, three or more areas). NHS Trust and PCT combined Reference Costs 2007-08 [32]

c: Code DAP823 (Haematology-excluding anticoagulant services). NHS Trust and PCT combined Reference Costs 2007-08 [33]

Source: Novartis Submission. Table 7.6, p.125

In the economic model the cost of drug therapy with everolimus per cycle was added to the resource use costs of the stable disease health states for patients receiving everolimus.

5.1.7.3. Costs : Drug and non-drug therapy in progressive disease

The PenTAG economic model for aRCC drug therapies estimated resource use for medical management of progressed disease comprising one GP visit per month, 1.5 specialist palliative care community nurse visits per month, and pain medications.[29] These estimates, adjusted for an 8 week cycle, have been applied in the everolimus economic model as indicated in Table 11 below, resulting in an estimated cost for BSC of £641 per cycle.

Table 11 : Resource use frequency and unit costs in progressive disease

Resource	Mean frequency per 8 week cycle	Unit cost £	Total cost per 8 week cycle £
GP Visits	2 visits	52[a]	104
Specialist community nurse	3 visits	79[b]	237
Supportive therapy	60 vials	5[c]	300
Cost of ongoing resource use – per cycle			641

Sources for unit costs:

a: Curtis, 2008 [31]. PSSRU costs, table 8.8b – GP visit 17.2 minutes

b: Code 202AF- Band 2 Palliative/respite care: adult face-to-face NHS Trust and PCT combined Reference Costs 2007-08

c: Morphine sulphate injections. 1 dose per day (1 mg/ml, net price 50-ml vial prefilled syringe £5.00 per pack)

Source: Novartis Submission. Table 7.7, p.126

In the progressed disease state, the model incorporates costs based on a weighted average for a range of post trial treatments for everolimus plus BSC and initial placebo plus BSC patients combined. These treatments included further drug and non-drug therapies such as surgery, palliative radiotherapy, bisphosphonates and other salvage and investigational drug therapy. Costs are based on the proportion of patients using each therapy derived from the RECORD-1 post-trial treatment data available in the follow-up study for 130 patients.[17]

For drugs administered in progression, a dose intensity of 80% has been assumed (60% and 100% explored in sensitivity analysis). Table 12 presents the drug therapies, frequency of use and unit costs, demonstrating a weighted average cost of £3,373.30 (sum of treatment cost per 8 week cycle x frequency of use for each therapy). Based on the follow-up study it was assumed that 72% of patients received the package of therapy shown in Table 12, which represented the actual proportion of patients in the RECORD-1 trial who after disease progression received an active therapy. Therefore, a cost per 8 week cycle of £2,428.78 (72% of the total weighted cost) was added to the Progressive health state costs of resource use shown in Table 11 above.

Table 12 : Treatments and costs for progressive disease supportive therapy (per 8 week cycle)

Therapy (Units)	No. of units per 8 weeks (DI adjusted*)	Unit cost £	Freq. of treatment	Total 8 week cost £	Assumptions
Sorafenib - Nexavar® (per day)	44.80	106.45	31.43%	4,768.96	400mg twice daily (total of 800 mg) until no more treatment effect; Unit cost source: BNF 57, March 2009 [34]
Sunitinib - Sutent® (per day)	33.60	112	20.95%	3,763.20	One 50-mg tablet taken orally, once daily. Treatment cycles = 6 weeks (4 weeks on active treatment, 2 weeks off treatment) Unit cost source: BNF 57, March 2009 [35]
IFN alfa-2a – Roferon-A® (per week)	6.4	43.44	5.71%	278.02	9 MIU total per week (subcut x 3 per week, max 52 weeks or no more treatment effect; from bevacizumab trial [36]. Unit cost source: BNF 57, March 2009 [37]
Bevacizumab - Avastin® (per 2 weeks -76.5kg patient)	3.20	1,652.00**	14.29%	5,916.80	10 mg/kg administered intravenously once every other week until disease progression; cost includes infusion charge of £197 for each bi-weekly infusion. Drug cost of £924.40 per 400mg vial. Unit cost source: BNF 57, March 2009 [38]
Capecitabine - Xeloda® (per day)	33.60	22.64	0.95%	760.70	BNF-rec dose: mRCC 1.25g/m2 twice daily for 14 days, followed by 7 days off; Average person is 1.829m^2. Drug cost £2.46 per 500mg. Unit cost source: BNF 57, March 2009 [39]
Thoracotomy (per procedure)	1.00	4015.00	1.90%	4,015.00	Code DZ03B NHS Trust and PCT combined Reference Costs 2007-08: Major Thoracic Procedure without complications (CC)
Palliative Radiation Therapy (per day)	5.00	114.00	24.76%	570.00	Code SC22Z NHS Trust and PCT combined Reference Costs 2007-08:: Deliver a fraction of therapy on a megavoltage machine
TOTAL – weighted average cost of all treatments				£3,373.30	
Total cost per 8 week cycle (72% uptake of therapy)				£2,428.78	

Source: Novartis Submission. Table 7.8, p.127

5.1.7.4. Costs : Adverse Events

The costs of adverse events for the everolimus plus BSC and BSC only cohorts in the model were included within the *stable disease with adverse events* health state, and added to the costs of ongoing resource use for this health state. These values are outlined in Table 13 which also outlines the assumptions and unit costs applied for each adverse event included.

In the model it was assumed that adverse events were resolved within one cycle of entering the stable disease with adverse event health state. Resource use consisted of drug therapy, procedures such as oxygen therapy for dyspnoea, and hospital stay where required (i.e. dyspnoea and anorexia). Further detail on the treatment schedules and resource use assumed for each adverse event used in the model are provided in the Novartis submission (Appendix 6. p.208-10).

Table 13 : Adverse events and unit costs used in model

Adverse Event	Incidence (grade 3 and 4)	Unit Cost £	Cost applied in model (incidence x unit cost) £	Source/assumption
Anaemia	10.2% everolimus 5.1% BSC	1958.00	199.72 99.86	Treatment schedule as reported in Mickisch et al., 2008 [40]
Anorexia/Cachexia	1.5% everolimus	443.13	6.65	Treatment schedules based on: 2009 NCCN Palliative Care Guidelines [41]; Ross et al., 2001 [42]; Yavuzsen et al., 2005 [43] Drug unit costs from BNF 57 March 2009 [44]; Medical costs from NHS reference costs 2007-08 [45]
Nausea / Vomiting	3.7% everolimus	2,200.64	81.42	Treatment schedule as reported in Mickisch et al., 2008 [46]
Dyspnoea	7.7% everolimus 2.9% BSC	2,901.87	223.44 84.15	Treatment schedules based on: 2009 NCCN Palliative Care Guidelines [47]; Ripamonti et al., 1999 [48]; Thomas et al., 2003 [49] Drug unit costs from BNF 57, March 2009 [50]; Medical costs from NHS reference costs 2007-08 [51]
Infections/Infestations	3.0% everolimus	796.45	23.89	Treatment schedules based on: 2009 NCCN Prevention and Treatment of Cancer-Related Infections Guidelines [52]; Reusser et al., 2002 [53]; Vento et al., 2003 [54] Drug unit costs from BNF 57, March 2009 [55]; Medical costs from NHS reference costs 2007-08 [56]
Pneumonitis Single Term	2.6 % everolimus	201.03	5.23	Treatment schedule based on RECORD-1 re: treating non-infectious pneumonitis. Drug unit costs from BNF 57, March 2009 [57]; Medical costs from NHS reference costs 2007-08 [58]

Source: Novartis Submission. Table 7.9, p.129

5.1.8. Discounting

Future costs and benefits were discounted at 3.5% as specified in the NICE reference case[59] which is appropriate. However, discounting for both costs and benefits in the base case has been applied only after the first year of the model rather than from the initial cycle. Although this makes only a minor difference to outputs, normally we would expect discounting to be applied from the first cycle of model operation. The model does provide a facility to apply discounting from the initial cycle, however although Novartis show the impact when no discounting is applied in the model, no other sensitivity analysis is presented in their submission to show the affect of varying discount rates.

5.1.9. Sensitivity analysis

Both one-way sensitivity and probabilistic sensitivity analyses (PSA) were presented by Novartis in their report. These outputs are reported in Section 5.3 below. One-way sensitivity analysis was conducted on the following data parameters:

- Mortality hazard ratio between arms

- Stable state utility level
- Progressed state utility level
- Utility decrement of adverse events
- Drug intensity of everolimus used
- Cost of treatment in progressed disease state

For each of these one-way sensitivity analyses incremental outputs (costs, QALYs and ICER) were provided for scenarios 'with PAS' and 'without PAS'.

In addition to the univariate analyses listed above, Novartis included a probabilistic sensitivity analysis (PSA) in their submission which investigates the affect of parameter uncertainty in the model and presents these results in terms of a Cost-effectiveness Acceptability Curve (CEAC).

5.1.10. Model validation

In their report, Novartis state that extensively debugging and testing in the Markov model was performed and all bugs and errors identified were fixed in calculations, the Visual Basic code, cost-effectiveness calculations, and transition probability calculations. Despite this however, we did find significant errors in the way in which the hazard ratio multiplier had been applied in the model.

In addition Novartis state that model cross-testing was performed, where deterministic and probabilistic analyses were compared with each other in several scenarios. Results from both models were similar.

In terms of external validation, Novartis state that the cost-effectiveness model was reviewed by clinical and health economic experts who agreed that the model structure reflected the progression of the disease. No other external validation was provided for the economic modelling approach used.

5.2. Critique of approach used

In this section, we comment on Novartis' approach and methodology. First, we consider the model against checklists of good practice. Then we critically appraise the model structure and data as well as the methods used in the cost effectiveness analysis.

5.2.1. Critical appraisal frameworks

We assessed Novartis' economic evaluation against the following three widely-used study quality checklists for economic models:

- NICE Reference Case as presented in the NICE Methods guidance [59,60]. Table 14 below
- Drummond assessment criteria as specified in [61,62] - Table 15 below.
- Criteria for decision model-based economic evaluations Philips et al (2004)[63] - Table 16 below.

Table 14 : Critical appraisal checklist based on NICE Reference Case[60]

NICE reference case requirement		Critical Appraisal	Reviewer comment
Defining the decision problem	The scope developed by the Institute	✓	
Comparator	Therapies routinely used in the NHS, including technologies regarded as current best practice	✓	Comparator is BSC. Possibility of other comparators was referred to in the scope although these are far from clear given that there are no licensed comparators for Second Line aRCC.
Perspective on costs	NHS and PSS	✓	
Perspective on outcomes	All health effects on individuals	✓	
Type of economic evaluation	Cost-effectiveness analysis	✓	
Synthesis of evidence on outcomes	Based primarily on single trial (RECORD-1) evidence	✓	
Measure of health benefits	QALYs	✓	
Source of data for measurement of HRQL	Indirect values taken from other sources	?	
Source of preference data for valuation of changes in HRQL	Secondary sources used – though values seem reasonable.	✓	
Discount rate	3.5% pa for costs and health effects	?	Base case applies this after first year rather than from initial cycle of model.
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	✓	

Table 15 : Critical appraisal checklist from Drummond and colleagues[61,62].

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	✓	Defined within NICE scope for STA

Item	Critical Appraisal	Reviewer Comment
Is there a clear description of alternatives (i.e. who did what to whom, where, and how often)?	✓	
Has the correct patient group / population of interest been clearly stated?	?	The trial population differs in several ways from typical UK treatment population although this is argued not to be significant.
Is the correct comparator used?	✓	BSC (scope suggests other comparators might be considered, although no other licensed comparators are currently available)
Is the study type reasonable?	✓	Markov cost-utility model
Is the perspective of the analysis clearly stated?	✓	UK NHS & PSS
Is the perspective employed appropriate?	✓	NICE reference case
Is effectiveness of the intervention established?	✓	Quality of single RCT[64] is good. Everolimus clearly improves TTP compared to BSC. However, overall survival data of BSC is compromised by substantial post-treatment crossover from BSC arm to everolimus so cost-effectiveness analysis is less straightforward.
Has a lifetime horizon been used for analysis, if not has a shorter time horizon been justified?	✓	144 week time horizon. After 144 weeks, virtually all modelled patients are dead. Hence the time horizon is effectively life time, and appropriate.
Are the costs and consequences consistent with the perspective employed?	✓	All costs from UK NHS & PSS perspective.
Is differential timing considered?	✓	-
Is incremental analysis performed?	✓	-
Is sensitivity analysis undertaken and presented clearly?	✓	Univariate and probabilistic sensitivity analyses are presented.

Table 16 : Critical appraisal checklist of Philips et al. (2004)[63] for model-based analyses

Dimension of quality			Comments
Structure			
S1	Statement of decision problem/objective	✓	Everolimus *v.* BSC for second line treatment of RCC.
S2	Statement of scope/perspective	✓	NHS and PSS perspective. Cost and benefit inputs are consistent with the perspective. Scope of model stated.
S3	Rationale for structure	✓	Cohort model is appropriate.
S4	Structural assumptions	?	Model assumptions are mostly explained clearly in the report. Overall, we are satisfied with the structural assumptions. Some errors were encountered in model implementation.
S5	Strategies / comparators	✓	BSC is used since no other comparators are licensed for the condition.
S6	Model type	✓	Cohort model is appropriate.
S7	Time horizon	✓	Model time horizon is 144 weeks (18 cycles of 8 weeks). After 144 weeks, virtually all modelled patients are dead. Hence the time horizon is effectively life time, and appropriate.
S8	Disease states / pathways	✓	The disease states: Stable, progressed, death are commonly used for terminal cancers. The additional Stable with Adverse Events state allows for modelling of the effects of adverse events in patients.

Dimension of quality			Comments
S9	Cycle length	✓	8 weeks is appropriate.
Data			
D1	Data identification	✓	Data identification methods are well described.
D2	Pre-model data analysis	?	ICPW method is used to calculate mortality ratio and rationale is described in detail in the report. Questions are raised in this report about its use.
D2a	Baseline data	✓	Baseline data from the single RCT, which is appropriate.
D2b	Treatment effects	?	Base case treatment effect estimated using ICPW method. We understand that this method is appropriate, however, we have no guarantee that it has been implemented correctly.
D2c	Quality of life weights (utilities)	?	Utilities are based on reference sources but no clear evidence based approach.
D3	Data incorporation	✓	Data incorporated in the model is referenced and generally well described. Data incorporation is transparent. For the PSA, the choice of distribution for each parameter has been described and justified.
D4	Assessment of uncertainty	?	A PSA is presented but the implications are not fully explored.
D4a	Methodological	✓	Single type of model, which is adequate.
D4b	Structural	?	Further sensitivity analyses for the affect of varied progression rates would have been welcome.
D4c	Heterogeneity	✓	No patient subgroups, as appropriate.
D4d	Parameter	✓	Probabilistic and univariate sensitivity analyses performed.
Consistency			
C1	Internal consistency	X	There were serious errors in the implementation of the mortality hazard ratio between arms.
C2	External consistency	?	Reference was made only to expert opinion.

✓ indicates 'clear', X indicates 'concerns',? indicates 'some concerns'

5.2.2. Modelling approach and structure

The structure of Novartis' cohort-based cost-effectiveness model is relatively simple and broadly follows the convention used for terminal cancers. The use of the stable, progressed and death health states is appropriate and consistent with the clinical outcomes in oncology trials. The division of stable disease into the two states of those patients 'with' and those 'without' adverse events provides a means within the model to assess the affect of adverse events across the two arms. However, we believe this division is not strictly necessary and over-complicates the model structure. Conceptually a simpler and equivalent characterisation of the model using three states is possible as discussed in Section 5.2.2.1.

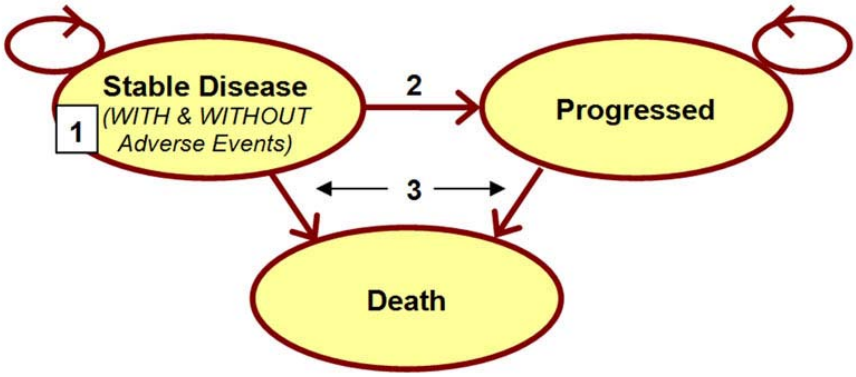
A 144 week time horizon was used in the model. As very few patients are predicted to survive 144 weeks after starting treatment, the time horizon is effectively lifetime and is

appropriate. The model cycle is 8 weeks, and a half-cycle model correction was not applied. We agree with Novartis that half-cycle correction is not required in the model.

5.2.2.1. A simplified representation of the Novartis model

In Novartis' model structure, within each arm, the transition probabilities from both stable disease states (SD and SD+AE) to the progressive state (PD) are equivalent and, within each arm, the transition probabilities from both stable disease states (SD and SD+AE) to death are equivalent. Given this, we found it helpful to re-configure the Novartis model as a three state model consisting of the following states: Stable Disease (with and without Adverse Events), Progressive Disease, and Death. In this simplified, but technically equivalent version, weighted averages are used to account for the cost and utility differences within the stable state due to varying proportions of patients with adverse events in the stable state at each cycle. This simplified version of the model structure, which generates precisely the same outputs as Novartis's representation, is shown in Figure 7.

Figure 7 : Simplified Representation of Novartis Model showing the three key sources of difference between everolimus and BSC only model arms.



On examination of the simplified model structure in Figure 7, it is possible to clearly identify the three main sources for the incremental costs and benefits generated by the model. These three main model drivers, as numbered in Figure 7, are described below:

1. Adverse event levels : The relative proportion of patients experiencing adverse events is greater for those patients treated with everolimus in the RECORD-1 trial thereby generating increased costs and reduced benefits for this arm of the model.

2. Progression rate : In the model, patients progress more slowly in the everolimus arm, represented by the lower transition probability from Stable to Progressed states. This generates a quality of life benefit in the everolimus for two main reasons:

- directly because the progressed state has a slightly lower utility than the stable state.

- in-directly since patients in the progressed state have a higher probability of death than patients in stable state hence a greater probability of progression for the patient population results in a greater probability of death.

3. Probability of Death: The different transition probabilities between arms for death from both stable and progressed states is a primary cause of incremental benefit. In the model a hazard ratio is calculated using the IPCW method which is then used to multiply the probability of death for BSC only arm. This results in a lower probability of death at each cycle in the everolimus arm from both these states.

It should be noted that by far the most important source of incremental cost and benefit in the model listed above is (3). That is to say, the modelled difference between arms for the transition probabilities to death from both stable and progressed states is the main model driver. This difference is derived in the analysis from the hazard ratio calculated using the IPCW statistical approach which is discussed in Section 5.2.3.3 below.

5.2.3. Data Inputs

5.2.3.1. Patient Group

The modelled patient group is based on the population used for the RECORD-1 trial on which the analysis is based.[17] As previously noted (see Section 3.1) there are clear differences between the trial population and the typical presenting UK population for aRCC, however after consultation with our expert clinical advisor, we are confident that these differences do not significantly affect the validity of the modelled outcomes.

5.2.3.2. Clinical Effectiveness Data

Clinical effectiveness within the model is represented by the transition probabilities between patient states and is based directly or in-directly on data from the RECORD-1 trial outcomes.

For the everolimus arm of the model transition probabilities have been calculated directly from RECORD-1 trial data, no attempt to parameterise the survival of patients within the stable disease state but rather the trial outcome data has been used directly to set up time dependent transition probabilities in the model. For the BSC arm of the model, whilst the transition probabilities for progression have been taken from the RECORD-1 trial data, the

transition probabilities for mortality have been calculated by applying a mortality hazard ratio (calculated using the IPCW method) as a multiplier to the corresponding mortality probabilities of the everolimus arm. As previously stated, in using the hazard ratio in their model we believe that Novartis unfortunately made some errors. The corrected transition probabilities are therefore shown in Table 17. We re-ran the model using the transition probabilities shown in Table 17 and the results are reported in Section 6.2.

Table 17 : Corrected Transition Probabilities for Base case Model

BSC ONLY		**Model Cycle**							
From State	**To State**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7-18**
Stable	Stable + AE								
Stable	Progressed								
Stable +AE	Progressed								
Progressed	Death								
Stable	Death								
Stable + AE	Death								
EVEROLIMUS + BSC		**Model Cycle**							
From State	**To State**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7-18**
Stable	Stable + AE								
Stable	Progressed								
Stable +AE	Progressed								
Progressed	Death								
Stable	Death								
Stable + AE	Death								

5.2.3.3. Application of Inverse Probability of Censoring Weight

The use of IPCW method to adjust for the cross-over bias in the RECORD-1 trial data forms a critical part of the cost effectiveness analysis presented by Novartis in their report. The importance of the adoption of the IPCW approach in Novartis analysis is demonstrated by the fact that when unadjusted intention-to-treat (ITT) data are used, the model outputs an ICER of £91,256 per QALY (with PAS) and £109,627 (without PAS) whereas with the application of the IPCW method outputs in the model, the reported base case ICER values are £51,613 and £61,330 respectively.

5.2.3.3.1. Description of IPCW approach

In their submission, Novartis provide the following summary of the IPCW approach that was applied to data from the RECORD-1 trial and provide a detailed description of the method within the appendices of their report (see Novartis submission, Appendix 4. p.201-6)

1. *Firstly, data from RECORD-1 was divided into 4 week segments ('months') corresponding to the frequency of visits in the RECORD-1 trial. Information on baseline characteristics and time varying assessments such as disease progression status was obtained.*

2. *The placebo plus BSC patients were artificially censored in the month in which they crossed-over to receive everolimus (known as cross-over or IPCW censoring).*

3. *This informative censoring is likely to introduce time dependent selection bias due to the patients crossing-over not being the same as those not crossing over e.g. none of the patients who did not cross over had disease progression. Inverse probability of censoring weights were generated to correct for the potential selection bias due to this cross-over censoring. Therefore, pooled logistic regression analysis was performed to estimate the probability of remaining IPCW uncensored (i.e. not crossing-over to receive everolimus). To develop the weights the logistic regressions were performed for a set of patient baseline characteristics (e.g. age, race, MSKCC category, prior treatments) adjusted for monthly time varying assessments (e.g. progression status, grade 3 or 4 AEs, death, cross-over status). The final variable selection was based on the best fitting model determined using goodness of fit statistics.*

4. *A stabilised weight per patient-month (SW_i) of follow-up was generated. Time periods following cross-over were excluded from analysis. Overall, there was data for 523 uncensored placebo plus BSC patient-months with an average of 3.8 months of uncensored follow-up. From this analysis the mean SW was 0.7912 (Std Dev 0.4231).*

5. *Everolimus plus BSC patient months were assigned SWi = 1, the placebo plus BSC patient months that were IPCW censored were assigned SWi = 0. The uncensored placebo plus BSC patient-months were assigned the weights generated by the pooled logistic regression analysis. A Cox proportional hazards model was applied to all patients in RECORD-1 (including the treatment indicator and all baseline characteristics), weighted by SW_i to estimate the monthly risk of mortality in the 'hypothetical' absence of cross-over in the placebo plus BSC arm.*

6. *An IPCW adjusted Cox hazard ratio for risk of death per patient month for everolimus plus BSC versus placebo plus BSC is generated for patients who in any given month could be stable or in disease progression. This hazard ratio was therefore used to generate the transition probabilities for stable and disease progression states leading to death in the Markov model for BSC.*

5.2.3.3.2. Rationale for use of IPCW in this analysis

Novartis justify the use of the IPCW method with reference to the following points:

1. IPCW falls into a family of methods (such as the Rank Preserving Structural Failure Time (RPSFT) model) which have previously accepted as appropriate by NICE.

2. The IPCW approach is likely to have a lower risk of model misspecification for estimating treatment effect on survival outcomes as it only utilises data for patients who follow the regime of interest whereas structural models like RPSFT 'borrow' information from subjects who do not follow the regime (e.g. who cross-over).

3. The hazard ratio for mortality generated by the IPCW Cox model was simple to apply to the everolimus transition probabilities (from RECORD-1) to generate the BSC transition probabilities for states leading to death in the Markov model. Whereas the RPSFT method models treatment effect in terms of time to event so transition probabilities need to be generated from predicted survival times.

Novartis also highlight a key limitation of the method in that it generates a very wide confidence interval around the hazard ratio limit. We would also question the second of the stated benefits above which, according to a statistical expert consulted by the ERG, could be considered a weakness rather than a strength due the assumption of 'no unobserved confounders' implicit in the IPCW approach (see Appendix 3 below).

In their report, Novartis state that they consulted with independent statistical experts about their use of the IPCW method and that these experts 'deemed it an appropriate method to use' (p.205 Novartis submission). On request, Novartis provided a brief report reviewing their use of the IPCW method in this study by an independent statistician. The text of this brief report is included below in Appendix 2.

5.2.3.3.3. Evaluation of the use of IPCW by Novartis

In order to assess the appropriateness of the IPCW approach to cross-over bias within the RECORD-1 trial we consulted Ian White (MRC Biostatistics Unit, Cambridge) an independent statistical expert in the field.[65] The full text of his review of the application of the IPCW method in the Novartis submission is included in Appendix 3, a summary of points from this is given below:

- Novartis are correct to seek to adjust for cross-over bias in the analysis of overall survival in the RECORD-1 trial.
- IPCW rests on the key assumption of "no unmeasured confounders" in the placebo arm. This assumption could be questioned and relies on an epidemiological judgement that all factors have been included in the analysis which is important to substantiate. Crucially unmeasured variables may include unobserved confounders in the trial population.
- Some arguments made by Novartis against the alternative method of RPSFT are incorrect. RPSFT may be a preferred method since it does not require per-protocol analysis.

- The results derived by Novartis from their application of IPCW seem plausible, but their significance may be exaggerated.

- It would have been useful to see outputs from both IPCW and RPSFT approaches in order to compare the results from each of these approaches.

It should be stated that whilst we can comment on the general appropriateness of the use of IPCW in the Novartis submission, we did not have the trial data to make the calculations directly so have no way of ensuring that the IPCW method has been properly applied and that the calculations have been performed correctly.

5.2.3.3.4. Implementation of IPCW output in the economic model

Having used an IPCW approach to derive a mortality hazard ratio for everolimus versus BSC only treatments as described, Novartis apply this hazard ratio in their economic analysis.

To do this Novartis simply multiply the transition probabilities for mortality in the everolimus arm which are based directly on the RECORD-1 trial data by a factor of 1.818. This value is the IPCW calculated mortality hazard ratio for BSC only versus everolimus (i.e. the reciprocal of 0.55 - the everolimus versus BSC hazard ratio). The mortality hazard ratio is therefore applied in the model to calculate the key transition probabilities for the BSC only cohort of patients moving from stable disease states to death and from progressed state to death.

We believe in applying the mortality hazard ratio in this way, Novartis unfortunately made two important errors which are outlined here:

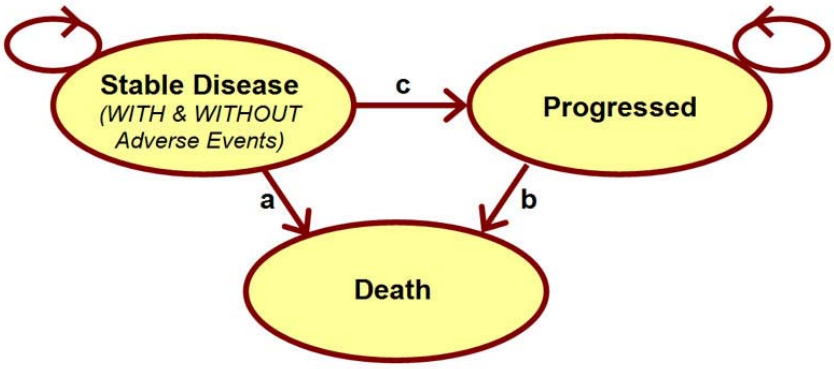
- Firstly, Novartis failed to convert the transition probabilities in their model to rates before applying the hazard rate multiplier. When transition probabilities are small this makes very little difference. However in the Novartis model these probabilities are relatively high and this is significant. The correct approach is to first convert each relevant transition probability (TP) in the everolimus arm to a rate using the following formula: -(ln (1-TP)). This rate can then be multiplied by the mortality hazard ratio to generate a new rate (NR). The calculated new rate can then be converted back to the revised transition probability using the formula: 1-exp(-NR)). This new transition probability can then be applied to the BSC only arm. When this conversion is performed correctly the overall effect is to raise the base case ICER from £51,613 to £53,479 per QALY (with PAS applied) and from £61,330 to £63,967 per QALY (without PAS applied)

- Secondly, in applying the mortality hazard ratio, Novartis failed to account for the incremental mortality in the BSC arm caused by the higher level of progression in this arm. This structural error, which is described in more detail below, leads to a serious over-estimate for mortality in the BSC only arm of the model. When we corrected for this error, in addition to correcting the rate conversion error described above, we found that the base case ICER increased further from a value of £53,479 to £64,988 per QALY (with PAS applied) and from £63,967 to £75,599 per QALY (without PAS applied)

Explanation of structural error in implementation of mortality hazard ratio in model

1. In both everolimus and BSC only arms of the model, the transition probability from progressed state to death (represented by arrow b in Figure 8) is much higher than from stable disease to death (arrow a in Figure 8).

Figure 8: Key Transitions in the Novartis Model ***(simplified representation of model as outlined in Section 5.2.2.1 above)***



2. Incremental overall survival of everolimus versus BSC only in the model is determined by two major factors:

    i) The relative values for transition probabilities between the two modelled arms of death from both stable and progressed states (arrows a and b in Figure 8).

    ii) The relative transition probabilities between arms for progression in the model (represented by arrow c in Figure 8). A higher rate of progression will incur a greater probability of death since the probability of death from progression is much higher relative to the probability of death from stable state.

3. In their model, Novartis use the reciprocal of the mortality hazard ratio of everolimus versus BSC only treatment (i.e. the mortality hazard ratio for BSC only versus everolimus) calculated using the IPCW method (this has a value of 1.818). This value has been applied as a multiplier to the transition probabilities in the everolimus arm model from stable and progressed states to death (arrows a and b in Figure 8) to derive the corresponding transition probabilities for the BSC only arm of the model.

4. However, because the rate of progression in the BSC only arm of the model is higher than for the everolimus arm, the effective mortality rate between the arms in the model is on average much greater than that calculated using IPCW. This is because of the additional cause of incremental death described in 2ii above. The mortality hazard ratios implied by the Novartis base case model are shown in Table 18 below.

Table 18: State Occupancies, aggregated transition probabilities and rates between arms of the model and the effective mortality hazard ratio implied by the Novartis base case model at each cycle.

	Everolimus Arm				BSC only arm				Hazard Ratio	
Cycle	Prop. Pop. Alive	Prop. Pop. Dead	Aggr.* Trans Prob.	Rate per cycle	Prop. Pop. Alive	Prop. Pop. Dead	Aggr.* Trans Prob.	Rate per cycle	BSC v. Ever	Ever. v. BSC
0	1.0000	0.0000			1.0000	0.0000				
1	0.9780	0.0220	0.0220	0.0222	0.9604	0.0396	0.0396	0.0404	**1.818**	***0.55***
2	0.8972	0.1028	0.0827	0.0863	0.7267	0.2733	0.2433	0.2788	**3.231**	***0.31***
3	0.7869	0.2131	0.1229	0.1312	0.4975	0.5025	0.3154	0.3790	**2.889**	***0.35***
4	0.6739	0.3261	0.1436	0.1550	0.3564	0.6436	0.2835	0.3334	**2.150**	***0.47***
5	0.5928	0.4072	0.1203	0.1281	0.2801	0.7199	0.2141	0.2410	**1.881**	***0.53***
6	0.4101	0.5899	0.3083	0.3686	0.1053	0.8947	0.6241	0.9784	**2.654**	***0.38***
7	0.3041	0.6959	0.2585	0.2991	0.0370	0.9630	0.6490	1.0470	**3.500**	***0.29***
8	0.2255	0.7745	0.2583	0.2988	0.0129	0.9871	0.6506	1.0514	**3.519**	***0.28***
9	0.1673	0.8327	0.2581	0.2985	0.0045	0.9955	0.6518	1.0549	**3.534**	***0.28***
10	0.1242	0.8758	0.2579	0.2983	0.0016	0.9984	0.6527	1.0576	**3.546**	***0.28***
11	0.0922	0.9078	0.2578	0.2981	0.0005	0.9995	0.6535	1.0598	**3.555**	***0.28***
12	0.0684	0.9316	0.2577	0.2980	0.0002	0.9998	0.6541	1.0615	**3.562**	***0.28***
13	0.0508	0.9492	0.2576	0.2979	0.0001	0.9999	0.6546	1.0629	**3.568**	***0.28***
14	0.0377	0.9623	0.2576	0.2979	0.0000	1.0000	0.6549	1.0640	**3.572**	***0.28***
15	0.0280	0.9720	0.2576	0.2978	0.0000	1.0000	0.6552	1.0649	**3.576**	***0.28***
16	0.0208	0.9792	0.2575	0.2978	0.0000	1.0000	0.6555	1.0657	**3.579**	***0.28***
17	0.0154	0.9846	0.2575	0.2978	0.0000	1.0000	0.6557	1.0662	**3.581**	***0.28***
18	0.0115	0.9885	0.2575	0.2977	0.0000	1.0000	0.6559	1.0667	**3.583**	***0.28***

** Aggregated transition probability represents the effective probability of death from all states in the model at each cycle.*

5. The mortality hazard ratio calculated using IPCW is an estimate for the patient population as whole. Given the way in which this has been applied, the model seriously over estimates the mortality hazard ratio for BSC versus everolimus over the time horizon which was estimated using the IPCW method to be 1.818 (i.e. seriously under estimates the overall survival hazard ratio everolimus versus BSC only treatment – calculated using IPCW as 0.55).

5.2.3.4. Drug costs

No issues were identified concerning how drug costs were dealt with in the model. The nature of the proposed PAS was clear.

5.2.3.5. Disease management costs

Again there were no major issues concerning the application of disease management costs in the model which were accurately translated from their source, a prior MTA report for NICE on drugs for the treatment of renal cell cancer.[29]

5.2.3.6. Adverse event costs

In contrast to a tendency to underplay the frequency of adverse events associated with everolimus, the additional costs, approximately £500 per patient suffering an adverse event per cycle, associated with managing those adverse events seem reasonable.

A potential weakness of the analysis is the way in which it models adverse events. Patients experiencing adverse events in the model are assumed in the model to experience a utility decrement for only one cycle after which their utility is assumed to return to a level equivalent to the state without adverse events. Costs for treatment are however assumed to remain. It should be noted that this means that only one episode of adverse events for each patient is supported in the model. Despite these limiting assumptions, the sensitivity analysis conducted on the model suggests that overall impact on model outputs is likely to be limited (see Section 5.3.1.2 and Section 6.2.3 below).

5.2.3.7. Health related quality of life

Although clearly outside the control of the manufacturer, the lack of any robust data on the utilities associated with health states experienced during renal cell cancer is a limitation, which has affected previous assessments of the cost-effectiveness of new treatments in this disease.[29] There has been insufficient time for calls for research on this topic to be implemented, but the further difficulties in this STA re-emphasise the need for robust data. The specific concern is that the difference in utility between stable disease and progressive disease is small, 0.76 vs 0.68, which may understate the benefit demonstrated for everolimus in delaying progression. This may be compounded to a degree by the possibility that stable disease, the initial model state, may not be equivalent in terms of utility between first line treatment (the situation in the prior appraisal from which the utility value was taken) and last line treatment (the situation operating in this STA) .

5.2.4. Assessment of uncertainty

From an analysis of the outputs it is clear that the main source of uncertainty in the model is due to the mortality hazard ratio used to derive the transition probabilities for mortality between the model arms. This is revealed most clearly in the results from the one-way sensitivity analysis which show this to be a key model driver whilst other changes to other model parameters have relative little impact.

Given that the mortality hazard ratio is such a critical component in the model it is important to be clear about the appropriateness of the IPCW method which has been used to derive its value. It should also be noted that the IPCW method generated a wide confidence interval from 0.31 to 0.97. These limits are explored in the one-way sensitivity analysis and demonstrate the high range of ICER output associated with this source of uncertainty.

5.3. Results included in manufacturer's submission

Here we present a summary of model outputs as given in the Novartis submission (see Section 7.3 p.136-145 of Novartis report for further details). The results in this section are as they appear in the Novartis submission despite the fact that, in our view, there are significant structural errors in the Novartis model that cast doubt on these values. A presentation of outputs from a corrected version of the model is provided in Section 6.2.

5.3.1. Deterministic Results

5.3.1.1. Base Case

Base case outputs derived from the model are shown below. Table 19 shows these summary outputs for the scenarios when PAS is applied and without PAS.

Table 19 : Base case results presented for the Novartis Cost-Effectiveness model

Base Case Cost-Effectiveness results per patient :WITH PAS APPLIED	**Everolimus plus BSC***	**BSC alone**	**Incremental**
Total costs £	25,222	9,517	15,704
QALYs	0.607	0.302	0.304
Incremental cost per QALY gained £			**51,613**
Base Case Cost-Effectiveness results per patient :WITHOUT PAS APPLIED	**Everolimus plus BSC***	**BSC alone**	**Incremental**
Total costs £	28,178	9,517	18,661
QALYs	0.607	0.302	0.304
Incremental cost per QALY gained £			**61,330**

Source: Adapted from Novartis Submission. Tables 7.11 and 7.12, p.137

In addition to the base case outputs which result when the IPCW method is applied to correct for cross-over bias, we requested Novartis to provide outputs for the model when intention to treat data are used in the model. These outputs are shown in Table 20.

Table 20 : Base case output based on ITT data analysis using data from the February 2008 cut-off (without application of IPCW)

Base Case Cost-Effectiveness results per patient :WITH PAS APPLIED	**Everolimus plus BSC***	**BSC alone**	**Incremental**
Total costs £	25,222	14,758	10,463
QALYs	0.607	0.492	0.115
Incremental cost per QALY gained £			**91,256**
Base Case Cost-Effectiveness results per patient :WITHOUT PAS APPLIED	**Everolimus plus BSC***	**BSC alone**	**Incremental**
Total costs £	27,328	14,758	12,570
QALYs	0.607	0.492	0.115
Incremental cost per QALY gained £			**109,627**

5.3.1.2. One-way sensitivity analysis

A range of one-way deterministic sensitivity analysis are provided in the Novartis submission and reproduced in Table 21. These show the incremental values for both scenarios of drug costing with PAS and without PAS.

Table 21 : One-way sensitivity outputs presented by Novartis

	Without PAS			**With PAS**	
Variable	Inc. cost £*	Inc. QALY	ICER everolimus v. BSC	Inc. cost	ICER everolimus v. BSC
Base Case	**18,661**	**0.304**	**61,330**	**15,704**	**51,613**
Lower 95% CI for mortality HR = 0.31	21,008	0.408	51,375	18,052	44,298
Upper 95% CI for mortality HR = 0.97	15,097	0.165	92,074	12,141	73,605
Lower 95% CI for SD utility = 0.70	18,661	0.290	64,376	15,704	54,177
Upper 95% CI for SD utility = 0.81	18,661	0.316	59,003	15,704	49,655
Lower 95% CI for PD utility = 0.61	18,661	0.300	62,275	15,704	52,409
Upper 95% CI for PD utility = 0.76	18,661	0.310	60,284	15,704	50,733
Everolimus DI = 100%	20,179	0.304	66,321	16,959	55,736
Everolimus DI = 80%	16,475	0.304	54,148	13,899	45,680
Utility of SD with AE state for BSC = 0.76, and 0.68 for everolimus	18,661	0.300	62,225	15,704	52,366
Cost of PD health state (inc. post trial costs) +50% per cycle = £4,605	19,319	0.304	63,493	16,363	53,777
Cost of PD health state (inc. post trial costs) -50% per cycle = £1,535	18,003	0.304	59,167	15,046	49,451
Progressive disease drug and non-drug. DI=100%. Cost = £2,997	18,904	0.304	62,130	15,948	52,414
Progressive disease drug and non-drug.	18,417	0.304	60,529	15,461	50,813

DI=60%. Cost = £1,861					

Note: the sensitivity analysis for assuming SD with AE utility for BSC = 0.76, costs of GP visits and tests for SD, and costs of CT scan for SD, cost of AEs for everolimus and BSC (all +/-50%), zero cost for end of life palliative care, and 0% discount rate have not been included in the table above due to negligible impact on ICERs.

† Dose intensity adjustment of 91.8% has been incorporated

**Costs have been rounded to the nearest £1*

NB: Results are generated from the model so there are some rounding differences in the table

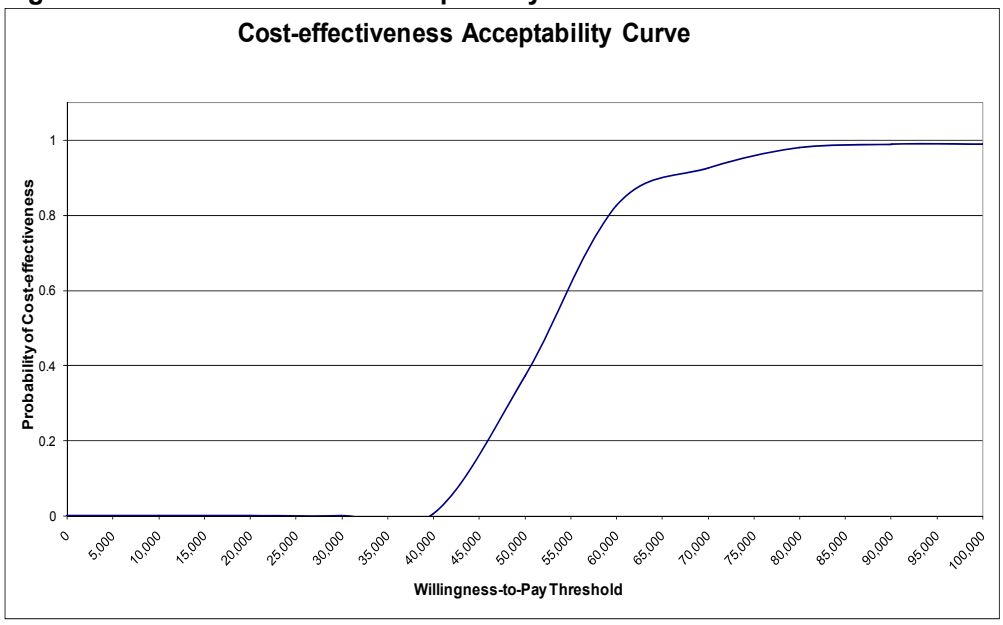
Source: Novartis Submission. Tables 7.14, p.141

5.3.2. Probabilistic Results

In addition, to the one-way sensitivity analysis, Novartis present a probabilistic sensitivity analysis (PSA) based on their model. In the PSA, parameter uncertainty is represented by using probabilistic distributions rather than fixed values for model input parameters. Monte Carlo simulation is then used to generate a large number of model outputs based on these randomly input parameters sampled from these probabilistic distributions.

The cost-effectiveness acceptability curve (CEAC) derived from the PSA conducted by Novartis is shown in Figure 9.

Figure 9 : Cost-effectiveness Acceptability Curve from Model



Source: Novartis submission. Figure 7.3, p.145

5.4. Comment on validity of results presented with reference to methodology used

In general, the modelling methods, construction and parameterisation of the model are well presented and explained in the Novartis submission. We welcomed especially the extensive

explanation offered for the rationale and use of the IPCW statistical approach, central to the cost-effectiveness analysis, which is used to correct for cross-over bias in the RECORD-1 trial data which is the primary data source for the model.

Having investigated the use of the IPCW method in the economic analysis, there are several questions we would raise about its adoption for the trial data in this study and these are discussed in Section 5.2.3.3 above. Although in general we are satisfied that Novartis are justified in applying statistical methods to correct for cross-over bias in the trial and that IPCW is a valid option, we are less convinced that IPCW represents the best method in preference to other techniques such as the Rank Preserving Structural Failure Time (RPSFT) approach. Specifically we would question some of the assumptions underlying the IPCW method and disagree with some of the rationale provided by Novartis for the use of IPCW in preference to RPSFT. The main limitation underlying the use of IPCW is its assumption of no unmeasured confounders in the placebo arm of the trial which would invalidate the approach.

The main problem identified with the cost-effectiveness analysis presented in the Novartis submission is in the implementation of the statistical outputs of the IPCW in the economic model. Here we identified two important errors of implementation of the mortality hazard ratio calculated using IPCW which significantly bias the model outputs in favour of everolimus. These errors are outlined in detail in Section 5.2.3.3 above.

In order to re-assess cost-effectiveness, we re-ran the model with corrections made to the two errors identified. These results are presented in Section 6.2.

5.5. Summary of uncertainties and issues

- Novartis have used a simple state-transition Markov model
- Quality of life data have been estimated from second source data and are not based on EQ-5D sources
- The statistical approach used to adjust for cross-over bias in the trial data. Whilst this is a recognised approach several questions have been raised about its underlying assumptions and use in preference to other approaches.
- Novartis incorrectly applied the mortality hazard ratio in their model resulting in a serious bias in favour of everolimus. We have attempted to re-calibrate the mode to correct for the errors and present the corrected results in Section 6.2 below.

6. Additional work undertaken by the ERG

6.1. Clinical effectiveness

No additional work was undertaken on the clinical effectiveness evidence beyond a detailed appraisal of the manufacturer submission and the main trial comprising this evidence. This included scrutiny of the full trial report.

6.2. Cost Effectiveness Analysis

6.2.1. Corrections for errors in Novartis Model

In order to adjust for identified errors we made the following changes to the Novartis base case model:

1. We corrected for the error in the application of the mortality hazard rate multiplier by first converting transition probabilities to rates before multiplying by the respective hazard ratio and then converting these new rates back to transition probabilities.

2. In order correct for structural error in the model relating to the application of the hazard rate multiplier (described in Section 5.2.3.3.4 above) we applied a time dependent mortality hazard multiplier in each cycle such that a constant hazard ratio for overall survival was maintained throughout the time horizon of the model. The values for these multiplier values are shown in italics in Table 22 below.

Table 22 : Corrected hazard multiplier for model and its effects on mortality transition probabilities, rates and state occupancies (alive versus dead) in each arm.

		Everolimus Arm				BSC only arm				Hazard Ratio	
Cycle	*Hazard Multplr*	Prop. Pop. Alive	Prop. Pop. Dead	Aggr. Trans Prob.	Rate per cycle	Prop. Pop. Alive	Prop. Pop. Dead	Aggr. Trans Prob.	Rate per cycle	BSC v. Ever	Ever. v. BSC
0		1.0000	0.0000			1.0000	0.0000				
1	***1.818***	0.9780	0.0220	0.0220	0.0222	0.9604	0.0396	0.0396	0.0404	1.82	0.55
2	***0.991***	0.8972	0.1028	0.0827	0.0863	0.8210	0.1790	0.1452	0.1569	1.82	0.55
3	***1.100***	0.7869	0.2131	0.1229	0.1312	0.6468	0.3532	0.2121	0.2384	1.82	0.55
4	***1.450***	0.6739	0.3261	0.1436	0.1550	0.4879	0.5121	0.2456	0.2819	1.82	0.55
5	***1.738***	0.5928	0.4072	0.1203	0.1281	0.3865	0.6135	0.2078	0.2330	1.82	0.55
6	***1.223***	0.4101	0.5899	0.3083	0.3686	0.1978	0.8022	0.4884	0.6702	1.82	0.55
7	***0.953***	0.3041	0.6959	0.2585	0.2991	0.1148	0.8852	0.4195	0.5438	1.82	0.55
8	***0.940***	0.2255	0.7745	0.2583	0.2988	0.0667	0.9333	0.4192	0.5434	1.82	0.55
9	***0.932***	0.1673	0.8327	0.2581	0.2985	0.0387	0.9613	0.4188	0.5427	1.82	0.55
10	***0.927***	0.1242	0.8758	0.2579	0.2983	0.0225	0.9775	0.4184	0.5420	1.82	0.55
11	***0.925***	0.0922	0.9078	0.2578	0.2981	0.0131	0.9869	0.4185	0.5421	1.82	0.55
12	***0.924***	0.0684	0.9316	0.2577	0.2980	0.0076	0.9924	0.4185	0.5422	1.82	0.55
13	***0.923***	0.0508	0.9492	0.2576	0.2979	0.0044	0.9956	0.4184	0.5420	1.82	0.55
14	***0.922***	0.0377	0.9623	0.2576	0.2979	0.0026	0.9974	0.4182	0.5416	1.82	0.55
15	***0.922***	0.0280	0.9720	0.2576	0.2978	0.0015	0.9985	0.4183	0.5418	1.82	0.55

16	***0.922***	0.0208	0.9792	0.2575	0.2978	0.0009	0.9991	0.4183	0.5418	1.82	0.55
17	***0.922***	0.0154	0.9846	0.2575	0.2978	0.0005	0.9995	0.4183	0.5419	1.82	0.55
18	***0.922***	0.0115	0.9885	0.2575	0.2977	0.0003	0.9997	0.4184	0.5419	1.82	0.55

3. Finally, in accord with normal practice, we applied discounting to costs and benefits (at 3.5%) from the first cycle of the model rather than applying discounting after the first year only as per the Novartis base case (the effect of this change is relatively small).

6.2.2. Corrected Base case outputs

With these changes made to the parameters of the model the following base case outputs were obtained (shown in Table 23).

Table 23 : Base case results for corrected Novartis cost-effectiveness model

Cost-Effectiveness results per patient	**Undiscounted**			**3.5% discounting (costs and benefits)**		
WITH PAS APPLIED	Everolimus plus BSC*	BSC alone	Incremental	Everolimus plus BSC*	BSC alone	Incremental
Total costs £	25,335	12,341	12,994	24,701	12,091	12,610
QALYs	0.609	0.408	0.200	0.595	0.402	0.193
Incremental cost per QALY gained £			**64,826**			**65,231**
WITHOUT PAS APPLIED	Everolimus plus BSC*	BSC alone	Incremental	Everolimus plus BSC*	BSC alone	Incremental
Total costs £	27,441	12,341	15,101	26,796	12,091	14,705
QALYs	0.609	0.408	0.200	0.595	0.402	0.193
Incremental cost per QALY gained £			**75,335**			**76,070**

6.2.3. One-way sensitivity analysis

We re-ran the one-way sensitivity analyses presented by Novartis in their submission with our corrected model parameters. The results are shown in Table 24.

Table 24 : Recalculation of one-way sensitivities based on corrected Novartis model.

	Without PAS			With PAS	
Variable	Inc. cost £*	Inc. QALY	ICER everolimus v. BSC	Inc. cost	ICER everolimus v. BSC
Base Case	**14,705**	**0.193**	**76,070**	**12,610**	**65,231**
Lower 95% CI for mortality HR = 0.31	17,434	0.307	56,877	15,338	50,041
Upper 95% CI for mortality HR = 0.97	10,434	0.032	329,605	8,339	263,419
Lower 95% CI for SD utility = 0.70	14,705	0.180	81,733	12,610	70,086

Upper 95% CI for SD utility = 0.81	14,705	0.204	71,918	12,610	61,670
Lower 95% CI for PD utility = 0.61	14,705	0.196	74,074	12,610	63,519
Upper 95% CI for PD utility = 0.76	14,705	0.187	78,486	12,610	67,303
Everolimus DI = 100%	16,097	0.193	83,404	13,818	71,596
Everolimus DI = 80%	12,645	0.193	65,516	10,822	56,070
Utility of SD with AE state for BSC = 0.76, and 0.68 for everolimus	14,705	0.189	77,820	12,610	66,732
Cost of PD health state (inc. post trial costs) +50% per cycle = £4,605	13,940	0.193	72,229	11,848	61,390
Cost of PD health state (inc. post trial costs) -50% per cycle = £1,535	15,422	0.193	79,909	13,331	69,070
Progressive disease drug and non-drug. DI=100%. Cost = £2,997	14,407	0.193	74,648	12,315	63,809
Progressive disease drug and non-drug. DI=60%. Cost = £1,861	14,956	0.193	77,490	12,864	66,651

† Dose intensity adjustment of 91.8% has been incorporated

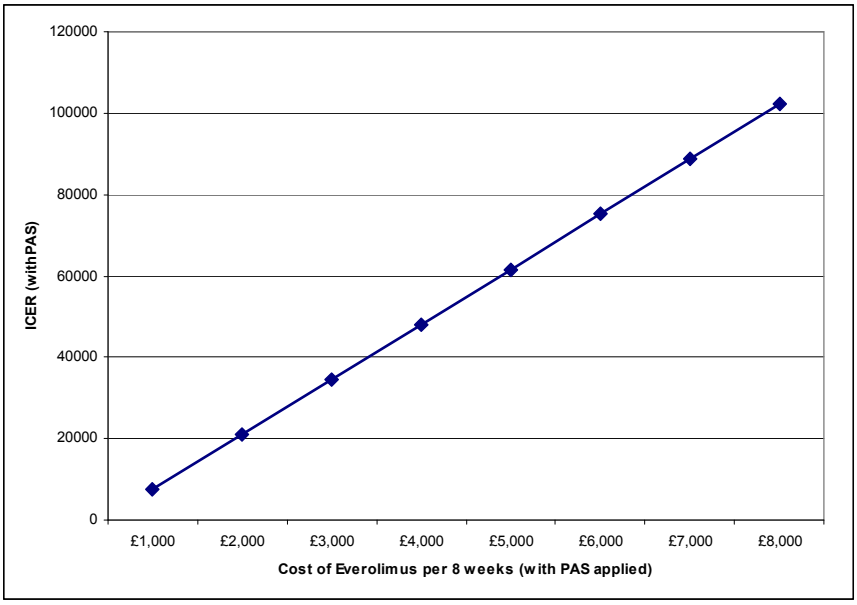
**Costs have been rounded to the nearest £1*

NB: Results are generated from the model so there are some rounding differences in the table

6.2.3.1. One-way sensitivity analysis of drug cost

Another area of interest was the relationship between the price of everolimus and the model ICER. In order to explore this we conducted a series of one way analyses looking at the impact on the model ICER for different levels of drug cost for everolimus in our corrected version of the model. The results of these analyses are presented in Figure 10 and suggest a fairly linear relationship between the drug price of everolimus (Afinitor©) and the ICER ouput by the model. For the model to output an ICER of lower than £30,000 per QALY a price reduction from the base case level of £5267 to approximately £2663 per eight weeks treatment would be necessary. To achieve an ICER output of lower than £20,000 the price would need to be reduced to £1924 per eight weeks of treatment.

Figure 10 : Threshold analysis showing relationship between cost of everolimus (Afinitor©) per 8 week cycle and base case ICER.



6.2.4. Component Analysis of incremental utility

Within the Novartis model we identified three principle sources which drive the incremental benefit derived in the everolimus treatment arm. These are listed below:

1. The utility gain due to the improved *overall survival* in the everolimus arm. This gain is generated by the mortality hazard ratio between the model arms which favours survival in the everolimus arm.

2. The utility gain due to the utility difference between stable and progressed states. The lower levels of *progression* in the everolimus treatment arm relative to the BSC only arm lead to a greater proportion of the alive population in the everolimus arm in stable state (rather than progressed) relative to BSC only.

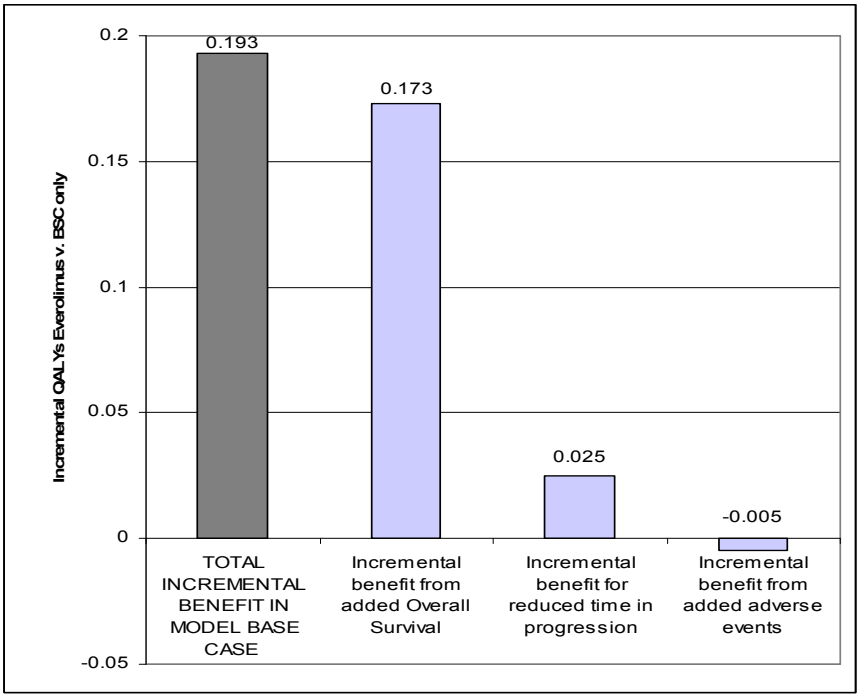
3. The utility decrement due to increased adverse events associated with the Everolimus.

In order to estimate the relative proportion of benefits associated with each of these three sources we carried out a simple component analysis as follows. Firstly we re-calibrated the corrected base case model (as described in Section 6.2.1 above) such that the mortality hazard for both model arms was the same (hazard ratio = 1). The resulting reduction in incremental benefit was then assumed to represent that component of benefit attributable to the reduced risk of death in the Everolimus arm. The remaining incremental benefit was then assumed to represent the combined effect of benefit due to reduced progression (the second

of the sources outlined above) and the utility decrement due to the increased adverse events associated with everolimus (item three above). In order to determine the relative contribution of each of these we set the utility of the stable state with adverse events to the same value as for the stable without adverse events, the resulting increase in incremental QALYs in the model was then assumed to be an estimate for the reduction in incremental benefit due to increased adverse events in the everolimus arm. The residual incremental benefit output by the model was then assumed to due to the reduced time spent in progression versus stable states for the everolimus cohort in the model.

The relative proportions of the three identified sources of incremental QALY are shown below in Figure 11 . This demonstrates the over-riding contribution of overall survival in driving the incremental benefit output from the model.

Figure 11 : Relative contributions of separate sources to incremental benefit in corrected base case model outputs.



7. Discussion

7.1. Summary of clinical effectiveness issues

A systematic review of the effectiveness of everolimus was submitted. It focused on the RECORD-1 RCT. This was a placebo-controlled randomised controlled trial of 416 participants. 277 were randomised to 10mg everolimus once a day, in addition to best supportive care (BSC), and 139 to an identical placebo tablet in addition to BSC. The manufacturer submission summarised the identified benefits as:

67% reduction in the risk of disease progression or death (HR=0.33, 95% CI 0.25-0.43), equating to a mean progression free survival of 4.90 months for everolimus plus BSC, versus 1.87 months for placebo plus BSC, a difference which was highly statistically significant ($p<0.001$)

A non-statistically significant treatment related difference in overall survival (HR=0.82; 95%CI 0.57-1.17; p=0.137), but a result which was highly likely to have been influenced by a very high level of patients in the placebo arm swapping to everolimus treatment after progression had been detected.

Improved rate of partial or stable tumour response in 69% of patients with everolimus against 32% in the placebo arm.

Stable quality of life/patient reported outcomes in everolimus compared to placebo.

The ERG appraisal indicates that the evidence identified is relevant and complete. The interpretation is reasonable, although the ERG would place greater emphasis on the much higher frequency of adverse events, of a severity likely to have an impact on patient quality of life, in the everolimus arm of the trial relative to the placebo arm. The trial data available indicate that patient health related quality of life was identical in the early stage of the trial, despite there being response to treatment in the everolimus arm.

Concerning major issues, although the overall survival results from the RECORD-1 RCT are clear and uncontroversial indicating an improvement which could have been accounted for by chance alone, the adjustment of the results for switching of placebo patients to everolimus after progression is an area of genuine academic debate, particularly concerning the most appropriate analytical method.

7.2. Summary of cost effectiveness issues

The ERG confirmed that there was no existing estimation of cost-effectiveness, and that it was appropriate for the manufacturer submission to focus on a de novo cost-effectiveness model.

This was a Markov state-transition cost-utility model implemented in Microsoft Excel© which compared treatment with everolimus and BSC with BSC alone, mirroring the question addressed in the RECORD-1 RCT. The four states were stable disease, stable disease with adverse events, progressive disease and death, and the outputs expressed as cost per QALY. The base- case incremental cost-effectiveness ratio was £61,330; this estimate was somewhat reduced when a patient access scheme was introduced, but this estimate was still substantially greater than £30,000.

The ERG appraisal indicated that the model was generally well presented and reported. A number of important issues were however identified:

Model errors. The manufacturer incorrectly applied the mortality hazard ratio in their model resulting in a serious bias in favour of everolimus. We attempted to re-calibrate the model to correct for this and the result was an ICER of £76,070 (this is without the PAS and includes discounting during the first year of the model, omitted from the base-case in the manufacturer submission).

The statistical approach (IPCW) used to adjust for cross-over bias in the trial data. Whilst this is a recognised approach several questions have been raised about its underlying assumptions and use in preference to other approaches. Use of some sort of adjusted analysis was generally felt reasonable by the ERG and its advisers, but the impact of using it needs to be appreciated. The ICER using the unadjusted overall survival estimate from RECORD-1 produces was £109,627 (again without PAS and not incorporating correction for the model errors above)

Quality of life data have been estimated from second source data and are not based on EQ-5D sources. The resulting lack of confidence in the utility parameters in models dealing with advanced and metastatic renal cancer has been commented on in NICE appraisals before.

7.3. Key issues

The manufacturer submission offers a clear presentation of its case on the effectiveness and cost-effectiveness of everolimus for advanced renal cell carcinoma whose disease has

progressed on or after treatment with VEGF-targeted therapy. The case on clinical effectiveness is generally clear but judgements need to be made on the effect that the model errors, approach to adjustment to switching and uncertainty about utilities have on the proffered estimate of cost-effectiveness.

A further issue, beyond the direct scope of this report is the impact end-of life considerations, although it seems likely that these do apply.

7.4. Implications for research

Concerning the estimates of cost-effectiveness in renal cell cancer, the observations in this ERG provide strong further support for research collecting rigorous estimates of utilities associated with the main health states likely to be experienced by patients with renal cell cancer. This specific appraisal highlights the possibility that the utility values associated with stable disease/progressive disease may vary depending on the number of additional further potentially effective lines of further treatment available.

Switching in clinical trials for new cancer treatments as last line, is a common and recurring problem in trial analysis. This STA has considered a number of statistical approaches to adjustment. However the issues highlighted have general applicability to other topics where switching from placebo to active treatment occurs when the primary end-point has been reached, and this may be further enhanced by methodological research. Such research could, for example, focus on the appropriateness of alternative approaches in this context and towards the development of coherent guidelines for both the application of these statistical methods in HTA more generally as well as their integration in cost-effectiveness modelling.

Further investigation of the role of everolimus earlier in the management of renal cell cancer appear to be in progress and would not currently seem to be a priority for further research.

8. References

1 National Institute for Health and Clinical Excellence. Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma: Final Scope. 2009.

2 Cheville JC, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. American Journal of Surgical Pathology 200327(5):612-624.

3 National Institute for Health and Clinical Excellence. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. 2009. Report No.: NICE technology appraisal guidance 169.

4 National Institute for Health and Clinical Excellence. 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. 2009. Report No.: NICE technology appraisal guidance 178.

5 Novartis Pharmaceuticals. Everolimus Summary of Product Characteristics (SPC) [draft]. 2009.
Ref Type: Generic

6 National Institute for Health and Clinical Excellence (NICE). Renal cell carcinoma (second line metastatic) - everolimus. Last accessed 17th July 2009. http://guidance.nice.org.uk/TA/WaveCRS1/48.
Ref Type: Generic

7 Pfizer Limited. Sutent® Summary of Product Characteristics. 2009. http://emc.medicines.org.uk/medicine/18531/SPC/SUTENT+12.5mg%2c+25mg%2c+37.5mg+and+50mg+Hard+Capsules/.
Ref Type: Generic

8 National Institute for Health and Clinical Excellence (NICE). NICE technology appraisal guidance 169: Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. March 2009.
Ref Type: Generic

9 National Institute for Health and Clinical Excellence (NICE). NICE Technology Appraisal Guidance TA178: 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. August 2009.
Ref Type: Generic

10 Bayer plc. Nexavar® Summary of Product Characteristics. 2009. http://emc.medicines.org.uk/medicine/18520/SPC/Nexavar+200mg+film-coated+tablets/.
Ref Type: Generic

11 National Institute for Health and Clinical Excellence (NICE). NICE Technology Appraisal Guidance TA178: 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. August 2009.
Ref Type: Generic

12 Wyeth Pharmaceuticals. Torisel® Summary of Product Characteristics. 2009. http://emc.medicines.org.uk/medicine/21260/SPC/TORISEL+25+mg+ml+concentrate+and+diluent+for+solution+for+infusion/.
Ref Type: Generic

13 National Institute for Health and Clinical Excellence (NICE). NICE Technology Appraisal Guidance TA178: 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. August 2009.
Ref Type: Generic

14 Roche Products Limited. Avastin® Summary of Product Characteristics. 2009. http://emc.medicines.org.uk/medicine/15748/SPC/Avastin+25mg+ml+concentrate+for+solution+for+infusion/.
Ref Type: Generic

15 National Institute for Health and Clinical Excellence (NICE). NICE Technology Appraisal Guidance TA178: 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. August 2009.
Ref Type: Generic

16 Nathan P, Wagstaff J, Porfiri E, Powles T, Eisen T. UK guidelines for the systemic treatment of renal cell carcinoma. British Journal of Hospital Medicine 200970(5):284-286.

17 Kay A, Hollaender N, Urbanowitz G. A randomized, double-blind, placebo-controlled, multicenter phase III study to compare the safety and efficacy of RAD001 plus Best Supportive Care (BSC) versus BSC plus Placebo in patients with metastatic carcinoma of the kidney which has progressed on VEGF receptor tyrosine kinase inhibitor therapy. 2009. Report No.: Clinical DevelopmentRAD001:RAD001C2240.

18 Tolley K, Strickson A. Afinitor [everolimus] for renal cell carcinoma: A systematic review. Final report. Tolley Health Economics Ltd for Novartis Pharmaceuticals; 2009.

19 Motzer RM, Escudier B, Oudard S, et.al. Efficacy of everolimus in advanced renal cell carcinoma:a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008;372(9637):449-56.

20 Escudier B, Ravaud A, Oudard S, et.al. Phase-3 randomised trial of everolimus (RAD001) vs Placebo in metastatic renal cell carcinoma. Annals of Oncology 19[(Supplement 8)]. 2008.
Ref Type: Abstract

21 Kay A, Motzer RJ, Figlin RA, et.al. Updated data from a phase III randomized trial of everolimus (RAD001) versus PBO in metastatic renal cell carcinoma (mRCC). 45th American Society of Clinical Oncology Meeting, Orlando, FL, USA, 29th May-2nd June, 2009 . 2009.
Ref Type: Abstract

22 Beaumont J, Cella D, Hutson TE, et.al. Patient-reported outcomes in a randomised trial of everolimus with metastatic renal cell carcinoma patients. Journal of Clinical Oncology 27[(supplement)]. 2009.
Ref Type: Abstract

23 Motzer RJ. RAD001 plus best supportive care (BSC) vs BSC plus placebo in patients with metastatic renal cell carcinoma (RCC), which has progressed on VEGFr-TKI therapy: results from a randomized, double-blind, multicenter Phase-3 study (Oral presentation). 44th American Society of Clinical Oncology Meeting, San Francisco, CA, USA, 14th-16th February, 2008 . 2009.
Ref Type: Abstract

24 Amato RJ, Jac J, Giessinger S, et.al. A phase 2 study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metastatic clear cell renal cell cancer. Cancer 1115[11], 2438-2446. 2009.
Ref Type: Abstract

25 Jac J, Amato RJ, Giessinger S, et.al. A phase II study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metatstatic renal cell carcinoma which has progressed on tyrosine kinase inhibition therapy. 44th American Society of Clinical Oncology Meeting, San Francisco, CA, USA, 14th-16th February, 2008 . 2009.
Ref Type: Abstract

26 Novartis. Everolimus Plus Best Supportive Care (BSC) Versus BSC Plus Placebo in Patients With Metastatic Carcinoma of the Kidney Which Has Progressed After Treatment With Sorafenib and/or Sunitinib. Clinical Trials gov 2009http://clinicaltrials.gov/ct2/show/NCT00410124

27 Guyatt G, Bassler D, Montori V. To what extent do trials stopped early benefit overestimate treatment effects? The Cochrane Library Supplement 2009 [Abstracts of the 17th Cochrane Colloquium: Singapore 11-14 October 2009]. 2009.
Ref Type: Abstract

28 Novartis Pharmaceuticals. Full Clinical Study Report - Addendum Report: A randomised, double-blind, placebo-controlled, multicentre phase III study to compare the safety and efficacy of RAD001 plus Best Supportive Care (BSC) versus BSC plus Placebo in patients with metastatic carcinoma of the kidney which has progressed on VEGF receptor tyrosine kinase inhibitor therapy.
Ref Type: Generic

29 Thompson-Coon J, et.al. Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma:
a systematic review and economic evaluation. 2009.

30 Doyle S., Lloyd A., Walker M. Health state utility scores in advanced non-small lung cancer. Lung Cancer 2008 Dec;62(3):374-80.

31 Curtis L. Unit costs of health and social care. 2008. Personal Social Services Research Unit (PSSRU), The University of Kent.
Ref Type: Generic

32 Department of Health. NHS Reference Costs 2007/08.
http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098945.
Ref Type: Generic

33 Department of Health. NHS Reference Costs 2007/08. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098945.
Ref Type: Generic

34 British National Formulary. BNF 57. March 2009. http://www.bnf.org/bnf/.
Ref Type: Generic

35 British National Formulary. BNF 57. March 2009. http://www.bnf.org/bnf/.
Ref Type: Generic

36 Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007 Dec 22;370(9605):2103-11.

37 British National Formulary. BNF 57. March 2009. http://www.bnf.org/bnf/.
Ref Type: Generic

38 British National Formulary. BNF 57. March 2009. http://www.bnf.org/bnf/.
Ref Type: Generic

39 British National Formulary. BNF 57. March 2009. http://www.bnf.org/bnf/.
Ref Type: Generic

40 Mickisch G, Escudier B, Gore M, Walzer S, Sabaté E, Nuijten M. Cost of Managing Side Effects in the Treatment of First-line Metastatic Renal Cell Carcinoma in Germany, France, and the UK: Bevacizumab + Interferon Alpha-2A Compared with Sunitinib.Poster 5110. 44th American Society of Clinical Oncology Meeting, San Francisco, CA, USA, 14th-16th February, 2008.
Ref Type: Generic

41 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™ Palliative Care, V.I.2009.
Ref Type: Generic

42 Ross DD, Alexander CS. Management of common symptoms in terminally ill patients: Part I. Fatigue, anorexia, cachexia, nausea and vomiting. Am Fam Physician 2001 Sep 1;64(5):807-14.

43 Yavuzsen T, Davis MP, Walsh D, LeGrand S, Lagman R. Systematic review of the treatment of cancer-associated anorexia and weight loss. J Clin Oncol 2005 Nov 20;23(33):8500-11.

44 British National Formulary. BNF 57. March 2009. http://www.bnf.org/bnf/.
Ref Type: Generic

45 Department of Health. NHS Reference Costs 2007/08. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098945.
Ref Type: Generic

46 Mickisch G, Escudier B, Gore M, Walzer S, Sabaté E, Nuijten M. Cost of Managing Side Effects in the Treatment of First-line Metastatic Renal Cell Carcinoma in Germany, France, and the UK: Bevacizumab + Interferon Alpha-2A Compared with Sunitinib.Poster 5110. 44th American Society of Clinical Oncology Meeting, San

Francisco, CA, USA, 14th-16th February, 2008.
Ref Type: Generic

47 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™ Palliative Care, V.I.2009.
Ref Type: Generic

48 Ripamonti C. Management of dyspnea in advanced cancer patients. Support Care Cancer 1999 Jul;7(4):233-43.

49 Thomas JR, von Gunten CF. Management of dyspnoea. J Support Oncol 2003 May;1(1):23-32.

50 British National Formulary. BNF 57. March 2009. http://www.bnf.org/bnf/.
Ref Type: Generic

51 Department of Health. NHS Reference Costs 2007/08. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098945.
Ref Type: Generic

52 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™ Prevention and Treatment of Cancer-Related Infections. V.I.2009.
Ref Type: Generic

53 Reusser P. Management of viral infections in immunocompromised cancer patients. Swiss Med Wkly 2002 Jul 13;132(27-28):374-8.

54 Vento S, Cainelli F. Infections in patients with cancer undergoing chemotherapy: aetiology, prevention, and treatment. Lancet Oncol 2003 Oct;4(10):595-604.

55 British National Formulary. BNF 57. March 2009. http://www.bnf.org/bnf/.
Ref Type: Generic

56 Department of Health. NHS Reference Costs 2007/08. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098945.
Ref Type: Generic

57 British National Formulary. BNF 57. March 2009. http://www.bnf.org/bnf/.
Ref Type: Generic

58 Department of Health. NHS Reference Costs 2007/08. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098945.
Ref Type: Generic

59 National Institute for Health and Clinical Excellence. Guide to the methods of technology appraisal. 2008. Report No.: N1618.

60 National Institute for Health and Clinical Excellence. Guide to the Methods of Technology Appraisal. 2008. London, NICE.
Ref Type: Generic

61 Drummond M, O'Brien B, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes. Oxford, UK: Oxford University Press; 1997.

62 Drummond M, O'Brien B, Stoddart G, Torrance G. Methods for the economic evaluation of health care programmes. 2nd ed. Oxford: Oxford University Press; 1997.

63 Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 2004;8(36).

64 Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006 Oct 14;368(9544):1329-38.

65 White IR. MRC Biostatistics Unit : Ian White. Medical Research Council Statistics Unit, Cambridge 2009 November 30Available from: URL: http://www.mrc-bsu.cam.ac.uk/People/IWhite.html

Appendix 1: Critique of manufacturer's systematic review

Heading	Subheading	Descriptor	Reported? (Y/N)	Page number
Title		Systematic review		
		Describe		
Introduction		The primary objective of the systematic review is specified. *What is the clinical efficacy, safety, and cost-effectiveness of everolimus plus BSC for the treatment of advanced renal cell carcinoma (aRCC) which has progressed following or on VEGF-targeted therapy (sunitinib, sorafenib, bevacizumab) compared to BSC alone? (Submission, p36; Section 6.1)*	Y	36
Methods	Searching	Appropriate sources have been identified and the specific databases used to locate studies are listed. The search was run in DATASTAR and the search strategy and terms used are listed in the submission (see p192-194). *Searches were carried out using DATASTAR. The computerized bibliographic databases that were searched were: MEDLINE 11950 to June 2009], and MEDLINE IN PROCESS; EMBASE [1980 to June 2009]; BIOSIS [1985 to June 2009].* *A search was carried out to identify relevant conference abstract for everolimus from*	Y	191

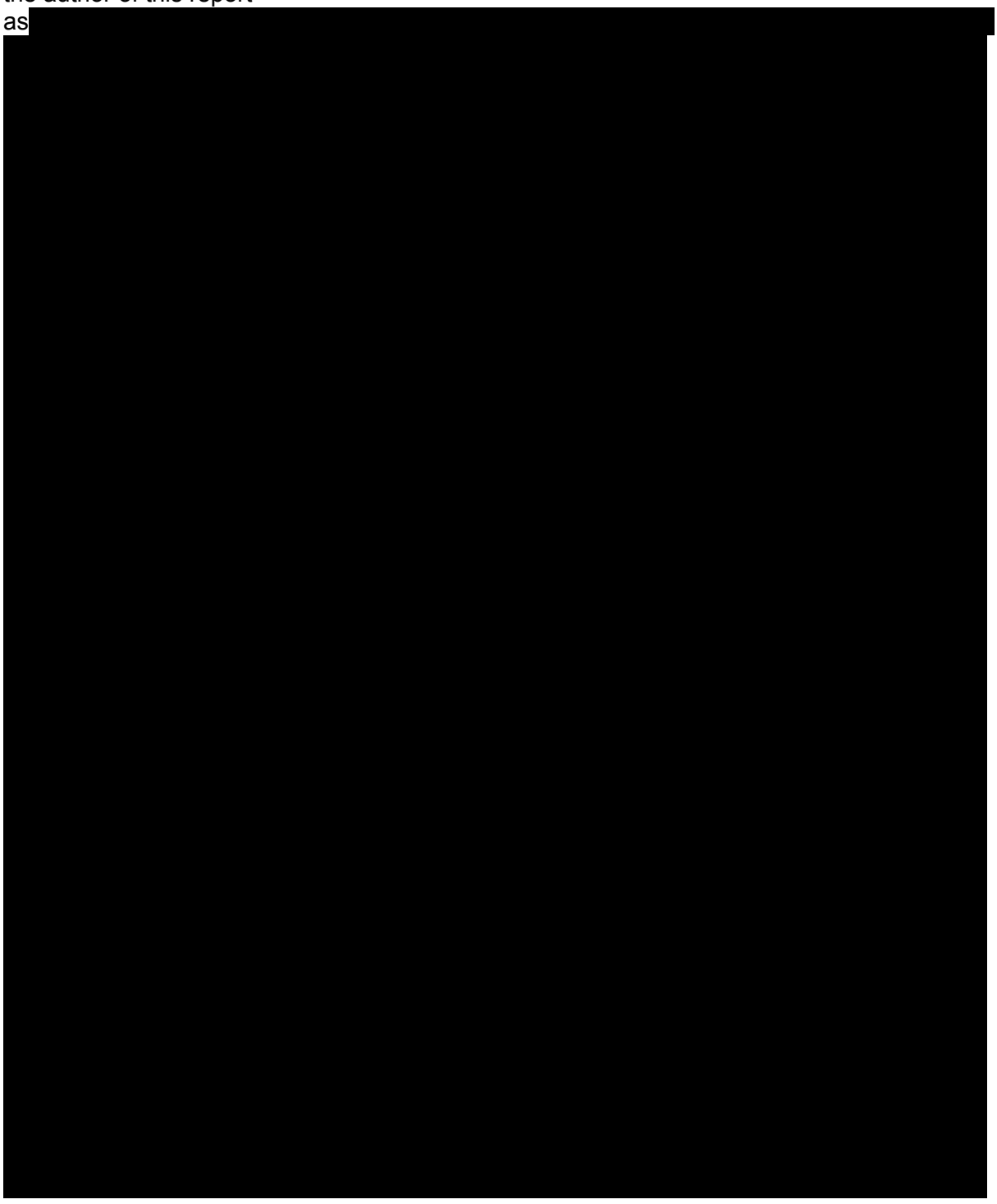
		selected cancer meetings between 2005 and 2009. The conference websites searched were ASCO (American Society of Clinical Oncology main conferences and satellite symposia from 2005–2009); ECCO (European CanCer Organisation 2006,2008); and, ESMO (European Society for Medical Oncology 2005,2007). *In addition to the sources above, the following sources were reviewed for additional published or unpublished data on the clinical effectiveness and safety of everolimus:* ▪ *HTA database (CRD) website* ▪ *Database of abstracts of review effects (DARE) (CRD website)* ▪ *NHS Economic Evaluation Database (NHS EED) (CRD website)* ▪ *Cochrane Database of Systematic Reviews (CDSR)* ▪ *Cochrane Register of Controlled Trials (CCTR)* ▪ *clinicaltrials.gov* ▪ *Current Controlled Trials (www.controlled-trials.com)* ▪ *NICE and NIHR Health Technology Assessment website* ▪ *Hand searching of selected primary selected study references (Submission, p191-194; Section 10.2.1)*		
Selection	The inclusion and exclusion criteria are specified and adequate – participants, interventions and comparisons, study outcomes, and study designs.*:* *Study population: consisting of patients with aRCC which has progressed following or on at least one prior VEGFr-TKI therapy* *Interventions of interest were everolimus plus BSC versus placebo plus BSC as the comparator* *Outcomes covered related to efficacy (overall survival, progression free survival, and tumour response rate), HRQoL/PRO, and safety (Grade III or IV adverse events (AEs) or high volume Grade I/II AEs)* *Study design for primary data extraction was RCTs. Outcomes of interest were to be extracted from systematic reviews of phase II or III RCTs and single RCTs (both parallel, cross-over designs, and studies comparing different doses or schedules of the drugs of interest0 that may either be blinded or unblinded and published (with additional unpublished materials from clinical study reports if available). The systematic review protocol also allowed for data from secondary level designs to be considered, which included single-arm trials and observational studies, and expanded*	Y	40

		access programmes, if in the opinion of the reviewers this source provided valuable supplementary evidence to the primary RCT evidence. *Language only English language publications and abstracts were considered.* *Specific exclusion criteria covered: pre-clinical and biological studies; animal studies; phase I clinical trials; editorials, opinions, commentaries, reviews (other than systematic reviews); non-English language studies; reports/abstracts where there were insufficient methodological details to judge study quality. (Submission, p40; Section 6.2.2)*		
	Validity assessment	Eligibility has been checked by two reviewers who independently scanned all titles and abstracts identified in the searches. The strategy used to resolve disagreements is specified and a log of excluded studies was kept. This is noted in Figure 6.1 (Submission, p45) but is not discussed in full; however, the systematic review report is referred to (see Submission, p195; Section 10.2.7). *The records identified in the electronic and other searches were assessed for inclusion by two reviewers from Tolley Health Economics Ltd. Each reviewer independently scanned all titles and abstracts identified in the searches to identify reports that might be relevant for clinical and economic review, using the inclusion/exclusion criteria, outcomes/endpoints, and study designs. Disagreements were resolved by discussion and consensus. (Submission, p; Section 10.2.7)*	Y	195
	Data abstraction	Data extraction follows accepted methods; i.e. a data extraction form not shown in the submission but is referred to; and two reviewers were used. No mention is made of whether the reviewers were blinded to authors, institutions or journals. *Data extraction for the review of clinical effectiveness was also carried out by two reviewers. Standardised data extraction forms (DEFs) were used. The DEF was based on that used in the PenTAG assessment of aRCC drugs, but with additional fields to obtain a greater depth of study information and data. Data was extracted by one reviewer and then checked by the second. (Submission, p195; Section 10.2.7)*	Y	195
	Study characteristics	The searches identified one RCT in the relevant patient population. A summary is given in Table 6.1 of the submission. (Submission, p39)	Y	39

	Quantitative data synthesis	No quantitative data synthesis carried out	N/A	N/A
Results	Trial flow	Trial flow is described adequately in the submission. A flow chart for the selection of RCTs and non-RCTs is given in Figure 6.1 (Submission, p45).	Y	45
	Study characteristics	The searches identified one RCT in the relevant patient population. A summary is given in Table 6.1 of the submission. (Submission, p39)	Y	39
	Quantitative data synthesis	No quantitative data synthesis carried out	N/A	N/A
Discussion		The discussion summarises key findings and this is a fair representation of the results in the RECORD-1 study. The issue of cross-over from placebo plus BSC to everolimus plus BSC using the IPCW method to correct for bias is discussed. The applicability of study results to clinical practice is covered in Section 6.9.2 of the manufacturer's submission.	Y	36–45 39 43 44

Appendix 2: IPCW critique – independent statistical opinion forwarded by manufacturer

The following report referred to as 'available on request' in the Novartis submission (Appendix 4. p.205) was forwarded by Novartis on request from the ERG. Novartis identify the author of this report as [redacted]



Appendix 3: IPCW critique – independent statistical opinion solicited by ERG

The following comments were received from Ian White, (Programme Leader, MRC Biostatistics Unit, Cambridge) a statistical expert in the field, who was consulted by the ERG with reference to the use of the IPCW method by Novartis.

The use of IPCW in the Everolimus submission to NICE

Context: analysis of overall survival

106 of the 139 placebo patients started everolimus after disease progression – they call this "cross-over", but to avoid confusion with cross-over trials, I'll call it "switching"

1. The unadjusted hazard ratio estimates the effect of everolimus from the start compared with a regime including a large probability of everolimus after progression. This is likely to under-estimate the benefit of everolimus compared with no everolimus. The applicant is therefore correct to want to adjust for treatment switching in the analysis of overall survival.

2. Given that this adjustment is to be made, it is essential that the cost of everolimus should also be adjusted for switching. That is, the cost of everolimus must be compared with a regime of no everolimus, not a regime of switching to everolimus after progression. It is likely that this has been done, but I have not checked.

3. IPCW rests on the crucial assumption of "no unmeasured confounders" in the placebo arm. It may be viewed as a sophisticated per-protocol analysis that attempts to remove the bias induced by censoring patients who switch to everolimus.

4. Per-protocol analysis implicitly assumes that patients who switch to everolimus can have their everolimus-free outcome validly represented by those who remained *not* on everolimus. This is highly implausible, since patients who switch have mostly progressed and hence have worse survival. IPCW includes covariates in the model predicting switching and therefore can make the implicit assumption more plausible. In particular, if "confirmed disease progression" has been included in the model predicting switching (as suggested on p112 l12), then patients who switched to everolimus have their everolimus-free outcome represented by those who remained

not on everolimus *after progression*. The latter assumption is more plausible, but it remains highly questionable, and should be carefully assessed on clinical grounds. Why do some patients not switch after progression? Is it just physician preference, in which case IPCW may be fine, or is it (for example) because they are too ill to tolerate everolimus?

5. The independent statistician's report commissioned by Novartis [Appendix 2 above] misses this point: it assumes the model predicting switching is OK if it includes all covariates in the PH model (i.e. allowing for all *observed* confounders), but the validity of the method requires there to be no *unobserved* confounders.

6. The alternative to IPCW is, as the Novartis application says, the Rank Preserving Structural Failure Time Model (RPSFTM). The arguments made by Novartis against this in the response to the ERG query [Appendix 4 below] are wrong: if you go back to the original RPSFTM (Robins & Tsiatis, 1991) then it doesn't require a parametric model (unlike Branson and Whitehead's version), and it can be used to estimate a hazard ratio (White et al, 1999).

7. The results of the IPCW analysis are plausible, but their significance may be exaggerated. The hazard ratio for overall survival is 0.82 (95% CI 0.57-1.17) by ITT and 0.55 (0.31-0.97) by IPCW. The decrease in the hazard ratio is explained by the large amount of switching. The gain of significance is not really justified, since it comes from moving towards a per-protocol analysis, while a RPSFTM is based on an ITT analysis.

8. Given that previous analyses of a related drug (sunitinib) used RPSFTM analysis, it would be useful to know whether the applicant performed an RPSFTM analysis as well as the IPCW analysis and chose not to report it, or only performed the IPCW analysis.

References:

Robins, J.M.; Tsiatis, A.A. (1991). "Correcting for non-compliance in randomized trials using rank preserving structural failure time models". *Comms in Statistics-Theory and Methods* 20(8): 2609–2631

Branson M, Whitehead J. (2002) Estimating a treatment effect in survival studies in which patients switch treatment. Stat Med.; 21(17):2449-63.

White IR., Babiker AG., Walker S. and Darbyshire JH. (1999) Randomization based methods for correcting for treatment changes: Examples from the Concorde trial. Statistics in medicine 1999; 18: 2617-2634.

Appendix 4 : Comments given by Novartis in response to ERG query about use of ICPW

The following text was received by the ERG from Novartis in response to the following query:

[redacted]

[redacted]

This report should be referenced as:

Pitt M, et.al. Everolimus for the second-line treatment of advanced and/or metastatic renal cell cancer: A systematic review and economic evaluation. 2009

National Institute for Health and Clinical Excellence
Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Everolimus for the second line treatment of metastatic renal cell carcinoma

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from *Peninsula Health Technology Assessment Group (PenTAG)* to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by **5pm 10th December 2009** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

3rd December 2009

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 11, section 1.2: *"…the ERG would place greater emphasis on the much higher frequency of adverse events (AEs), of a severity likely to have an impact on patient QoL, in the everolimus arm of the trial relative to the placebo arm. The trial data available indicate that patient health-related quality of life (HRQoL) was identical in the early stage of the trial, despite there being response to treatment in the everolimus arm."*	*"…the ERG would place greater emphasis on the much higher frequency of adverse events (AEs), but note this did not lead to a detrimental impact on patient QoL, in the everolimus arm of the trial relative to the placebo arm. The trial data available indicate that patient health-related quality of life (HRQoL) was equivalent in the early stage of the trial, despite there being response to treatment in the everolimus arm."*	Novartis feel the original statements in the ERG report are inaccurate and do not consider the QoL data in a balanced manner. Whilst it is true to state the QoL data is not different on the placebo arm from those patients on everolimus there are important considerations for why this is positive. i) The primary reason for questionnaires to be missing from the Full Analysis Set, from time window 2 onwards, was the discontinuation of patients before their assessment could take place. This was consistently more pronounced in the placebo group. Considering the main reasons for treatment discontinuation, i.e. disease progression or adverse event, the corresponding missing data are likely to be informative of an unobserved impaired quality of life or symptom status (data missing not at random). This may bias the assessment of patient reported symptoms or quality of life. The group in which proportionately more patients discontinue treatment for reasons possibly related to impaired health or	We have carefully reviewed the suggested amendments and justifications. However, we remain confident that the original statements made in our ERG report do not contain factual inaccuracy and do not accept the suggested amendments.
Page 42, section 4.2.1.2.4. states: *"In the manufacturer's submission the interpretation that maintenance of HRQoL with everolimus is reassuring, might also be regarded as disappointing, given that some additional benefit might also be expected to arise from tumour response in the everolimus arm of the study."*	*"In the manufacturer's submission the interpretation that maintenance of HRQoL with everolimus is reassuring, it might be expected that some additional benefit might arise from tumour response in the everolimus arm of the study in QoL although adverse event rates were higher in the everolimus arm, however active treatment did not lead to a decline in health-related quality of life despite possible reporting bias in the placebo arm."*		

In addition page 44, section 4.2.3: *"The interpretation is reasonable, although the ERG would place greater emphasis on the much higher frequency of AEs, of a severity likely to have an impact on patient QoL, in the everolimus arm of the trial relative to the placebo arm. The trial data available indicated that patient HRQoL was identical in the early stages of the trial, despite there being response to treatment in the eveolimus arm."*	*"The interpretation is reasonable, as the trial data available indicated there was no detrimental impact on patient quality of life which was identical in the early stages of the trial, despite there being response to treatment in the everolimus arm."*	quality of life, thereby preventing the assessment of a poor status, is likely to show, on average, a more positively biased health or quality of life level. ii) The analyses of time to definitive deterioration in performance status better account for the expected systematic decline in QoL or worsening of symptoms than the longitudinal analyses. Even with the expected impact of adverse events from the active treatment, the time to definitive symptom or quality of life deterioration was maintained in the RAD001 group compared to the placebo group. iii) It should be noted that in the Motzer et al Lancet 2008 publication of the second interim analyses results the author commented on adverse event rates and subsequent QoL impact stating "The overall rate of severe events was low, and the benefit-risk ratio was acceptable in the context of an apparent clinical benefit in patients with a life-threatening disease. Moreover, no detrimental effect on health-related quality-of-life was evident for everolimus compared with placebo when assessed with the EORTC QLQ-C30 and FKSI-DRS questionnaires." The statement is important because it represents the	
In Addition page 81, section 7.1: The ERG report states: *"The interpretation is reasonable, although the ERG would place a greater emphasis on the much higher frequency of adverse events, of a severity likely to have an impact on patient quality of life, in the everolimus arm relative to the placebo arm. The trial data available indicated that patient health related quality of life was identical at an early stage of the trial, despite there being response to treatment on the everolimus arm."*	*"The interpretation is reasonable, as the trial data available indicated there was no detrimental impact on patient quality of life which was identical in the early stages of the trial, despite there being response to treatment in the everolimus arm."*		

		opinion of internationally recognised leading clinicians who were the key authors on this study, that even though the patients were on active treatment there was no detrimental effect to patients QoL.	

Issue 2

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 11, Section 1.3. There is an omission as the PAS has now been approved by the DoH. Therefore the ICERs with PAS should be specified explicitly to facilitate decision-making.	Where base case ICERs are quoted, the ICERs with PAS should be explicitly stated in the following sections: page 11, section 1.3 - summary of submitted cost-effectiveness evidence, summary of ; page 82, section 7.2 – summary of cost-effectiveness issues.	As the PAS has received formal approval from the Department of Health, the Appraisal Committee will require the ICER with PAS in order to inform their decision making.	Although factually correct, this was not apparent at the time we compiled the report. We have thus not amended the ERG report and have confirmed with NICE that this is unnecessary.

Issue 3

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 12, Section 1.3. This section states, "…several questions have been raised about its underlying assumptions and use in preference to other approaches." It is not correct to raise this as a serious issue. If a method such as	References to the debate regarding choice of statistical approach should be excluded from the summary of the document.	Although, the discussion as to which approach would be the preferred statistical approach is interesting, it is still the subject of "genuine academic debate". There are as yet no standard or preferred methods in this respect. Therefore the discussion as to why a	This is not a matter of factual accuracy; no amendments have been made.

IPCW is appropriate, accurately calculated and, and correctly applied in the model then a decision should be made on that basis. The debate as to which is the preferred method is an academic one particularly as RPSFT was not an "accepted" method when the analysis of everolimus was being conducted.		particular approach was taken should not contribute to the decision at hand. In the absence of guidance on this matter and the lack of a "gold standard" a decision should be made on whether the method used is valid and robust rather than why another approach was not adopted.	

Issue 4

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 12, section 1.3. this section states, *"The ICER using the unadjusted OS estimate from RECORD-1 was £109,627 (again without PAS and not incorporating correction for the model errors above)"*	As the PAS has now been formally approved by the DoH, it is more relevant to present the ICER with PAS ie £91,356. In addition, the statement, "…and not incorporating model errors above" is incorrect as the "model errors" relate to application of the HR from the IPCW analysis. As the results presented relate to the ITT analysis the "model errors" do not apply to these results. The sentence should therefore be corrected as follows, *"The ICER using the unadjusted OS estimate from RECORD-1 was £91,356 (with PAS)"*	The uncorrected statement implies that the ICER might be different if it were corrected. However, the correction does not apply to the ITT analysis. Also, due to the high proportion of patients in the BSC arm receiving everolimus after progression (76%) and the fact that over half of these patients switched to everolimus within 8 weeks of randomisation, the ITT analysis cannot be considered to be informative regarding the survival benefit associated with everolimus.	The suggested amendment concerning the ICER with PAS is unnecessary for the same reason as indicated for Issue 2. We are happy to accept the amendment relating to the omission of: "*and not incorporating correction for the model errors above."*

Issue 5

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 12, section 1.3. this section states, *"QoL data are not based on EQ-5D sources. The resulting lack of confidence in the utility parameters in models dealing with aRCC and metastatic renal cell cancer (mRCC) has been commented on in NICE appraisals before."* There is an omission in this section as it should be highlighted that, as acknowledged elsewhere in the ERG Report (page 51), the difference in mean utility between stable/PFS and PD states of 0.08 is likely to be on the conservative side.	In order to account for this omission, we propose the following amendment, *"QoL data are not based on EQ-5D sources. The resulting lack of confidence in the utility parameters in models dealing with aRCC and metastatic renal cell cancer (mRCC) has been commented on in NICE appraisals before. However, as the model uses a difference in mean utility between stable/PFS and PD states of 0.08, it is likely to be on the conservative side"*	By making the suggested change it highlights the fact that although there is uncertainty, the assumptions regarding utility are likely to be conservative. The impact of this would be to inflate the ICER.	This is not a factual inaccuracy in our report. The point made is correct but Novartis have drawn attention to it in this document and so no further amendment has been made.

Issue 6

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
The ERG report states on page 14 paragraph 4 *"It should be noted that the median survival of six to 12 months cited in the submission is correct for the cytokine era; however, approved first-line treatments used in current clinical practice give longer median survival."*	We propose the following amendment, *"It should be noted that the median survival of six to 12 months cited in the submission is correct for the cytokine era and is likely to be more representative of median survival of untreated patients in the second line setting."*	The statement, "…however, approved first-line treatments used in current clinical practice give longer median survival." is not relevant to the context of this appraisal. The scope of the NICE review is to concentrate on everolimus within its licensed indication which is for use after progression on or after treatment with VEGF targeted therapy. Other than everolimus there are no licensed or NHS recommended therapies for use after VEGF targeted therapy and benefit from first line therapy has not been demonstrated to show improved outcomes in 2nd line therapies.	We do not accept that this is a factual inaccuracy, and disagree that the suggested amendment clarifies the meaning of the sentence in question. We have made no alteration to the ERG report.

Issue 7

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On page 33, section 4.1.7.3. Paragraph 2 states, "…*the pre-specified efficacy stopping boundary of p≤0.057*…"	The correct figure is p≤0.0057.	As noted in the Lancet 2008 paper (p.3) and CSR ref 40 (p.94)	Corrected.

Issue 8

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 40, section 4.2.1.2.1. this section states, *"This suggests that HR=0.82 should have been used in the base case."* This figure (0.82) relates to the HR from the ITT analysis. However, because of the high proportion of patients that switched to everolimus after progression (76%) and the fact that over half of those patients that switched did so within 8 weeks of randomisation, the ITT analysis is not meaningful in the context of survival benefit associated with everolimus.	The implication that 0.82 should be used as the base case is inappropriate and should be removed.	The survival benefit associated with everolimus treatment in aRCC patients cannot be represented in the base case by the ITT analysis as the results were confounded by the large proportion of BSC patients that switched to everolimus (76%) and the speed with which they did so.	We have carefully re-examined this statement in the light of the justification and believe it remains a reasonable point appropriately expressed. No further action has been taken.

Issue 9

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
On page 43, section 4.2.1.2.4. This section states *"…only 2.5% of the patients receiving everolimus plus BSC treatment in*	This should read, "… *only 3.6% of the patients receiving everolimus plus BSC treatment in the RECORD-1 study and there were no cases of Grade 4*	See reference [40] p.168 which confirms the Grade 3 pneumonitis rate on everolimus. This was an error in	Thanks to Novartis for notifying us of this error in their original submission. We accept the suggested

the RECORD-1 study and there were no cases of Grade 4 penumonitis reported."	*penumonitis reported."*	the original submission by Novartis.	amendment.

Issue 10

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
(CIC information removed)In general, the ERG states that the manufacturer submission understates the nature and likely impact of the observed AEs on patient quality of life."	(CIC information removed)	See Issue 1 for justification. In summary Novartis do not believe the data supports a statement that everolimus has a negative impact on QoL when the data demonstrates QoL is comparable between active treatment and placebo arm, despite there being a possible reporting bias leading to under reporting on the placebo arm of events e.g. progression, likely to have negative implications for a patient's QoL outcomes.	As for Issue 1 we have carefully reviewed the sentence in question and believe it remains a justifiable point which is not factually inaccurate We have not taken up the suggested amendment.

Issue 11

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 47, section 5.1.2. This	We propose the following change, *"The*	We do not believe that the	We believe it is incorrect to directly

section states, *"The hazard ratio (HR) multiplier was incorrectly applied to the transition probabilities in the placebo i.e. BSC only arm of the model. This multiplier had been applied directly to the transition probabilities, rather than first converting these probabilities to rates before multiplying and then converting the revised rates back to transition probabilities. Since these probabilities are relatively high this error is significant."*	*hazard ratio (HR) multiplier was applied to the transition probabilities in the placebo i.e. BSC only arm of the model. This multiplier had been applied directly to the transition probabilities, rather than first converting these probabilities to rates before multiplying and then converting the revised rates back to transition probabilities. If the hazard ratio is applied to the rate the base case ICER increases from £51,613 to £53,479. "*	methodology employed is an error, rather a matter of technical debate, nor does the result arising from the suggested adjustment constitute a "significant error" as the difference, accepting PenTAG's adjustment, increases the ICER by less than £2k. While the probability-to-rate conversion is a technically valid approach, we feel that our calculations of the transition probabilities are essentially equivalent to a transition rate. Firstly, the time interval of 8 weeks (one cycle) was set for each transition probability calculation, so the time component is intrinsic to the transition probability calculation. Furthermore, the RECORD-1 study assessed patients' disease status once every 8 weeks. We felt that, in essence, the tumour assessment points would serve as a continuous time variable since we do not have data on the patients' tumour status in between assessments. We believe that converting the transition probability to a rate introduces inaccuracies as performing a conversion produces a mortality hazard that is not based on empirical evidence. Lastly, we would like to highlight that our IPCW-adjusted hazards ratio was calculated on an interval of 28 days, so the resulting hazard is interval-based as opposed	multiply the transition probabilities in the model without first converting them to rates. This error is demonstrated very clearly when the method is applied to the reported lower value in the 95% confidence range for the hazard ratio (everolimus/BSC only). If this value of 0.31 is entered in the model and the method of direct multiplication, advocated by Novartis is applied, then logically impossible transition probabilities of greater than one (i.e 1.434) are generated for the transition probabilities from the progressive state to death. We therefore stand by our assertion that the approach of directly multiplying the transition probabilities in the model is an error in the original Novartis analysis and do not believe this is a 'matter of technical debate'. We are, in fact, surprised that Novartis should seek to defend this method.

		to an instantaneous hazard.	

Issue 12

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 47, section 5.1.2 This section states, *"In applying the HR multiplier to mortality probabilities in the BSC only arm, the model fails to account for increased death caused by greater progression in this arm. This leads to a bias which exaggerates the death rate for patients in the BSC arm (i.e. underestimates the hazard ratio for overall survival of everolimus versus BSC only)."* *See also page 58, section 5.1.10, page 68, section 5.2.3.3.4, page 82, section 7.2.*	Further detail should be provided on the calculations underpinning PenTAG's calculations. In particular how the figures in Tables 17, 18 and 22 were derived. As we are unable to verify the calculations it is not possible to verify their accuracy. In addition, we would like to request the opportunity to submit further analysis to address the concern raised by PenTAG regarding the application of the IPCW HR in the model.	Having considered PenTAG's comments regarding the application of the IPCW HR in the economic model and the possibility that survival in the BSC arm is under-estimated we agree that PenTAG may have a point. However, the calculations underpinning PenTAG's approach to resolving this issue are not transparent and therefore it is not possible to comment on the accuracy of their results. We are now considering how this issue can be addressed.	Please refer to our response to Novartis' subsequent analysis based on the Rank Preserving Structural Failure Time method.

Issue 13

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 50, section 5.1.5. This section states, *"It is instructive to*	We propose you change this to,	The mortality rates for the BSC only arm from the ITT analysis are not	It is "instructive" to compare these values because it demonstrates how

compare the mortality transition probabilities used in the base case model which have been derived using the hazard ratio calculated from the IPCW statistical approach, with the values that directly reflect the intention to treat trial data for the BSC only arm." This is not correct.	*"It is not particularly meaningful to…"*	instructive as they include the 76% patients who switched to everolimus treatment following progression and over half of these did so within 8 weeks of randomisation.	central the IPCW analysis is in determining the cost-effectiveness outputs. Nothing is implied in the use of this phrase about how valid or 'meaningful' either of these approaches is. We do not therefore accept this amendment.

Issue 14

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 50, table 6. The figures presented for the BSC only – trial data (ITT values) are incorrect in the table for the Progressed to Death states and the Stable to Death states.	Corrected Table provided in Appendix 1.	Incorrect values in table.	Correction accepted.

Issue 15

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 57, Section 5.1.8. this section states, *" Although this only make a minor difference to*	We do not believe that it is correct in this case to discount from cycle 1 ie week 8.	In view of the short cycle length and in the context that these patients have limited life expectancy, we do not feel	We have checked this point carefully and believe Novartis is manifestly incorrect. No further action has been

outputs, normally we would expect discounting to be applied from the first cycle of model operation." We do not agree that it is "normal" to discount from the first cycle for all models.		that it is appropriate to discount from the first cycle. For example, in practice this would mean that a patient values benefit in 2 months time less than benefit today. Intuitively given the patient is at the end of life this does not seem appropriate.	taken.

Issue 16

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 65, section 5.2.3.3.1, states, *"A stabilised weight per patient-month (SWi) of follow-up was generated. Time periods following cross-over were excluded from analysis. Overall, there was data for 523 uncensored placebo plus BSC patient-months with an average of 3.8 months of uncensored follow-up. From this analysis the mean SW was 0.7912 (Std Dev 0.4231)."*	We propose modifying this statement to read: "*A stabilised weight per patient-month (SW) of follow-up was generated. Time periods following cross-over were excluded from analysis. Overall, there was data for 523 placebo plus BSC patient-months with an average of 3.8 months of follow-up. From this analysis the mean SW was 0.7912 (Std Dev 0.4231). There was data for 418 uncensored placebo plus BSC patient-months where the mean SW was 0.99 (Std Dev 0.164). Among uncensored patient-months, a mean stabilised weight close to 1 indicates that the IPCW-adjusted Cox model appropriately corrects the treatment hazard rate*	Excluding the patient months where a patient is already censored and therefore assigned an SW = 0, allows for a more accurate estimate of a mean stabilised weight since including patient months post-censoring would underestimate the mean SW. It is important to report the SW for uncensored patient-months because a mean SW close to 1 confirms that the IPCW-adjusted model will appropriately correct the hazard rate estimate for biases due to crossover and that we have chosen a final stabilised weight model with minimal or no violations to the exchangeability or positivity assumptions.	This cited section of our report is a quotation taken from Section 6.3.4.6. (p.65) of Novartis' original submission. If Novartis wish to amend their original text we have no objections.

	estimate for biases due to crossover."		

Issue 17

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 70, Section 5.2.3.6, second paragraph states that the model assumes that patients who experience an AE have a utility decrement for only one cycle, after which, their utility is assumed to return to a level equivalent to the state without adverse events.	It is assumed that a patient who experience an adverse event will have it resolved within the first cycle he or she will enter the "stable disease with adverse event" state, and therefore the cost of the AE will be applied only to the initial cycle in that health state, after which, standard stable disease management cost will apply. The utility decrement (-0.05) however, will be applied for the entire duration that the patient is in the health state until he or she moves onto disease progression or death.	This misinterpretation of the utility decrement application assumes that the model underestimates the utility impact of adverse events (or, reversely, overestimates the utility values for patients with AEs). As the decrement is applied for the entire duration that a patient is in the stable disease with adverse event state, the model conservatively estimates the quality-adjusted life years.	Section 7.2.6.2 (p.116) of the Novartis submission states: *" It was assumed that once AEs were experienced they would be resolved within one cycle, after which patients would be assigned the utility and costs associated with stable disease (SD)."* Our statement as reported is thus based on the original Novartis report and as such it is not really a 'misinterpretation'. Having examined the model, however, it seems clear that the utility decrement has been applied as described in the proposed amendment.

Issue 18

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 76, table 23, the title of the	The label of the 2nd column should be		This column heading is correct. No

second column is “Undiscounted”. This is incorrect.	“Discounted from the beginning of year 2.		amendments are needed. We have not reported results for discounting from the beginning of Year 2 (as we do not believe this is a valid approach to discounting).

Issue 19

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 96, Appendix 3, point 4, Ian White makes the following statement, *“Per-protocol analysis implicitly assumes that patients who switch to everolimus can have their everolimus-free outcome validly represented by those who remained not on everolimus. This is highly implausible, since patients who switch have mostly progressed and hence have worse survival. IPCW includes covariates in the model predicting switching and therefore can make the implicit assumption more plausible. In particular, if “confirmed disease progression” has been included in the model predicting switching (as suggested on p112 l12), then*		We would like to offer some clarification of the IPCW methodology and our stabilised weight models which predict not crossing over. The models predict the probability of a BSC patient not crossing over to everolimus at each visit, and therefore it is important to adjust for all possible predictors of crossover. The model does in fact include disease progression as this is an important predictor of crossing over to everolimus. Each patient is assigned a stabilised weight which represents the likelihood that this patient will not have crossed over to everolimus at each patient visit. Based on this model, patients with a high probability of crossing over at a particular visit who did not in fact crossover to everolimus during this visit will have the greatest weight and	The clarification offered is useful and will be available via this document to the Appraisal Committee. We have made no amendments to the ERG report and none were suggested.

patients who switched to everolimus have their everolimus-free outcome represented by those who remained not on everolimus after progression. The latter assumption is more plausible, but it remains highly questionable, and should be carefully assessed on clinical grounds. Why do some patients not switch after progression? Is it just physician preference, in which case IPCW may be fine, or is it (for example) because they are too ill to tolerate everolimus?"		therefore in the IPCW-adjusted Cox model, these patients will represent the patients who actually did crossover to everolimus at a particular visit and therefore cannot be considered in modelling survival. Since this probability of crossover is based on a model adjusted for all predictors of crossing over, we feel it is plausible to assume that the patients who do not crossover to everolimus at a particular visit, but still have a high probability of crossing over based on the model, can represent the patients who did crossover. These patients will have similar baseline characteristics and time-varying confounders since the probability of crossing over is based on these strong predictors.	

Issue 20

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**PenTAG response**
Page 97, Appendix 3, point 8. this section states, *"… it would be useful to know whether the applicant performed an RPSFTM analysis as well as the IPCW analysis and chose not to report it, or only…"*	In order to address this issue we would be willing to undertake an RPSFTM analysis. If acceptable to NICE we would be happy to submit this prior to the Appraisal Committee meeting.	In this section Ian White states that it would be useful to know whether an RPSFTM analysis was conducted but not submitted. The answer to this question is that we had not conducted a cost-effectiveness analysis based on this method	We have now appraised this additional analysis from Novartis (received on 18 Dec 09) and comment upon it in a separate report. We were interested to discover that Novartis had previously commissioned an analysis of the everolimus trial data based on the

		at the time of the submission. It is important to note that when we were conducting our analysis NICE had not yet reviewed the RPSFT approach and therefore there was no precedent or "preferred" approach. We had not conducted a cost-effectiveness analysis based on RPSFTM at the time of our submission.	Rank Preserving Structural Failure Time method in April 2009.

Issue 21

Description of problem	Description of proposed amendment	Justification for amendment	PenTAG response
Page 98, point 5 states, *"The independent statistician's report commissioned by Novartis [Appendix 2 above] misses this point: it assumes the model predicting switching is OK if it includes all covariates in the PH model (i.e. allowing for all observed confounders), but the validity of the method requires there to be no unobserved confounders."*		We feel confident that we included the most important time-varying cofounders, and while it is not possible to know for sure if we have included all unobserved time-varying confounders as meeting this exchangeability assumption is difficult to prove, we feel comfortable with those confounders we included in the logistic model we used to estimate the denominator of the weights. Progression status, adverse event status,	The clarification offered is useful and will be available via this document to the Appraisal Committee. We have made no amendments to the report and none were suggested.

		and KPS score at each patient-month post-randomization are the three time-varying confounders we included in the logistic models used to calculate the IPCW. These measures are known as time-varying joint risk factors for crossover and mortality. Baseline risk factors collected during the RECORD-1 trial, including MSKCC risk score, were also considered for inclusion in models. As argued by Cole and Hernan, 2008, including too many potential confounders in relation to the number of observations may introduce several biases, including finite-sample bias from possible non-positivity, decreased statistical efficiency, and selection biases related to the addition of a non-confounding variable. A mean stabilised weight of close to 1 in the BSC population supports the fact that we have chosen a final stabilized weight model with minimal or no violations to the exchangeability or positivity assumptions. This stabilised weight distribution also provides comfort in our final IPCW-adjusted Cox model and results from this model. It is	

		possible that there are additional unmeasured or unrecognised risk factors for both crossover and death. If these were positively correlated with both crossover and death, the estimated hazard ratio would further decrease. However, it is likely that the major risk factors have been taken into account, in which case adjustment for further risk factors would result in lesser changes in the estimated hazard ratio.	

(please cut and paste further tables as necessary)

Appendix 1 – Corrected Table 6

Table 1 : Base case model values for mortality transition probabilities base case values compared to intention to treat data for the BSC arm.

BSC ONLY – base case values from IPCW method		Model Cycle							
From State	To State	0	1	2	3	4	5	6	7-18
Progressed	Death	[redacted]							
Stable	Death	[redacted]							
Stable + AE	Death	[redacted]							
BSC ONLY –trial data (ITT values)		0	1	2	3	4	5	6	7-18
Progressed	Death	[redacted]							
Stable	Death	[redacted]							
Stable + AE	Death	[redacted]							

Everolimus for the Treatment of Advanced Renal Cell Carcinoma (aRCC) - Additional Analysis Using RPSFT

Thank you very much for the opportunity to submit additional analysis in relation to the above technology appraisal of everolimus for the treatment of aRCC.

Background

When the data from the pivotal, randomised, placebo-controlled trial (RECORD-1) were analysed, it became apparent that the intention-to-treat (ITT) overall survival (OS) analysis was of limited value in demonstrating the survival benefits associated with everolimus treatment. This was because at the February 2008 data cut-off, 76% of the patients randomised to the placebo arm of the RECORD-1 trial had switched to everolimus treatment following progression. In addition, more than half of these patients switched to everolimus treatment within 8 weeks of randomisation. Therefore the ITT OS results are highly confounded and do not represent a meaningful comparison of treatment effect on survival.

In order to correct for this confounding a number of statistical approaches were considered including the (inverse probability of censoring weights) IPCW and the rank preserving structural failure time (RPSFT) method. At that time there was no guidance or precedents that would indicate which approach would be preferred by NICE. In the absence of such information, it was decided at a global level that we would use the IPCW approach to inform our economic analysis. Although, there is academic debate regarding the most appropriate statistical approach, our choice was based mainly on the perceived simplicity of the practical application of a HR directly within the current economic model. The base case results as presented in our submission, are therefore based on the IPCW approach using data from the February 2008 data-cut. No economic analysis using results from a RPSFT approach have been available until now.

The global Novartis statistics team instigated an RPSFT analysis based on longer term follow up data from RECORD-1, that has become available (November 2008 data-cut). It should be noted that by the time of this analysis, 81% of the patients randomised to the placebo plus BSC arm of the RECORD-1 trial had switched to everolimus treatment following progression. Following a review of the ERG Report, and in acknowledgement that a comparison of the results from both the IPCW and RPSFT approaches would be informative, we have now conducted an analysis using the results from the RPSFT method in our economic model which was originally submitted on 30th September 2009.

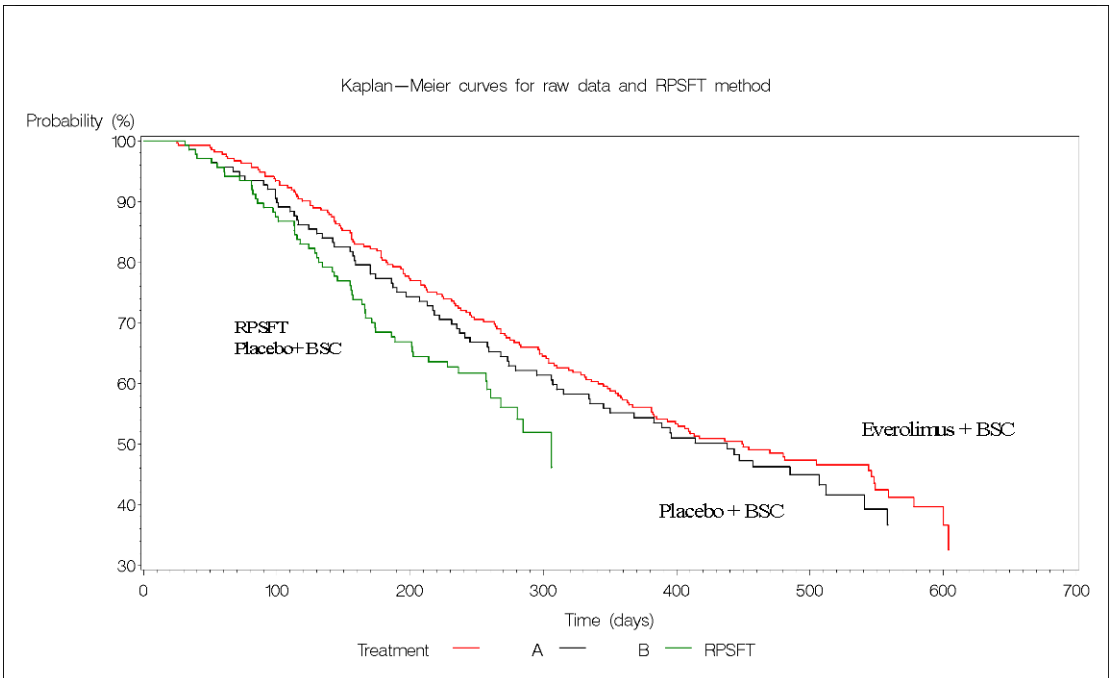
The results of this analysis are presented below.

RPSFT Analysis

The RPSFT statistical analysis is fully described in Appendix 1, and is based on the November 2008 data-cut. It was also presented in poster format at the 15th and 34th ESMO Congress, Berlin 20th-24th September 2009.[i] At this analysis, based on the ITT analysis the median OS for the everolimus plus BSC arm was 14.78 months and for the placebo plus BSC arm the median OS was 14.39 months (HR=0.87, 95% CI: 0.65 – 1.17, p=0.177). In addition, 81% of patients randomised to placebo had switched to everolimus treatment following progression (compared to 76% reported in the submission for the February 2008 cut-off).

A post-hoc exploratory analysis of OS was conducted using the RPSFT method. This is an accelerated failure time model which uses a structural assumption of time proportionality. This method provides an estimate of treatment effect based on randomisation thus correcting for the bias introduced due to patients switching from the placebo plus BSC arm to the everolimus plus BSC arm of the trial. Using the RPSFT approach, the corrected median OS for the placebo plus BSC arm is 10 months versus the unadjusted median OS of 14.4 months.[i] The results from this analysis estimate a relative survival time that is 1.93 fold longer in the everolimus plus BSC arm than the placebo plus BSC arm (95% CI: 0.5 – 8.5).[i] These data were used to generate an RPSFT corrected Kaplan Meier OS curve for the placebo plus BSC arm of the trial. The Kaplan Meier curves of OS based on the raw data for the two treatment arms and the RPSFT corrected OS for the placebo plus BSC arm are presented in the figure below.

Figure 1 - Kaplan Meier Curves of OS based on November 2008 Data-cut[i]



Kaplan-Meier survival curves from the original data (red and black lines) and the placebo group after adjusting for the treatment switch (green line, RPSFT)

Application of the RPSFT Results in the Economic Model

The Kaplan Meier curve for the RPSFT corrected OS for the placebo plus BSC arm of the study was used to generate the BSC transition probabilities to death ie for following state transitions: progression to death; stable disease without adverse events (AE's) to death and stable disease with AE's to death. As the RPSFT results do not allow differentiation of the conditional probability of death by health state we have assumed the same transition probabilities to death in the placebo plus BSC arm for each of the states to death**.** The remaining transition probabilities for the BSC arm are calculated directly from the RECORD-1 trial using the November 2008 data-cut ie for the following state transitions: stable disease with AE's to progression; stable disease without AE's to progression and risk of AE's. All of the transition probabilities for the everolimus arm were calculated directly from the RECORD-1 trial using the November 2008 data-cut. All other base case assumptions in the model remain unchanged.

The transition probabilities are presented in Table 1, below.

Table 1 – RPSFT corrected transition probabilities

Per Patient Model BSC: RPSFT-Adjusted

	Cycle	0	1	2	3	4	5	6	7	8	9	10	11 to 18
1->2	AE Risk												
1->3	Progression Risk SD w/o AE												
2->3	Prog. Risk from SD w/AE												
3->4	Death from PD												
1->4	Stable N-Death												
2->4	Stable w/ AE N-Death												

Per Patient Model Afinitor

	Cycle	0	1	2	3	4	5	6	7	8	9	10	11 to 18
1->2	AE Risk												
1->3	Progression Risk SD w/o AE												
2->3	Prog. Risk from SD w/AE												
3->4	Death from PD												
1->4	Stable N-Death												
2->4	Stable w/ AE N-Death												

The cost-effectiveness results based on the RPSFT approach are presented in Table 2 below.

Table 2 – Cost-effectiveness results from the RPSFT analysis using the November 2008 cut off

	Evero-limus plus BSC QALY	BSC alone QALY	Everolim-us plus BSC LYG (months)	BSC alone LYG (months)	Inc LYG (months)	Inc QALY	Everolim-us plus BSC cost (£)	BSC alone cost (£)	Inc cost (£)	**ICER for everolimus plus BSC versus BSC alone (£/QALY)**
Base case with PAS* (IPCW Feb 2008 cut-off)	0.607	0.302	0.841 (10.09 months)	0.426 (5.11 months)	0.414 (4.97 months)	0.304	£25,222	£9,517	£15,704	**£51,613**
With PAS: RPSFT (Nov 2008 cut-off)	0.912	0.454	1.265 (15.18 months)	0.639 (7.67 months)	0.626 (7.51 months)	0.458	£36,168	£11,824	£24,344	**£53,128**
Without PAS: RPSFT (Nov 2008 cut-off)	0.912	0.454	1.265 (15.18 months)	0.639 (7.67 months)	0.626 (7.51 months)	0.458	£38,312	£11,824	£26,488	**£57,808**

* As presented in the original Novartis submission.

The results from the RPSFT analysis give an incremental cost-effectiveness ratio (ICER) of £53,128 with PAS.

Conclusion and Discussion

As acknowledged in the ERG Report, the appropriate statistical approach to correct for confounding due to crossover is still an area of genuine academic debate. Therefore the opportunity to compare estimates of cost-effectiveness based on two different statistical approaches is of interest as well as providing reassurance that the original IPCW method we adopted does not generate overly favourable results compared to the RPSFT approach. The results generated when applying the RPSFT statistical approach suggest that everolimus, within it's licensed indication, is likely to be cost-effective within acceptable limits when applying the end of life criteria.

It should be noted that the longer term, November 2008 data-cut suggests greater survival than the February 2008 data-cut. This means that using the November analysis there are more everolimus patients still alive in the final cycle of the economic model. Unfortunately, there was insufficient time to add further cycles to the model to account for this. However, the overall impact will be to reduce the ICER as there will be greater LYG in the everolimus arm but no further everolimus treatment costs as these are only applicable for the stable disease states.

In summary, everolimus fulfils an unmet clinical need as it is a clinically-effective treatment for a small population of aRCC patients who do not have any NICE recommended, licensed or effective treatment options. If left untreated these patients are likely to have limited life expectancy and poor prognosis. Everolimus is the only available oral mTOR inhibitor to be licensed for the treatment of aRCC and therefore represents an innovative approach to treating aRCC. Results from the double-blind, RCT, RECORD-1 trial demonstrated that everolimus reduced the risk of disease progression by 67% (HR=0.33, 95%CI: 0.25-0.43) and improved median progression free survival by 3 months. For these reasons it is anticipated that everolimus will meet the "end of life" criteria. Furthermore, in order to facilitate early access for

patients, Novartis are offering a Patient Access Scheme (PAS) to be considered as part of this appraisal. The Department of Health have confirmed that they are happy for NICE to consider the PAS as part of this appraisal.

References

[i] Korhonen P, Haas T, Zuber E, Kay A, Lebwohl D, Motzer R. Overall Survival Among Metastatic Renal Cell Carcinoma Patients Corrected for Crossover Using a Rank Preserving Structural Failure Time (PSFT) Model: Analyses From the Everolimus Phase 3 Trial. Abstract, P-7155, Joint ECCO 15th and 34th ESMO Congress, Berlin 20th-24th September 2009.

PENTAG RESPONSE TO ADDITIONAL NOVARTIS ANALYSIS BASED ON RANK PRESERVING STRUCTURAL FAILURE ANALYSIS

The additional analysis presented by Novartis based on a Rank Preserving Structural Failure Time Approach (RPSFT) to cross-over bias was received by PenTAG on 18th Dec 09.

On examination of the additional information, we were interested to observe that the Novartis' revised analysis based on the RPSFT data, reported a base case ICER which is close to Novartis' original submitted base case ICER. This is despite the fact that we believe their original ICER value was incorrect due to the erroneous application of the Everolimus/BSC hazard ratio within the model (as fully outlined in our ERG report). These respective values are summarised in Table 1 below.

Table 1 : Summary of Novartis base case outputs and the PenTAG corrected base case output (in bold)

Model	Base Case ICER with PAS applied	Base Case ICER without PAS applied
Original Novartis Base case (based on model using IPCW analysis of cross over bias) *	£51,613	£61,330
Novartis Re-analysis of Base case (based on RPSFT analysis of cross over bias) **	£53,128	£57,808
Base case from corrected model as presented and outlined in PenTAG's ERG report * **	**£65,231**	**£76,070**

** Reported in original Novartis submission (Table 31. p 16. ** Reported in Novartis additional RPSFT analysis (Table 2 p.4). *** Reported in PenTAGs ERG report (Table 23 p.73).*

We therefore examined the newly submitted analysis presented by Novartis based on the RPSFT outputs. Firstly, we entered the transition probabilities shown in the revised RPSFT analysis into their model and replicated their reported ICER. Then, given that the key driver for incremental benefit in the model is incremental overall survival, we plotted the overall survival curves as generated by the revised Novartis model (i.e. using the transition probabilities as shown on page 3 of the Novartis RPSFT additional analysis).

Figure 1 below shows (in dotted lines) the model base case overall survival curves for each arm in Novartis' re-analysis. Figure 1 also shows (solid lines) the survival curves derived from the RPSFT analysis which are reproduced from the Kaplan-Meier curves on page 2 of the Novartis RPSFT re-analysis document.

Figure 1 shows clearly that the calculated value of £53,128 from the Novartis re-analysis relies on an unrealistic extrapolation of the overall survival curve for the BSC only population which we believe over-estimates the mortality in this arm. This model extrapolation has been based on a single trial data point and we believe this approach is clearly erroneous (as graphically illustrated in Figure 1).

[redacted]1

PenTAG re-analysis based on RPSFT data

In order to illustrate the impact of a more realistic extrapolation of overall survival for the BSC only population based on the RPSFT analysis, we re-ran the Novartis model using the revised transition probabilities for the BSC only arm of the model shown in Table 2 below (we did not alter the transition values used by Novartis for the Everolimus arm in their re-analysis). For our analysis we used a value of [redacted] (shown in bold in Table 2) for the mortality transitions for cycles 6 to 18 in the model calculated as the mean of cycles 4 and 5 (this value in the Novartis' re-analysis was [redacted] All other model transition values in our re-analysis were the same as those used in the Novartis re-analysis.

Table 2 : Transition probabilities used for BSC only arm in the PenTAG reanalysis based on the RPFST data.

	BSC: RPSFT-Adjusted						
Cycle	0	1	2	3	4	5	6 to 18
AE Risk	[redacted]						
Prog. Risk SD w/o AE	[redacted]						
Prog. Risk from SD w/AE	[redacted]						
Death from PD	[redacted]						
Stable N-Death	[redacted]						
Stable w/ AE N-Death	[redacted]						

Using the revised transition probabilities as shown in Table 2 the model generates the overall survival curves for each arm shown in Figure 2 below. In Figure 2, the overall survival derived from the RPSFT analysis are again shown in solid lines and the modelled survival curves based on our re-analysis shown using dotted lines.

[redacted]2

When the model is parameterised using the transition probabilities in Table 2, the following base case outputs (Table 3 below) were generated.

Table 3 : Base case outputs from PenTAGs re-analysis using the RPFST outputs

	Incremental Costs £s	Incremental Benefit QALYs	ICER £s/QALY
Without PAS (discounted @ 3.5%)	21,471	0.255	**84,079**
Without PAS (undiscounted)	*22,228*	*0.268*	*82,938*
With PAS (discounted @ 3.5%)	19,338	0.255	**75,725**
With PAS (undiscounted)	*20,083*	*0.268*	*74,935*

Conclusion

The additional RPFST analysis recently supplied by Novartis reinforces our conviction that base case analyses and ICERs presented by Novartis are incorrect

because they over-estimate the mortality risk for the BSC only population and therefore underestimate the base case ICER. In the original Novartis submission this over-estimation of mortality risk came about due to a structural error in the model (as fully outlined in the ERG report). In their revised analysis, based on the RPSFT data, the over-estimation of mortality risk in the BSC only arm has been brought about by an erroneous extrapolation of overall survival curve for the BSC only population (as demonstrated graphically in Figure 1).

In our re-run of the Novartis model using the data provided by the RPSFT analysis, we calibrated the transition probabilities to give a more realistic extrapolation of overall survival for BSC only patients. This leads to a base case ICER for the model of £84,079 without PAS and £75,725 with PAS.

In summary, the analysis above shows that the base case ICER from Novartis' economic model of £53,128 (with PAS) is only sustainable if one is prepared to believe the extrapolation of the RPSFT overall survival curve for BSC only arm population shown in Figure 1. For more realistic extrapolations of overall survival (e.g as illustrated in Figure 2) the model returns a significantly higher base case ICER of £75,727 (with PAS). The analysis also re-affirms that the key model drive for incremental benefit is the overall survival difference between model arms.

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL (STA) FOR EVEROLIMUS (AFINITOR®) IN ADVANCED RENAL CELL CARCINOMA

SPECIFICATION FOR MANUFACTURER/SPONSOR SUBMISSION OF EVIDENCE

Update to reflect the new

Guide to the Methods of Technology Appraisals

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List of Abbreviations

AE	Adverse Event
AJCC	American Joint Cancer Committee
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aRCC	Advanced Renal Cell Carcinoma
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
BSC	Best Supportive Care
CEAC	Cost-effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CR	Complete Response
CRD	Centre for Reviews and Dissemination
CSR	Clinical Study Report
CT	Computerised Tomography
DEF	Data Extraction Form
ECCO	European CanCer Organisation
ECOG	Eastern Cooperative Oncology Group
EMEA	European Medicines Evaluation Agency
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FKSI-DRS	Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease Related Symptoms
HR	Hazard Ratio
Hb	Haemoglobin
HRQoL	Health Related Quality of Life
ICD	International Classification of Diseases
ICER	Incremental Cost-effectiveness Ratio
IFN-α	Interferon-alpha
IL-2	Interleukin-2
IPCW	Inverse Probability of Censoring Weights
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-To-Treat
IV	Intravenous
K-M	Kaplan-Meier
KPS	Karnofsky Performance Scale
mRCC	Metastatic Renal Cell Carcinoma
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan-Kettering Cancer Centre
MTA	Multiple Technology Appraisal
mTOR	Mammalian Target of Rapamycin
N/A	Not Applicable
NICE	National Institute for Health and Clinical Excellence
ORR	Overall Response Rate
OS	Overall Survival

PAS	Patient Access Scheme
PenTAG	Peninsula Technology Assessment Group
PF	Physical Function
PFS	Progression-free Survival
PR	Partial Response
PRO	Patient Reported Outcomes
QALY	Quality Adjusted Life Year
QL	Quality of Life
RCC	Renal Cell Carcinoma
RCT	Randomised Controlled Trial
RECIST	Response Evaluation Criteria in Solid Tumours
RECORD-1	REnal Cell cancer treatment with Oral RAD001 given Daily-1
RPSFT	Rank Preserving Structural Failure Time
SAE	Serious Adverse Event
SD	Stable Disease
SMC	Scottish Medicines Consortium
SPC/SmPC	Summary of Product Characteristics
SR	Systematic Review
STA	Single Technology Appraisal
TKI	Tyrosine Kinase Inhibitor
TNM	Tumour Node Metastasis
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
VEGFr	Vascular Endothelial Growth Factor Receptor
vs	Versus

Section B

3 Executive summary

Renal cell carcinoma (RCC) is the most common primary renal malignant neoplasm in adults, and the eighth most common cancer in England and Wales. It accounts for approximately 90% of renal tumour malignancies and 3% of all new cases of cancer diagnosed in men and just over 2% of all cancers in women in the UK (excluding non-melanoma skin cancer). RCC is more common in men than in women (ratio 3:2), and it most often occurs in patients from the age of 40 with the highest rates in the over 75's. In 2006 there were 6,906 new registrations of RCC in England and Wales and 3,255 deaths in 2007.

The most common histological subtype of RCC is clear cell carcinoma. RCC is often asymptomatic until it reaches a late stage; one quarter to one third of patients present with metastatic disease. The main risk factors for RCC include obesity, smoking, hypertension and some genetic conditions. Of all those diagnosed with RCC in England and Wales, about 44% live for at least five years after initial diagnosis and about 40% live for at least 10 years. However, the prognosis following diagnosis of metastatic disease is poor and approximately 90% of people diagnosed with metastatic RCC have died at five years after diagnosis. If untreated, patients with advanced renal cell carcinoma (aRCC) have a short remaining life expectancy, with a median survival of less than 12 months. Analysis of survival in aRCC prior to starting second line therapy based on the Memorial Sloan-Kettering Cancer Centre (MSKCC) prognostic risk factor system found a median survival of 22 months, 11.9 months and 5.4 months in patients with zero (good prognosis), one (intermediate prognosis), and two/three (poor prognosis) risk factors, respectively.

Renal cell carcinoma can be staged using the American Joint Cancer Committee Tumour Node Metastasis system. Advanced RCC is covered by stages III-IV.

Until recently, the current standard of treatment for RCC in the NHS was radical nephrectomy and cytokine therapy with interleukin-2 or interferon-alpha (IFN-α). In March 2009, NICE approved sunitinib (Sutent®), for first-line use in patients with aRCC who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. However, there is currently no NICE recommended treatment for patients with aRCC who do not respond to first-line VEGF-targeted therapy (sunitinib).

A Multiple Technology Appraisal for sunitinib and other VEGF-targeted therapies sorafenib (Nexavar®) and bevacizumab (Avastin®), plus the mTOR (mammalian target of rapamycin) inhibitor temsirolimus (Torisel®) was recently published on 26th August 2009. The final guidance states that bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with aRCC, while sorafenib and sunitinib are not recommended as second-line treatment options. There are currently no recommended second-line therapies for aRCC in England and Wales following the use of first-line sunitinib or cytokine therapy.

Everolimus (Afinitor®) is a selective kinase inhibitor that blocks the action of the mTOR protein, which plays an important role in regulating key cellular functions, such as cell proliferation, survival, growth, and angiogenesis. It is the only mTOR inhibitor available in an oral form for the treatment of patients with advanced renal cell carcinoma. European Union Marketing Authorisation for everolimus for the treatment of adult patients whose disease has progressed on or after treatment with VEGF-targeted therapy was granted on 3rd August 2009.

Everolimus is available as a 5mg or 10mg tablet for oral use. Tablets are contained in a double-sided blister pack (30 tablets). The recommended dose of everolimus is 10mg/day. Treatment is to be continued for as long as a clinical benefit is observed or until discontinuation for toxicity reasons. Dose interruption or reduction to 5mg/day may be required to manage suspected adverse reactions. The NHS list price for one blister pack containing 30 tablets of 10mg everolimus is £2,970 per month. A patient access scheme (PAS) has been discussed with the Department of Health and is pending Ministerial approval. This scheme offers the first months supply (10mg or 5mg tablets x 30) of everolimus at zero cost to the NHS. Subsequent one month packs (30 x 10mg tablets) will be offered to the NHS at a cost £2,822. This equates to 5% discount on the list price. NB This 5% discount applies to packs of the 10mg tablets only. The duration of treatment for everolimus will vary from one individual to another. The mean duration of exposure to everolimus in the pivotal phase III trial (RECORD-1 [also known as study C2240]) was 156 days (median of 141 days). However, as this includes patients who have withdrawn from the trial for various non-drug related reasons such as loss to follow-up, it is likely to underestimate the actual duration of treatment in routine clinical practice. The economic model used in this submission adjusts for this estimating a mean duration of treatment of 172.27 treated days (based on a dose intensity of 91.8%, allowing for dose interruptions from the RECORD-1 trial) or 187.67 days mean duration of treatment without dose intensity

adjustment. The estimated average cost of everolimus to the NHS is £13,613 per patient via the PAS (i.e. based on 30 days provided free of charge followed by 157.67 days duration at 91.8% dose intensity). This estimate has been used in the England and Wales budget impact calculations in Section 8 of the submission.

In the pivotal phase III trial (RECORD-1), best supportive care (BSC) was assigned to the everolimus and placebo treatment arms. Therefore, this trial can be considered to include an appropriate comparator, as BSC alone represents current clinical practice in the UK for patients who have failed on previous VEGF-targeted therapy. NICE have not recommended sunitinib or sorafenib for second-line use in aRCC patients. Hence, these VEGF-targeted therapies cannot be considered appropriate comparators for the relevant patient population being considered in this appraisal. Furthermore, no other treatments are licensed in this second-line setting.

The clinical evidence in this submission is derived from a high quality, robustly designed phase III, multicentre, double-blind, randomised clinical trial (RCT), RECORD-1, (Section 6.3) comparing everolimus 10mg/day with placebo, both in conjunction with best supportive care. Analysis of data from the RECORD-1 trial demonstrated:

- A 67% reduction in risk of disease progression or death (HR=0.33, 95%CI: 0.25-0.43) for everolimus plus BSC compared to placebo plus BSC. This equates to a median progression free survival (PFS) of 4.90 months for everolimus plus BSC versus 1.87 months for placebo plus BSC. The difference was highly statistically significant ($p<0.001$). These results far exceeded expectations as defined in the statistical plan. The study was powered to detect a clinically meaningful improvement in PFS, specified as a 33% reduction in risk of disease progression events i.e. a HR of 0.67 which represents a 50% improvement in time to PFS. This is as compared to the observed HR of 0.33 (67% reduction in risk) which represents a 100% improvement in time to PFS. This was achieved in a population of patients that were in the advanced stage of RCC and had already failed a number of treatments including a targeted VEGF therapy.

- The difference in median PFS was statistically significant across all pre-specified sub-groups categorised by MSKCC prognostic risk (favourable, intermediate and poor) and across all other sub-groups investigated (number of prior VEGFr-TKI therapies, age, and gender). In particular, type of prior

therapy was not associated with any differences in outcomes. The reduction in risk of progression or death for prior treatment with sunitinib (recommended by NICE for first-line use in aRCC) was 66% for the everolimus plus BSC patients versus placebo plus BSC (HR=0.34, 0.23, 0.51, p<0.001), which is almost the same as the overall risk reduction of 67%.

- Cross-over to open-label everolimus following disease progression for patients randomised to placebo confounded the detection of any treatment-related difference in overall survival. As a consequence, a statistically significant treatment-related difference in overall survival was not found (HR=0.82; 95%CI: 0.57-1.17; p=0.137). However, post hoc statistical analysis was performed to address the confounding in the intention to treat survival analysis.

- Partial or stable tumour response in 69% of patients compared to 32% for placebo plus BSC alone.

- Despite risks of toxicity associated with any active anti-cancer treatment, patients receiving everolimus demonstrated stable quality of life/patient reported outcomes (PRO) compared to placebo plus BSC alone.

The RECORD-1 trial is supported by two secondary level phase II non-RCT studies.

The cost-effectiveness of everolimus plus BSC versus BSC alone

A cost-effectiveness analysis was performed to compare everolimus plus best supportive care (BSC) versus BSC alone in patients with aRCC whose cancer had progressed following, or on VEGF-targeted therapy (i.e. sunitinib, sorafenib or bevacizumab). The primary data source for clinical effectiveness was the RECORD-1, RCT of everolimus plus BSC versus placebo plus BSC (reported in Section 6). The cost-effectiveness model was developed in Microsoft Excel incorporating both a deterministic Markov cohort model and a probabilistic Markov second order Monte Carlo simulation analysis. The model consists of four health states: stable without adverse events (the entry state into the model), stable with adverse events, disease progression, and death. The time horizon was life-time, which due to the late stage of disease was 144 weeks as all patients would have been expected to have died by this time (18 cycles of 8 weeks each). The economic model predicted that 93% of BSC patients had died within 1.5 years compared to 83% of the everolimus patients.

The analysis was conducted from an NHS and Personal Social Services perspective in England and Wales. Costs and benefits were generated for the everolimus and BSC arms in order to estimate the incremental cost per life years gained and QALY's gained. A discount rate of 3.5% has been applied to both costs and benefits as specified by the NICE reference case.

Markov models are frequently used to evaluate the cost-effectiveness of anti-cancer interventions, including aRCC. The modelling approach extrapolates beyond the clinical trial data to assess life years gained (LYG) and perform QALY calculations. However, there was significant bias in the intention-to-treat overall survival analysis from the trial as the majority of patients in the placebo arm of the trial were allowed to cross-over to receive everolimus. A statistical method, the Inverse Probability of Censoring Weight (IPCW) model was used to correct for the confounding due to cross-over. This enabled estimation of a mortality hazard ratio for everolimus plus BSC versus placebo plus BSC of 0.55 [95%CI: 0.31 – 0.97, p=0.0389].

The IPCW adjusted Cox modelling represents a robust approach to adjusting for selection bias associated with informative censoring and has been extensively used to address such bias to explore survival outcomes in HIV treatment RCTs and observational studies. Advice was obtained on the use of the IPCW approach from independent statistical experts, who deemed it an appropriate method to address the selection bias associated with cross-over in the everolimus phase III trial. Although other methods exist (e.g. the rank preserving structure failure time model), IPCW has the advantage of not imposing a structural model so potentially reducing risk from model miss-specification for measuring the effect of treatment on survival outcomes.

The key results from the economic model are presented with and without incorporating the PAS. When the PAS is taken into account, everolimus plus BSC is associated with an estimated discounted incremental cost of £15,704 per patient, for an additional 0.414 life years (4.97 months) and 0.304 QALY's. The incremental cost per QALY gained is £51,613 (£37,893 per LYG). The life years gained estimate was derived from an estimated mean survival of 10.1 months for everolimus plus BSC compared to 5.1 months for BSC alone. These results appear plausible based on evidence from the literature that without treatment aRCC patients have a median survival of six to 12 months, and particularly as the RECORD-1 patient population were at a relatively advanced stage of aRCC having failed a number of previous treatments including one or more VEGF-targeted therapies. If everolimus is used

earlier in the treatment pathway i.e. following first-line sunitinib, it is possible that the benefits of everolimus may be greater than those observed in the trial as in practice, patients are likely to be less advanced than those evaluated in the trial.

Sensitivity analysis demonstrated that the ICER does not vary significantly with variation in resource use assumptions, or other parameters. The greatest impact is associated with the estimate of survival benefit. When the 95% confidence intervals for the IPCW adjusted mortality hazard ratio are applied the ICER ranges from £44,300 to £73,600 (rounded, PAS applied). Without the PAS, everolimus plus BSC is associated with an incremental cost of £18,661 per patient, and an estimated incremental cost per QALY gained of £61,330. The 'with and without PAS' base case results are presented in Table 3.1 below.

Although, the base case ICER is higher than conventionally accepted thresholds of cost-effectiveness, it is comparable to estimates for other 'end-of-life' treatments including sunitinib for aRCC, which have been recently approved by NICE. Other therapies for the treatment of aRCC were recently considered to be end of life treatments. It is anticipated that everolimus will also meet the end of life criteria. Evidence from the RECORD-1 RCT demonstrates that everolimus prolongs survival by at least 3 months in a sub-population of aRCC population whose life expectancy is likely to be much less than 24 months. The QALY weight that would be required to achieve a cost/QALY, for everolimus versus placebo, of £30,000 is 1.72. This is comparable to other treatments that have been recommended by NICE under the 'end of life' criteria.

Table 3.1 Base case cost-effectiveness results for everolimus plus BSC versus BSC alone (discounted)*

	Everolimus plus BSC	BSC alone	Everolimus plus BSC versus BSC alone
WITH PAS			
Drug costs (everolimus) (£)**	14,045	0	14,045
Other costs (£)***	11,177	9,517	1,660
TOTAL COSTS (£)	25,222	9,517	15,704
Life years	0.841	0.426	0.414
QALYs	0.607	0.302	0.304
Cost/LYG			37,893
Cost/QALY gained			**51,613**
WITHOUT PAS			

	Everolimus plus BSC	BSC alone	Everolimus plus BSC versus BSC alone
Drug costs (everolimus) £**	17,001	0	17,001
TOTAL COSTS (£)	28,178	9,517	18,661
Cost/LYG			45,027
Cost/QALY gained			**61,330**

* Results are generated from the model so there are some rounding differences in the table.

**Dose intensity adjusted drug cost

***Cost associated with healthcare resource use, palliative care, therapy used post disease progression on everolimus plus BSC or BSC alone, and adverse event costs.

Budget impact of everolimus

The drug budget impact of 10mg/day of everolimus in patients with aRCC in England and Wales has been estimated [redacted] The budget impact has been calculated on the basis that there are no other second-line treatments available for the target patient population. However, anecdotal reports suggest that some patients continue being treated with a VEGF-targeted therapy i.e. sunitinib post disease progression as there are no alternative NICE recommended treatment options. Hence, the actual net budget impact of everolimus is likely to be lower than presented in this submission, although there is as yet insufficient data with which to estimate the magnitude of this impact. If this is the case, the net budget impact of everolimus is likely to be lower than that presented in this submission.

Summary

Everolimus represents a clinically-effective treatment for a population of aRCC patients who do not have any NICE recommended or licensed treatment options. If left untreated, these patients are likely to have limited life expectancy and poor prognosis. Results from the double-blind, RCT, RECORD-1, demonstrated that everolimus reduced the risk of disease progression by 67% (HR=0.33, 95%CI: 0.25-0.43) and improved median PFS by 3 months (4.9 months for everolimus versus 1.87 months for BSC). These results are remarkable bearing in mind that these patients are end stage patients having failed on a number of previous therapies. In line with

other aRCC therapies, it is anticipated that everolimus will satisfy the criteria as an end of life treatment.

In order to facilitate access for patients, Novartis are offering a PAS to be considered as part of this appraisal. Our base case estimates of cost-effectiveness, taking into account the PAS, are comparable to other products for aRCC approved by NICE under the end of life criteria. [redacted]

In summary everolimus represents a clinically and cost-effective treatment for adult aRCC patients who have progressed on, or following previous targeted VEGF therapy such as sunitinib.

4 Context

4.1 Overview of Renal Cell Carcinoma

4.1.1 Kidney cancer and renal cell carcinoma epidemiology

In 2006 kidney cancer accounted for 3% of all new cases of cancer diagnosed in men and just over 2% of all cancers in women in the UK (excluding non-melanoma skin cancer) [1]. In 2006, there were 7,840 cases of newly diagnosed kidney cancer registered in the UK [1]. In England and Wales in 2006, 6,906 people were diagnosed with kidney cancer, consisting of 4,305 males (62%) and 2,601 females (38%) (International Classification of Diseases (ICD) code 64-66, 68) [1,2] (Table 4.1).

Table 4.1 Number of new cases of kidney cancer in England and Wales, 2006

	England	Wales
Cases		
Males	3,992	313
Females	2,414	187
Total	**6,406**	**500**

Adapted from: UK Kidney Cancer incidence statistics, Cancer Research UK [1]

Calculations using available cancer incidence data indicate that the incidence of kidney cancer has been increasing, estimated to be a 26% higher number of cases diagnosed in 2006 compared to 2000 in England, and 23% between 2003 and 2007, in Wales [2,3]. The incidence of kidney cancer begins to rise after the age of 40 and is highest in people older than 75 [1].

In the UK, kidney cancer is the tenth most common cause of cancer death in men and the thirteenth in women. In 2007, 3,255 people died from kidney cancer in England and Wales, accounting for over 2% of all cancer deaths [4].

Table 4.2 Number of deaths of kidney cancer in England and Wales, 2007

	England	Wales
Cases		
Males	1,868	129
Females	1,171	87
Total	**3,039**	**216**

Adapted from: UK Kidney Cancer mortality statistics, Cancer Research UK [4]

4.1.2 Kidney cancer histology

Approximately 90% of kidney cancers are renal parenchyma cancers, whilst the remainder arise in the renal pelvis and ureter [1]. Cancers of the renal parenchyma are also known as renal cell carcinomas (RCC). There are different subtypes of RCC which can be identified by their histology. The most common subtype is clear cell, accounting for most of the RCC cases [1]. Non-clear cell types include papillary (or chromophilic), chromophobic, collecting duct, and undifferentiated (or unclassified and rare tumour types such as renal sarcoma and Wilms' tumour in children) [1].

4.1.3 Symptoms

Renal cell carcinoma is often asymptomatic until it reaches a late stage. A large number of patients with RCC are diagnosed due to clinical symptoms, although few cases now present with the classical triad of palpable abdominal mass, flank pain and haematuria (blood in the urine) [5,6]. Other common symptoms of kidney cancer include back pain, fatigue, weight loss, sweats and anaemia [6].

4.1.4 Risk Factors

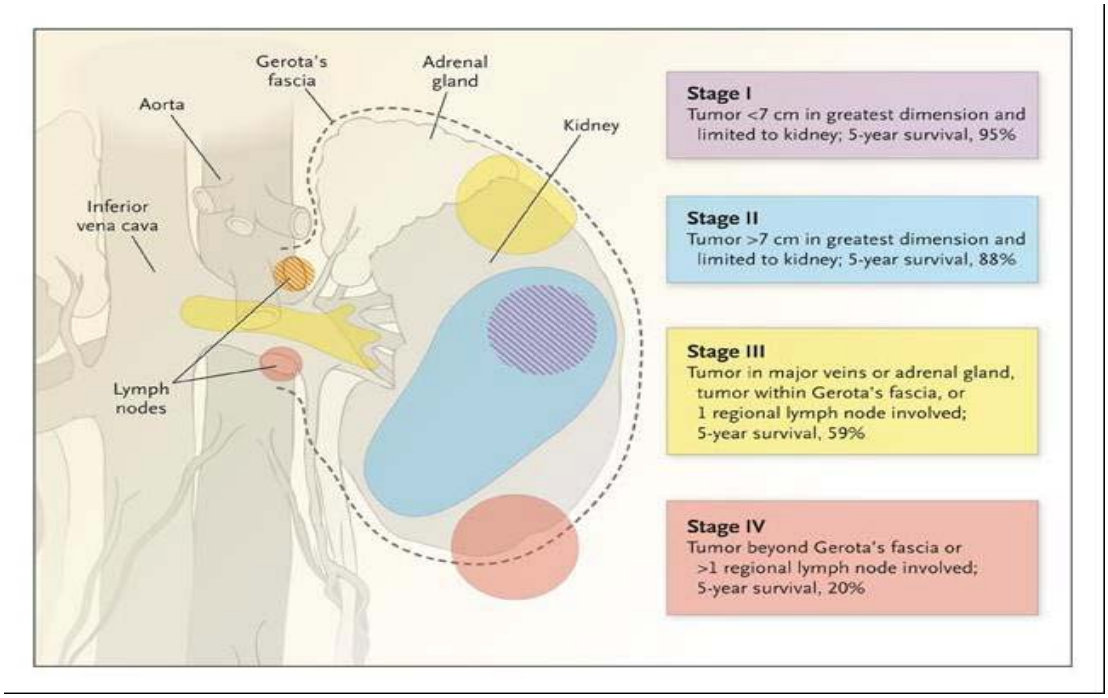
The main risk factors for RCC include obesity, [7-9] tobacco smoking [9,10], hypertension [9,11] and some genetic conditions [12]. The risk of kidney cancer increases with age and is more common in men than in women [9,13]. It has been estimated that approximately 25% of the cases of renal cell carcinoma diagnosed in Europe are attributable to obesity [8] and 24-32% of cases in men are attributable to smoking [8]. Somatic (non germ cell) mutations of the von Hippel-Lindau (*VHL*) tumour suppressor gene have been linked to the development of sporadic clear cell renal carcinomas. Defects in the *VHL* gene appear to be responsible for about 60-

80% of the cases of sporadic clear cell RCC [5,12] which represents a major portion of all cases of renal cell carcinoma.

4.1.5 Staging Criteria

Staging of RCC uses the American Joint Cancer Committee (AJCC) Tumour-Node-Metastasis (TNM system). Tumour stage is based on the combination of tumour size and extent of spread from the kidneys. TNM classifications are combined to produce stages I to IV and describe a patients' overall disease stage, as illustrated in Figure 4.1 below [5]. Advanced renal cell carcinoma (aRCC) is covered by stages III-IV. In stage III the tumour is locally advanced and/or has spread to regional lymph nodes, whilst stage IV represents metastatic RCC (mRCC) in which the tumour has spread beyond the Gerota's fascia to other parts of the body. The decision problem for this submission is concerned with aRCC and so covers stages III and IV. Of those presenting with RCC in England and Wales for whom staging information was available, an estimated 26% and 17% in 2006 had stage III and stage IV disease, respectively [14].

Figure 4.1 Disease stages in renal cell carcinoma



4.1.6 Prognosis and survival

The prognosis of patients with RCC can be influenced by anatomical factors (e.g. tumour size), clinical (e.g. patient performance) and molecular factors, and histological sub-type.

Advanced RCC patients with a clear cell component tend to have a relatively poor prognosis compared to non-clear cell histology [15]. In trials and clinical practice, performance is usually measured by either the Karnofsky Performance Scale (KPS) [16], or the World Health Organisation (WHO) Eastern Co-operative Oncology Group - Performance Status (ECOG-PS) [17], with good performance defined as KPS ≥70 or ECOG-PS 0-1 [17].

Several prognostic systems that combine independent prognostic factors have been developed. A commonly used measure in aRCC clinical trials, and in clinical practice, is the Memorial Sloan Kettering Cancer Centre (MSKCC) prognostic risk score [18]. The 2004 version focuses on patients who have had prior cytokine therapy (i.e. second line treatment) and categorises patients into three risk groups according to the number of pre-treatment risk factors present in aRCC patients: Favourable = none; Intermediate = one; Poor = two or three. The pre-treatment risk factors are:

- Low Karnofsky performance status (<80%)
- Haemoglobin level below the lower limit of normal
- High corrected serum calcium level (>10 mg/dL or 2.5 mmol/L)

Survival from kidney cancer is heavily dependent on the stage of disease at diagnosis. About 44% of the total population diagnosed with RCC in England and Wales live for at least five years after initial diagnosis and about 40% live for at least 10 years [19]. Patients diagnosed with aRCC have a median survival of six to 12 months [20-22] and 90% of people diagnosed with stage IV RCC die within five years of initial diagnosis [20,21]. Analysis of survival based on the MSKCC prognostic risk factor system found a median survival of 22 months, 11.9 months and 5.4 months in patients with favourable, intermediate and poor prognosis risk factors, respectively [18].

4.1.7 Measurement of disease progression and clinical benefit in aRCC

The Response Evaluation Criteria in Solid Tumours (RECIST) Guidelines provides a robust and valid method for assessing tumour response and related outcomes including progression free survival, objective response rate and duration of response in cancer clinical trials and in clinical practice [23,24]. RECIST has also been shown to correlate well with older WHO (World Health Organisation) criteria, which uses the same response categories but slightly different tumour measurement methods [25]. RECIST is also useful in clinical practice for aiding anti-cancer treatment decisions (Table 4.3).

Table 4.3 RECIST guidelines for tumour response assessment

Response	Notation	Definition
Complete Response	CR	Absence of all target lesions, confirmed at 4 weeks.
Partial Response	PR	At least 30% reduction in sum of longest diameter of target lesions taking as reference the baseline value, confirmed at 4 weeks, no appearance of new lesions.
Stable Disease	SD	Neither PR nor PD criteria met.
Progressive Disease	PD	At least 20% increase in sum of longest diameter of target lesions taking as reference smallest sum of longest diameter recorded since treatment started, or appearance of new lesions.

Adapted from: Park et al., 2003 [25]

Typically, as patients with aRCC have a poor prognosis the aim of intervention is to maintain at least stable disease status for as long as possible. This corresponds to the achievement of progression free survival (PFS), which is a well accepted standard primary endpoint in cancer clinical trials, including aRCC but also other advanced cancers such as colorectal, breast, and non-small-cell lung cancer [26-30]. PFS is a powerful measure of clinical benefit in cancer clinical trials because it represents an acceptable surrogate for overall survival [26], but also enables trials to be run as ethically as possible by allowing patients on placebo or comparative treatment to be crossed-over to the treatment showing clinical benefit as soon as is possible [31]. In order to facilitate faster double-blind trial completion, particularly in advanced/late stage cancers in patients at the end of life, a number of recent cancer trials have incorporated a cross-over design, with PFS as the primary endpoint rather than overall survival. These trial designs, with the use of PFS as an efficacy measure, have been accepted by the FDA (Food and Drug Administration) [32] and EMEA (European Medicines Agency). For example, sunitinib (Sutent®) was

approved for patients with gastrointestinal stromal tumours (GIST) following a phase III double-blind, placebo-controlled trial that allowed patients to cross-over to active therapy at the time of disease progression [33]. More recently, on 3rd August 2009, everolimus received EU (European Union) Marketing Authorisation based on PFS benefits over placebo plus BSC within a cross-over trial design [34].

Randomised trials of VEGF-targeted therapies in aRCC have reported an association between improvement in survival alongside an improvement in PFS [26,35]. A recent meta-analysis of 28 controlled trials of a range of treatments for aRCC covering 8,770 patients has been performed to explore the relationship between treatment effect on time to disease progression (PFS) and overall survival [36]. In linear regression analysis this study found a one month median difference in time to disease progression between treatment and comparator was associated with an overall 1.23 month difference in median overall survival (95%CI: 0.70-1.75, p<0.0001) [36]. However, evidence of a correlation was even stronger in sub-group analyses. Excluding studies with patient cross-over (N=24 studies remaining) produced a correlation of 1 month gain in time to disease progression resulting in 1.61 months overall survival benefit (95%CI: 0.70-2.52, p=0.0014) (the result for cross-over studies only was 1.07). In the studies where prior therapy had been received (N=16) there was a 1.42 gain in survival associated with a one month gain in time to disease progression (95%CI: 0.34-2.51, p=0.0137) [36].

Moreover, analyses of data from trials in other advanced cancers (colorectal cancer [37] and breast cancer [28]) have also found a strong correlation between PFS and overall survival (OS). The evidence available strongly supports the premise that PFS is an appropriate surrogate measure of OS. This evidence is in line with recent recommendations by Taylor and Elston on validating the use of surrogate outcomes for use in Health Technology Assessments [38]. Intention-to-treat (ITT) survival estimates for both everolimus and sorafenib as second-line treatments for their distinct aRCC populations have been confounded by cross-over from placebo, but have also demonstrated an association between PFS and overall survival when adjustment has been made for this confounding (Table 4.4). Further support for an association between PFS and OS with everolimus is provided by data from the independently conducted, phase II study in patients who had failed on at least one VEGFr-TKI therapy that preceded the RECORD-1 trial [39] (Table 4.4).

Table 4.4 Results of Progression-free survival from phase III trials in advanced RCC

Trial	Size	Type of Patients	Median progression-free survival (months)	Median overall survival (months)	Exploratory analysis of overall survival (months)
Everolimus plus BSC versus placebo plus BSC (CSR-addendum [40])	416	• Failed previous VEGF therapies. • Heavily pre-treated population • Good/intermediate/poor prognosis (MSKCC group)	4.9 versus 1.9 HR = 0.33; 95% CI [0.25, 0.43]	14.78 versus 14.39 HR = 0.87; 95%CI: [0.65, 1.17]*	Mean of 10.1 versus 5.1 HR=0.55; 95%CI:[0.32, 0.97]**
Everolimus plus BSC (single arm trial) [39]	22	• Failed previous VEGFr-TKI therapies	5.5 months	8 months	
Sorafenib versus placebo (Escudier et al., 2007 [41])	902	• Second line • Good/intermediate prognosis (MSKCC group)	5.5 versus 2.8 HR = 0.44; 95% CI [0.35, 0.55]	17.8 versus 15.2 HR = 0.78; 95% CI [0.74, 1.04]	Median of 17.8 versus 14.3 HR = 0.78; 95% CI [0.62, 0.97]†
*Confounded by required cross-over after positive PFS. **Mean survival estimated via the everolimus economic model after confounding due to cross-over addressed using IPCW approach. †Censored for crossed-over patients.					

4.1.8 Quality of life impact of aRCC

Advanced/metastatic RCC patients have a short life-expectancy and typically face a poor quality of life during their remaining months of survival because of toxicities with current treatments and complications associated with the end stage of disease [42]. Advanced RCC impacts on all domains of health related quality of life (HRQoL), with particular impact on physical functioning, but also on psychosocial functioning [42]. In a national cross-sectional study of adults with RCC, the five most frequent symptoms among 31 patients with localised disease were irritability (79%), pain (71%), fatigue (71%), worry (71%), and sleep disturbance (64%). Half the patients in the survey had advanced disease and of these, 82% reported fatigue, 65% weakness, 65% worry, 53% shortness of breath, and 53% irritability as the five most frequently experienced symptoms [43].

There are several general quality of life instruments for cancer patients that can be used to assess HRQoL and patient reported outcomes (PRO), both in clinical trials and in clinical practice. However, no standard PRO measures have been used consistently across clinical trials in aRCC treatments, thus making comparisons difficult. The two quality of life instruments used in the main phase III trial of everolimus (Motzer et al., 2008) [44] were the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30, a commonly used and validated instrument in cancer studies [45,46] and the Functional Assessment of Cancer Therapy – Kidney Symptom Index – Disease Related Symptoms (FKSI-DRS) which was developed and validated in an attempt to differentiate relief of disease-related symptoms from relief of those experienced as a result of treatment [47,48]. Both instruments have previously been used in aRCC trials with sunitinib and sorafenib [49,50].

The EORTC QLQ-C30 instrument consists of six scales and 30 items evaluating physical, emotional, role, cognitive, social functioning and global health status. Each scale is 0-100, and higher mean scores indicate better HRQoL. A change of at least 10 points on any scale is considered to be clinically relevant [49].

The FKSI originally consisted of 15 items/symptoms or concerns with a 10 item abbreviated option subsequently developed [47]. In the FKSI-DRS, there are 9 items identified previously as important in kidney cancer relating to: energy, pain, weight loss, bone pain, fatigue, shortness of breath, cough, fevers, and blood in urine. Each item experienced was rated from 0 (not experienced symptom) to 4 (very much

experienced), with a change of 2-3 points viewed as the minimally important difference (MID) [48].

4.1.9 Economic burden of RCC in the UK

A study by Gupta et al., concluded that the global epidemiologic burden of aRCC was substantial, with a high associated economic cost [42]. The cost was driven by surgery, and related in-patient admissions, systemic therapy and complications. The authors concluded that new molecularly targeted therapies have the potential to significantly reduce this burden. However, the economic burden of aRCC has not been well reported in the literature, with no specific studies estimating the economic burden for the UK [42]. A US study identified the relative importance of healthcare cost which represented 92.4% of the economic burden of RCC in the US, the rest was associated with productivity loss costs [51].

4.2 What was the rationale for the development of the new technology?

There is a significant unmet need within advanced RCC. Kidney cancer accounted for over 2% of all cancer deaths in the UK in 2007 [4]. Few patients with aRCC survive beyond one year [42], and can have poor quality of life due to treatment-related adverse events and complications associated with the end stage of disease [42,52]. Thus, the development of new treatments in aRCC that can improve patient outcomes without adversely impacting patient quality of life remains necessary.

The recently developed VEGF-targeted therapies sunitinib, sorafenib and bevacizumab have shown some activity and improvement in PFS for aRCC patients with good/intermediate prognosis [41,53,54]. It is estimated that 62% of patients will eventually experience disease progression following VEGF-targeted therapy [4]. There is therefore a need for a novel second-line therapy which is effective in an aRCC patient population who have failed on VEGF-targeted therapies, and for whom BSC remains the only option for treatment.

Everolimus (Afinitor®) is an oral, once-daily inhibitor of mammalian target of rapamycin (mTOR); hence has a different mode of action to the VEGF-targeted therapies. Temsirolimus (Torisel®) is an mTOR inhibitor that has shown clinical benefit versus interferon-alpha (IFN-α) in poor prognosis (i.e. three or more pre-treatment risk factors) aRCC patients. Therefore, temsirolimus is licensed for a different aRCC patient population than everolimus. Everolimus is a convenient oral formulation, whereas temsirolimus is delivered as a weekly intravenous infusion

requiring regular hospital visits which may be particularly burdensome to aRCC patients and their caregivers. In addition, this mode of administration will incur an additional resource burden with associated costs.

In contrast to the VEGF targeted therapies, everolimus is an mTOR inhibitor that acts on central regulation of cellular processes. This is a novel mode of action which has the potential to confer benefits earlier in the treatment pathway. Clinical trials are underway to evaluate other settings in RCC as well as other indications. A phase II study – 'Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-Line and Second-Line Treatment of Patients with Metastatic Renal Cell Carcinoma (RECORD3)' (Clinicaltrials.gov Identifier: NCT00903175) starts patient recruitment in Q4 2009.

4.3 What is the principal mechanism of action of the technology?

Everolimus is a selective kinase inhibitor that blocks the action of the mTOR (mammalian target of rapamycin) protein, which plays a central role in regulating key cellular functions, such as cell proliferation, survival, growth, and angiogenesis (formation of new blood vessels). It is well established that angiogenesis is necessary for cancerous tumours to keep growing and spreading. Without angiogenesis, tumour growth stops. The mTOR pathway is considered to be a major regulator of cell growth and angiogenesis. By inhibiting the mTOR pathway, everolimus has been shown to reduce tumour cell proliferation, and angiogenesis in solid tumours *in vivo*, and thus has the potential to block renal cell cancer growth [55].

The majority of protein kinases that are targets for approved cancer therapies are receptors located on the surface of the cell, including the vascular endothelial growth factor receptors [55]. In contrast, mTOR is found predominantly in the cytoplasm of the cell, where it acts as a central regulator of many biological processes essential for cell proliferation, angiogenesis, and cell metabolism [56]. mTOR is a key intracellular point of convergence for many important signalling pathways, which are located upstream from mTOR. These pathways are activated by input from a number of signalling proteins, including cell surface growth factor receptors such as VEGF [57]. Thus, mTOR is considered an exciting therapeutic target because it is situated downstream from a number of pathways that are abnormally activated in cancer [58,59]. Everolimus therefore represents an innovative approach to treating aRCC.

4.4 Positioning of everolimus in the treatment pathway

4.4.1 Surgery

The NICE manual on improving outcomes in urological cancers recommends that all patients who are fit to undergo surgery (including those with advanced (stage III-IV disease) should be offered surgical resection (radical nephrectomy) of the primary tumour, except those with small tumours [60], as this remains the most successful therapeutic outcome. Patients with small tumours should be considered for nephron-sparing surgery (partial nephrectomy) where appropriate. However, a high percentage of patients, (approximately 20-30%) still develop advanced disease following this procedure [61,62].

4.4.2 Cytokine therapy

Over the last 20 years, the mainstay first-line drug treatment for aRCC has been non-specific biological response modifiers IL-2 and IFN-α, administered by subcutaneous infusion. Immunotherapy with IL-2 and IFN-α in randomised controlled trials (RCTs) resulted in response rates of just 10-20% in aRCC patients, with long-term survival being achieved in only a few patients [20,61]. Increasing evidence shows that patients with intermediate or poor prognosis derive no benefit from cytokine therapy [63,64], and these therapies are associated with poor tolerability.

4.4.3 Novel targeted drug treatments

In the last 10 years the development of therapies that target biological pathways, e.g. VEGF, has been the main advance in the treatment of aRCC.

While VEGF is the predominant mediator of angiogenesis (with over-expression of VEGF resulting in tumour growth and angiogenesis), there are different strategies for inhibiting its pathway. Anti-VEGF strategies that target the receptor, such as tyrosine kinase inhibitors (TKIs) (sunitinib (Sutent®) and sorafenib (Nexavar®)) have a wider range of inhibitory effects and may disrupt other secondary pathways that are also mediated through receptor kinases [65]. Anti-VEGF strategies that specifically target the ligand, such as VEGF antibodies (bevacizumab (Avastin®)) inhibit only the VEGF pathway, and therefore may inhibit angiogenesis without disrupting other "off target" pathways [65].

These agents have recently undergone a NICE assessment in the form of a MTA (Multiple Technology Appraisal) with the final guidance issued August 2009 [66].

Table 4.5 below outlines the various EMEA approved aRCC therapies, their specific indications, and their NICE guidance recommendations.

Table 4.5 Summary of approved indications for leading aRCC treatments

Agent	Description and mechanism of action[57]	Approved EU indication	NICE Guidance
Everolimus (Afinitor®)	Oral drug that selectively inhibits mTOR, thereby reducing angiogenesis and inhibiting tumour growth	Treatment of patients with aRCC, whose disease has progressed on or after treatment with VEGF-targeted therapy [67]	Everolimus for the second-line treatment of mRCC. Expected date of FAD April 2010 with full guidance June 2010 [68]
Sunitinib (Sutent®)	Oral, small-molecule, multi-targeted TKI resulting in anti-cancer and anti-angiogenesis effects	Advanced and/or metastatic renal cell carcinoma (mRCC) [69]	• Recommended as a first-line treatment option for people with aRCC who are suitable for immunotherapy and have an (ECOG) performance status of 0 or 1 [14] • Not recommended second-line for the treatment of advanced and/or mRCC [66]
Sorafenib (Nexavar®)	Oral, multikinase inhibitor that decreases tumour cell proliferation *in vitro*	Advanced RCC who have failed prior IFN-α or IL-2 based therapy or are considered unsuitable for such therapy [70]	Not recommended first- or second-line for the treatment of advanced and/or mRCC [66]
Temsirolimus (Torisel®)	IV drug that inhibits mTOR kinase activity, resulting in cell death	Advanced renal cell carcinoma who have at least three of six prognostic risk factors [71]	Not recommended first-line for the treatment of advanced and/or mRCC [66]
Bevacizumab (Avastin®)	Monoclonal antibody preventing angiogenesis by targeting VEGF	First-line advanced and/or metastatic renal cell cancer, in combination with IFN-α-2a [72]	Not recommended first-line for the treatment of advanced and/or mRCC [66]

In March 2009, NICE approved sunitinib for the first-line treatment of advanced and/or mRCC [14]. Sorafenib, temsirolimus and bevacizumab have not been recommended for use in any of their licensed aRCC settings. In addition, sunitinib was not deemed to be clinically effective in the second-line setting [66]. This means

that there are no NICE recommended therapies, in England and Wales following failure of VEGF-targeted therapy, i.e. sunitinib first-line [14,66].

4.4.4 Everolimus or RAD001 (Afinitor®)

Everolimus is the only oral, once-daily selective inhibitor of the mTOR protein that controls tumour cell division, growth and angiogenesis [55]. Everolimus has also been granted orphan drug status [73].

Marketing Authorisation of everolimus has been based on data from RECORD-1 (Renal Cell cancer treatment with Oral RAD001 given Daily) (study C2240); the largest phase III clinical trial to study the effects of an oral mTOR inhibitor in aRCC patients whose cancer progressed despite prior treatment with a VEGF-targeted therapy. When compared with placebo, everolimus more than doubled median PFS in patients with aRCC (4.9 versus 1.9 months). Importantly, the data showed everolimus reduced the risk of disease progression or death by 67% (hazard ratio=0.33 with 95% confidence interval 0.25 to 0.43; P<0.001) [74]. This is a remarkable achievement considering the high degree of pre-treatment and very advanced stage of the disease.

Currently, there are no licensed treatment options for this recently established, distinct, heavily pre-treated population of aRCC patients whose disease has already progressed following targeted therapy. Everolimus will provide this group of patients with a new treatment option to fill this urgent unmet need.

4.4.5 Treatment Pathways

Guidelines for RCC with direct relevance for England and Wales clinical practice have been recently published by Nathan et al., 2009 [64]. These represent UK oncologist consensus guidelines based on a review of clinical evidence for aRCC drug therapies, and demonstrate where everolimus should be positioned in the aRCC treatment pathway. Surgical resection of a primary RCC is the first step, with or without adjuvant treatment (the guidelines note there is a lack of level 1 evidence to support the use of routine adjuvant treatment). Recommended first-line drug therapies for aRCC with level 1 evidence are immunotherapy with IFN-α or IL-2 or targeted therapies (e.g. sunitinib), dependent on patient prognosis (Table 4.6). Following this, the guidelines recommend either sorafenib or everolimus depending on what treatments patients have failed first-line (after IFN-α for sorafenib, and after VEGF-targeted therapy for everolimus). Table 4.6 below shows that everolimus

would be used to treat a distinct group of pre-treated aRCC patients who have failed first-line treatment.

The Nathan et al., 2009 guidelines suggest that it could be reasonable to consider further VEGFr-TKI therapy after failure of the first. However, this is based on evidence of no cross-resistance between sorafenib and sunitinib and not as a result of findings from RCTs [64,75].

Table 4.6 Treatment options based on level 1 evidence for first- and second-line treatment of aRCC with clear cell histology

Patient Group	First-line treatment	Positive NICE recommendation
Good prognosis	Sunitinib Bevacizumab and IFN-α IFN-α	Yes No N/A
Intermediate prognosis	Sunitinib Bevacizumab and IFN-α	Yes No
Poor prognosis	Temsirolimus	No
Previous treatment	**Second- line treatment**	
Cytokine	Sorafenib	No
VEGFR-TKI OR BEVACIZUMAB	**EVEROLIMUS**	TBD

Adapted from: Nathan et al., 2009 [64]

Table 4.6 also indicates current NICE recommendations for the therapies covered by the Nathan et al., Guidelines. Therefore, based on NICE guidance, first-line drug treatment is expected to be sunitinib. Results from a RCT demonstrate that everolimus is effective as a second-line therapy post sunitinib failure.

The new guidelines indicate the potential use of everolimus after VEGF-targeted therapy including bevacizumab therapy, based on evidence from the RECORD-1 trial which included patients failing on this treatment [44] [74].

4.5 Issues relating to current clinical practice

Historically there has been a dearth of available options for aRCC patients; hence the prognosis has been very poor for these patients for many years. Until recently, the only drug option was cytokine therapy with limited clinical effectiveness and poor tolerability, or BSC. From this low base the newer targeted therapies have increased

the number of options and the potential for clinical benefit. The new NICE guidance is intended to reduce the potential for variability in clinical practice, and so everolimus with its distinct aRCC patient population and positioning (i.e. post VEGF-targeted therapy) should not lead to any specific issues regarding appropriate use in relation to other aRCC treatments.

4.6 Relevant guidelines

The most relevant guideline for clinical practice in England and Wales is the recently published evidence based consensus guidelines of Nathan et al., 2009 [64] covered in Section 4.4.5 above.

European guidelines from the EUA (European Association of Urology (updated 2009) [76], and the European Organisation for Research and Treatment of Cancer (EORTC) (2009) [77], and US guidelines from the National Comprehensive Cancer Network (NCCN) for kidney cancer (2009) [78] all recommend treatment with everolimus in aRCC patients who have progressed following or on VEGF-targeted therapy. These guidelines recommend the use of surgery first, with drug therapy for those in whom surgery is unsuccessful or not appropriate, similar to the UK Nathan et al., 2009 guidelines [64].

5 Equity and equality

5.1 Identification of equity and equalities issues

5.1.1 Issues relating to equity and equality

There is no specific predisposition of any racial or socio-demographic group to risk of RCC. The patients included in the pivotal phase III clinical trial for everolimus were predominantly Caucasian, which represented the predominant race in the countries included in the trial (see Table 6.3 in Section 6). However, there is no expectation that outcomes would have been different had a different racial mix been included. There are more male than female patients with RCC in England and Wales (see Section 4.1.1) and patients are predominantly elderly, but these characteristics alone do not raise any particular equity issues that need explicitly to be taken into account in this submission.

However, an important consideration is the weight society gives to end-of-life treatments with evidence of clinical benefit for patients with short life expectancy. This has recently been captured by new criteria to be taken into account by the NICE Appraisal Committees when considering such treatments [79,80]. Everolimus for aRCC qualifies for consideration under this supplementary advice for the following reasons:

- Patients have a short life expectancy of less than 2 years.
- Evidence presented in Sections 6-7 of this submission demonstrates that everolimus can extend life compared to current practice of BSC by more than three months for heavily pre-treated RCC patients.
- Everolimus is intended to be used at a stage of aRCC when there are likely to be no other active treatment options with demonstrated efficacy available; hence offers a step change improvement over BSC.
- Advanced RCC is a small patient population and everolimus is not expected to be licensed for any other indications within the timeframe of the NICE appraisal.

In its appraisal of sorafenib and sunitinib, NICE determined that both therapies satisfied the end-of-life criteria, which meant that the Appraisal Committee was able to consider ICERs in excess of £30k [66].

5.1.2 Addressing equity and equality issues

Application of the end-of-life criteria to everolimus will ultimately be decided by the NICE Appraisal Committee. The supplementary advice states that if the criteria are met then the Appraisal Committee will consider the impact of giving greater weight to the additional QALYs generated and consider the size of the additional weight needed for the cost-effectiveness of everolimus to fall within the current threshold range (£20-30,000/QALY). We have estimated the QALY weights that would be required in order for everolimus versus placebo to achieve a cost/QALY of £20k and £30k and results are presented in Section 7.

6 Clinical evidence

6.1 Identification of studies

A systematic review of the clinical evidence relating directly to the appraisal decision problem previously presented in Section A of this submission was performed. The primary objective of the systematic review was to address the following decision problem.

"What is the clinical efficacy, safety, and cost-effectiveness of everolimus plus BSC for the treatment of advanced renal cell carcinoma (aRCC) which has progressed following or on VEGF-targeted therapy (sunitinib, sorafenib, bevacizumab), compared to best supportive care (BSC) alone?"

In line with this, data on the clinical efficacy and safety of everolimus was obtained by a systematic search and review of published research evidence and conference abstracts (with supporting poster or slide presentations), supplemented by unpublished trial data for everolimus supplied by Novartis.

The search strategy was based on that reported in the PenTAG (Peninsula Technology Assessment Group) Assessment Report for bevacizumab, sorafenib, sunitinib and temsirolimus, produced as part of the NICE MTA (Multiple Technology Appraisal) of drug therapies for aRCC [19]. The primary search included index terms for renal cell carcinoma and everolimus. No other drug therapies were included as everolimus is targeted for use in heavily pre-treated aRCC patients for whom BSC represents the only remaining option. A protocol for the search and review was developed and the final search was performed in June 2009.

The search strategy used and the electronic databases and other sources searched are reported in Section 10.2, Appendix2. In addition, a separate everolimus systematic review report provides further details [81].

6.2 Study selection

6.2.1 Complete list of RCTs

The search identified one RCT in the relevant patient population i.e. pre-treated aRCC patients who have progressed following or on VEGF-targeted therapy. This was the phase III RECORD-1 study (registration at Clinicaltrials.gov NCT00410124,

study C2240) to investigate the efficacy and safety of everolimus plus BSC versus placebo plus BSC in patients with aRCC with a clear cell component which has progressed following or on treatment with at least one VEGF-targeted therapy. Whilst this study was placebo-controlled it also compares everolimus with the appropriate comparator ie BSC. BSC is the appropriate comparator as the patients recruited to the study represent those aRCC patients for whom no other effective treatment options exist.

The systematic search confirmed that in addition to a final analysis report for the RECORD-1 study [40] (the primary source for this submission) there was an earlier clinical study report relating to a second interim analysis [82] and one full peer reviewed publication relating to this the second interim analysis, published by Motzer et al., in the Lancet in 2008 [44].

The full clinical study report for the final analysis (addendum report) [40] is particularly important for this appraisal as it provides the main source for the results from the final analysis at the end of the full double-blind period, the time point at which the trial was officially terminated (cut-off date of February 28th 2008). This is supported by an abstract and slide presentation of the key final analysis results at the 2008 ESMO meeting (Escudier et al., 2008) [74], and a further abstract reporting the same results at an ASCO Genitourinary Cancers Symposium (Kay et al., 2009) [83]. There is also an ASCO abstract reporting patient reported outcomes (PRO) results from the RECORD-1 trial final analysis [84].

The Motzer et al., [44] publication (supported by two 2008 ASCO meeting presentations, one a slide presentation [85] and the other a poster presentation [86] relating to the same abstract) provides results from the pre-planned second interim analysis time point, which reflects the time when the pre-specified efficacy objectives were met (cut-off date of 15th October 2007). An earlier version of the full clinical study report for the second interim analysis results is also available, although for this analysis cut-off the Lancet publication represents the primary evidence source [82].

Whilst the decision to terminate the trial due to outstanding efficacy was based on results at the earlier cut-off date, the final analysis results have greater relevance for the appraisal as they represent a longer duration of patient follow-up whilst retaining the robustness of the double-blind RCT design. The efficacy results in the everolimus SPC are also based on the final analysis data set (Section 10.1, Appendix 1).

Details of the primary references and supporting sources for the RECORD-1 RCT are summarised in Table 6.1.

Table 6.1 Summary of RECORD-1 trial and sources

Study	Primary publications and sources	Study type	Patients	N	Intervention and dose	Comparator and dose	Supplementary publications and sources
RECORD-1 Final analysis	Full clinical study report – addendum report, 2009 [40]	R, DB, PC, phase III, international, multicentre	Patients with aRCC with a clear cell component, which has progressed following or on VEGF-targeted therapy	416	Everolimus 10mg/day (2 x 5mg tablets) plus BSC	Placebo plus BSC	Escudier et al., 2008 [74] Kay et al., 2009 [83] Beaumont et al., 2009 [84]
RECORD-1 Second interim analysis	Motzer et al, 2008 [44], Full Clinical study report, 2008 [82]	R, DB, PC, phase III, international, multicentre	Patients with aRCC with a clear cell component, which has progressed following or on VEGF-targeted therapy	410	Everolimus 10mg/day (2 x 5mg mg tablets) plus BSC	Placebo plus BSC	Motzer et al., 2008 [86] Full clinical study report [82]

R – randomised, DB – double-blind, PC – placebo-controlled, BSC – Best supportive care

6.2.2 Inclusion and exclusion criteria

The inclusion criteria for study selection were defined as follows in line with the appraisal scope and in order to best address the decision problem for the appraisal:

- *Study population* consisting of patients with aRCC which has progressed following or on at least one prior VEGFr-TKI therapy.

- *Interventions of interest* were everolimus plus BSC versus placebo plus BSC as the comparator.

- *Outcomes* covered related to efficacy (overall survival, progression free survival, and tumour response rate), HRQoL/PRO, and safety (Grade III or IV adverse events (AE) or high volume Grade I/II AE).

- *Study design* for primary data extraction was RCTs. Outcomes of interest were to be extracted from systematic reviews of phase II or III RCT's and single RCT's (both parallel, cross-over designs, and studies comparing different doses or schedules of the drugs of interest) that may either be blinded or un-blinded and published (with additional unpublished material from clinical study reports if available). The systematic review protocol also allowed for data from secondary level designs to be considered, which included single-arm trials and observational studies, and expanded access programmes, if in the opinion of the reviewers this source provided valuable supplementary evidence to the primary RCT evidence.

- *Language* - only English language publications and abstracts were considered.

Specific exclusion criteria covered:

- Pre-clinical and biological studies
- Animal studies
- Phase I clinical trials
- Editorials, opinions, commentaries, reviews (other than systematic reviews)
- Non-English language studies
- Reports/abstracts where there were insufficient methodological details to judge study quality.

Full published papers for the selected studies were retrieved. This was supplemented by additional unpublished data from clinical study reports available from Novartis, and from conference abstracts and supporting slide/poster presentations. Data from conference abstracts and supporting slides/posters was also used to provide data for studies without a full publication or clinical study report available. From these sources relevant information was extracted for each study using a standardised data extraction form (DEF) (see the everolimus systematic review report for further details) [81].

6.2.3 List of relevant RCTs

The primary electronic database and abstract search contained a total of 106 hits. The records identified in the electronic searches were assessed for inclusion by two reviewers. Each reviewer independently scanned all titles and abstracts identified in the searches to identify reports that might be relevant, using the inclusion/exclusion criteria, outcomes/endpoints, and study designs outlined in Section 6.2.2 above. Details of the included and excluded publications and abstracts can be found in the everolimus systematic review. The inclusion of final full papers/abstracts retrieved were assessed independently by the two reviewers and agreement reached. A flow diagram (Figure 6.1) for study selection is provided at the end of Section 6.2.

As specified in Section 6.2.1 above, one relevant RCT (RECORD-1) that directly compares everolimus with the appropriate comparator, placebo plus BSC, was identified from the search. The relevant primary and supporting publications and unpublished sources for the RECORD-1 RCT have been presented in Table 6.1 above.

The RECORD-1 trial directly relates to the decision problem for the appraisal by comparing everolimus plus BSC with placebo plus BSC in patients with aRCC who have progressed on at least one prior VEGF-targeted treatment.

No relevant studies have been excluded from the assessment.

6.2.4 List of relevant non-randomised controlled trials

In addition to the phase III RCT, the systematic review identified two supportive secondary level phase II non-RCT studies considered by the reviewers to be relevant to the decision problem. The study selection for the non-RCT studies is captured within the flow diagram at the end of this section. These studies were:

- A phase II single arm study of everolimus in patients with progressive measurable aRCC whose disease had progressed following no more than one prior therapy (including but not exclusively VEGFr-TKI therapy) [59]. The aim of this study was to explore the anti-tumour activity of everolimus in aRCC.

- A phase II single arm study of everolimus in patients with aRCC whose disease has progressed after no more than two previous therapies, of which at least one should be a VEGFr-TKI. This is supported by a 2008 ASCO abstract and poster (Jac et al., 2008) [39]. The aim of the study was to explore the efficacy of everolimus in a specific aRCC patient population. It is primarily an extension of the above phase II study by the same study investigators, but is understood to include different patients. It is more directly relevant for the decision problem of this appraisal as efficacy and safety is investigated only in patients who have failed on at least one VEGFr-TKI (i.e. sorafenib, sunitinib).

Table 6.2 provides an overview of the selected non-RCT studies. Despite small patient numbers, these have been included as they provide supportive evidence to the RECORD-1 trial on key outcomes in aRCC patient populations of relevance to the decision problem (i.e. PFS, OS, and objective tumour response rate), especially the second trial conducted only in patients whose disease had progressed following or on VEGFr-TKI therapy. As a further justification for their inclusion in this submission, both were extremely important studies in the clinical development of everolimus because they gave the first indication of the significant efficacy and good tolerability of everolimus in heavily pre-treated aRCC patients for whom no other active treatment options exist. These studies were conducted independently

. The indication of efficacy from these studies was pivotal to the decision to conduct the larger phase III RECORD-1 trial to robustly prove the clinical benefits of everolimus in a late stage aRCC patient population.

Table 6.2 Summary of relevant non-RCTs

Study	Primary publications and sources	Study type	Patients	N	Intervention and dose	Comparator and dose	Supplementary publications and sources	Justification for inclusion
Phase II trial (A)	Amato et al., 2009 Cancer [59]	SA, NC, phase II	Patients with aRCC who have received no more than one other therapy (including VEGF-targeted therapy).	41	Everolimus 10mg/day (2 x 5mg tablets)	-	Amato et al., 2006 [87] Jac et al., 2007 [88]	Although some patients in the study are not those experiencing only VEGF-targeted therapy failure, the study provides additional data from an independent study on outcomes relevant to the decision problem, with the appropriate drug dose.
Phase II trial (B)	Jac et al., 2008 J Clin Oncol [39]	SA, NC, phase II	Patients with aRCC whose disease has progressed after no more than two therapies, one of which was a VEGFr-TKI.	22	Everolimus 10mg/day (2 x 5mg tablets)	-	-	Provides additional data from an independent study on outcomes relevant to the decision problem, with the appropriate drug dose and patient population, to complement the RECORD-1 data.

SA – single arm, NC– non-control, BSC – Best supportive care

6.2.5 Ongoing studies

No new trials are planned for everolimus in aRCC with clear cell histology following VEGF-targeted therapy failure. However, further analysis of survival outcomes for the ITT population based on two years follow-up from the phase III RCT (ClinicalTrials.gov identifier: NCT00410124) is planned.

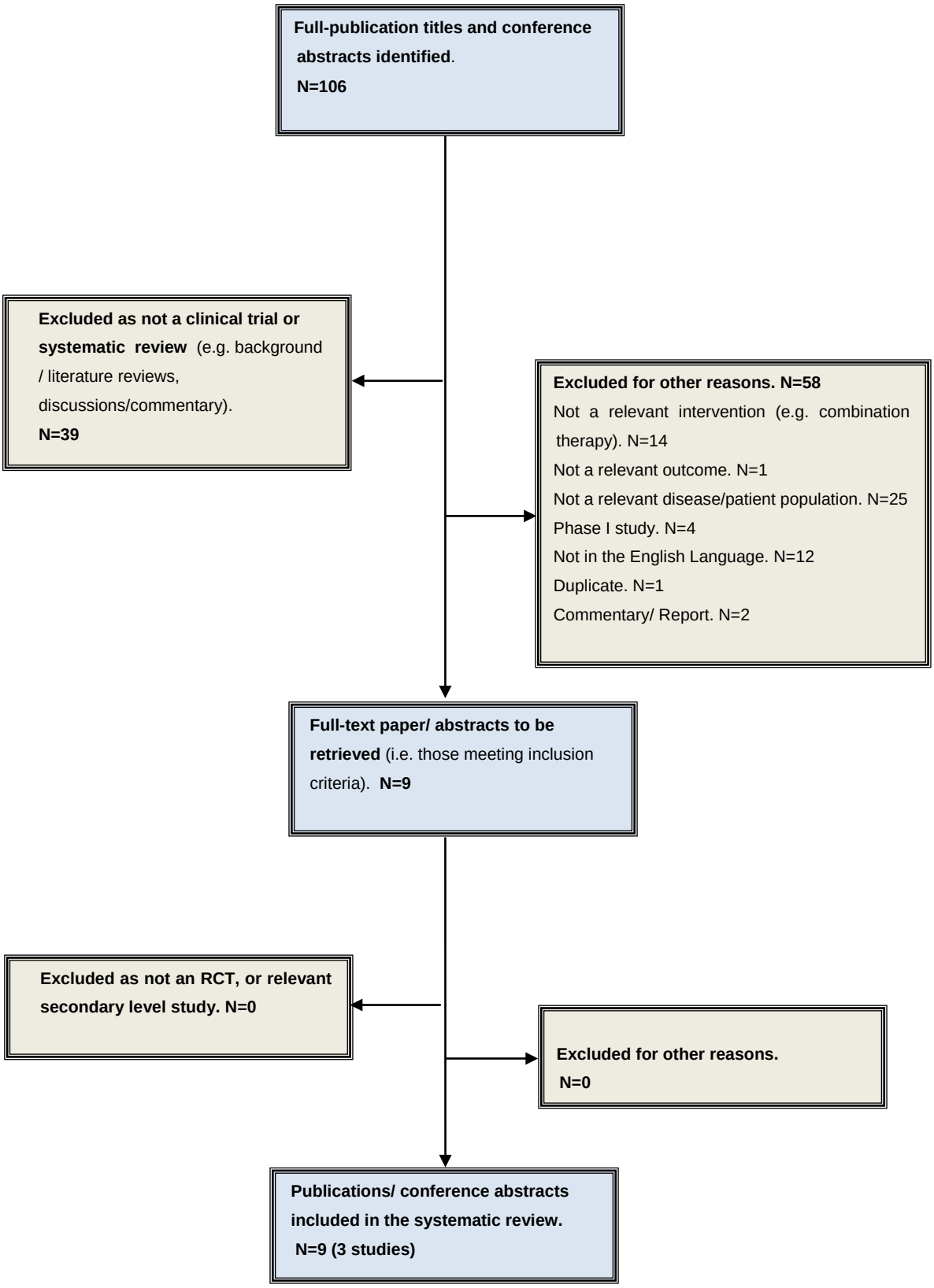
In addition, an international expanded access programme for everolimus (ClinicalTrials.gov identifier: NCT00655252) has been ongoing in the UK at the following centres:

- Mount Vernon Cancer Centre
- St Luke's Wing, Royal Surrey County Hospital
- British Haematology and Oncology Centre, Bristol
- CRUK, Glasgow
- Royal Bournemouth Hospital
- Singleton Hospital, Swansea
- Oncology & Haematology Clinical Trials Unit, Leicester
- Addenbrookes Hospital, Cambridge
- Southampton University Hospital NHS Trust
- Newcastle General Hospital
- Royal Marsden Hospital, London

The use of everolimus in an earlier aRCC context is also being investigated. A phase II study – 'Efficacy and Safety Comparison of RAD001 Versus Sunitinib in the First-Line and Second-Line Treatment of Patients with Metastatic Renal Cell Carcinoma (RECORD-3)' (Clinicaltrials.gov Identifier: NCT00903175) starts patient recruitment in Q4 2009. The primary objective of this trial is to assess if PFS after first-line of treatment in patients who receive everolimus will be non-inferior to the PFS of patients who receive sunitinib after first-line treatment.

A further phase II trial to evaluate the combination of everolimus plus bevacizumab versus IFN-α-2a plus bevacizumab in patients with mRCC (RECORD-2) (Clinicaltrials.gov Identifier: NCT007192674) is currently recruiting participants. In this trial the primary objective is to assess the treatment effect on PFS of these patients in order to estimate the chance of success of a possible subsequent phase III study.

Figure 6.1 Flow chart for RCT and non-RCT study selection



6.3 Summary of methodology of relevant RCTs

6.3.1 Methods

6.3.1.1 Rationale for the phase III RECORD-1 trial

The new targeted therapies for aRCC over the last five years have increased the range of first-line treatments licensed for drug-naïve patients. Post first-line the options for a patient whose disease has progressed is still extremely limited. Sunitinib is licensed for first and second-line use in aRCC [69]. Sorafenib is also licensed for first-line treatment in patients unsuitable for IFN-α or IL-2 therapy; and in second-line treatment in patients with disease progression following cytokine based therapy [70]. However, whilst sunitinib has been recently recommended by NICE for first-line use in aRCC [14], neither therapy has been recommended by NICE for use in second-line treatment [66]. Hence, in England and Wales there are currently no other licensed or NICE recommended treatment options for aRCC patients whose disease has progressed following first-line treatment.

The aim for the development of everolimus in aRCC was to meet an unmet clinical need and provide a treatment option for patients who have already failed on other treatments. At the time of planning the RECORD-1 trial, the VEGFr-TKI targeted therapies, sunitinib and sorafenib represented the most promising of the new targeted agents, so the trial was designed to investigate the efficacy of everolimus after failure on one or both of these drugs. In RECORD-1, patients could have received prior bevacizumab or cytokine therapy, radiotherapy, chemotherapy and almost all had prior surgery. Overall the patients represented a heavily pre-treated population reflecting the myriad of potential patient pathways in practice at the time. The RECORD-1 study hypothesis was that everolimus plus BSC could improve clinical outcomes over placebo plus BSC for these end stage patients who had already failed on the best available targeted drug options.

In terms of the clinical development history, 10mg/day of everolimus was established in phase I studies as a dose that demonstrated initial signs of strong anti-tumour activity with acceptable tolerability aRCC patients [89-91]. These studies supported the dose of 10mg/day used in the RECORD-1 trial. In addition, two single arm, phase II clinical trials of everolimus continuous daily therapy at 10mg/day demonstrated anti-tumour activity in pre-treated aRCC patients and reported benefits in PFS and other outcomes [39,59,87,88]. These studies confirmed the potential of everolimus to

confer benefits with acceptable tolerability for the treatment of aRCC, thus providing the rationale for further clinical investigation within a large scale RCT.

6.3.1.2 Design, location and duration of study

RECORD-1 was an international, multi-centre, double-blind, randomised, placebo-controlled, phase III trial designed to investigate the efficacy and safety of continuous daily treatment with everolimus (10mg/day) plus BSC versus placebo plus BSC in patients with aRCC with a clear cell component which has progressed following or on VEGF-targeted therapy [40].

The RECORD-1 study was designed to be a cross-over trial; hence patients receiving placebo plus BSC with documented radiological disease progression were allowed to cross-over to receive open-label everolimus treatment if the treating clinician felt that the patient could benefit from this treatment [40]. The rationale for this (as previously reported in other placebo-controlled cancer trials, including sunitinib for gastrointestinal stromal tumours), was that it was considered unethical to deny active effective therapy to end stage aRCC patients following evidence of further disease progression [31,92]. The study was conducted at 86 centres in Australia (6 centres), Canada (7 centres), Europe (34 centres), Japan (13 centres), and USA (26 centres). Patients were recruited and allocated to treatment groups between December 2006 and November 2007 [44].

6.3.1.3 Randomisation and blinding

Patients were randomised on enrolment into the study. Patients were assigned 2:1 to the everolimus plus BSC and placebo plus BSC arms, respectively. This was achieved by the investigator calling an automated, interactive voice response system to assign a unique randomisation number to each patient. A block randomisation was applied to ensure 2:1 randomisation (4 blocks for everolimus plus BSC, 2 for placebo plus BSC) [44].

The study was double-blinded up to the point of documented radiological disease progression by central radiological review. The allocated treatment arm was not revealed to the centre investigator or the patient until this point. In addition, the independent central review investigators who performed the selection of target lesions for tumour assessments and outcome assessments were also blinded. The randomisation data was kept confidential to all bar the independent data monitoring committee (IDMC) until time of un-blinding with the randomisation list kept under lock

within Novartis. Disclosure was only allowed once patients experienced disease progression, so that those receiving placebo could potentially be switched to everolimus or during a medical emergency when disclosure was necessary to provide optimum treatment. This was allowed for ethical reasons. However, blinding was successfully maintained up to this point in order to measure PFS, the primary endpoint in the trial [40].

Prior to randomisation, patients were stratified by whether they received one or two prior VEGFr-TKI therapies (sunitinib or sorafenib), and according to the 2004 MSKCC prognostic score (see Section 4.1.6). The prognostic risk factors in the 2004 MSKCC group were identified as being specific to aRCC patients who had failed prior cytokine therapy. As this was effectively considering 2nd line patients it was thought these are the most relevant for the RECORD-1 patient population. The 3 prognostic risk factors were:

- Low Karnofsky Performance Score (<80%)
- Low haemoglobin (≤11.5g/dl for females, ≤13g/dl for males)
- High corrected serum calcium (≥10mg/dl)

Based on the Memorial Sloan-Kettering Cancer Centre (MSKCC) prognostic risk factor system found a median survival of 22 months, 11.9 months and 5.4 months in patients with zero (good prognosis), one (intermediate prognosis), and two/three (poor prognosis) risk factors, respectively but a median overall survival time of 12.7 months.

A more favourable MSKCC profile is predictive of better survival. The combination of numbers of VEGFr-TKI therapies (2) and MSKCC categories (3) produced six different pre-specified strata in the trial [40].

Two interim analyses and a final analysis, when 290 PFS events were observed by independent central radiology review, were planned. The study was designed to be stopped early prior to 290 PFS events if outstanding efficacy were demonstrated based on reaching pre-specified efficacy stopping criteria, due to limited efficacy ('futility') or due to safety concerns. There were three main phases to the study [40]:

Screening/baseline: Performed within five weeks of first study dose to ensure each patient met the study inclusion/exclusion criteria. Evaluations included physical examinations and investigations, review of medical history, prior anti-cancer treatments. Advanced RCC was confirmed by radiological investigation and tumour

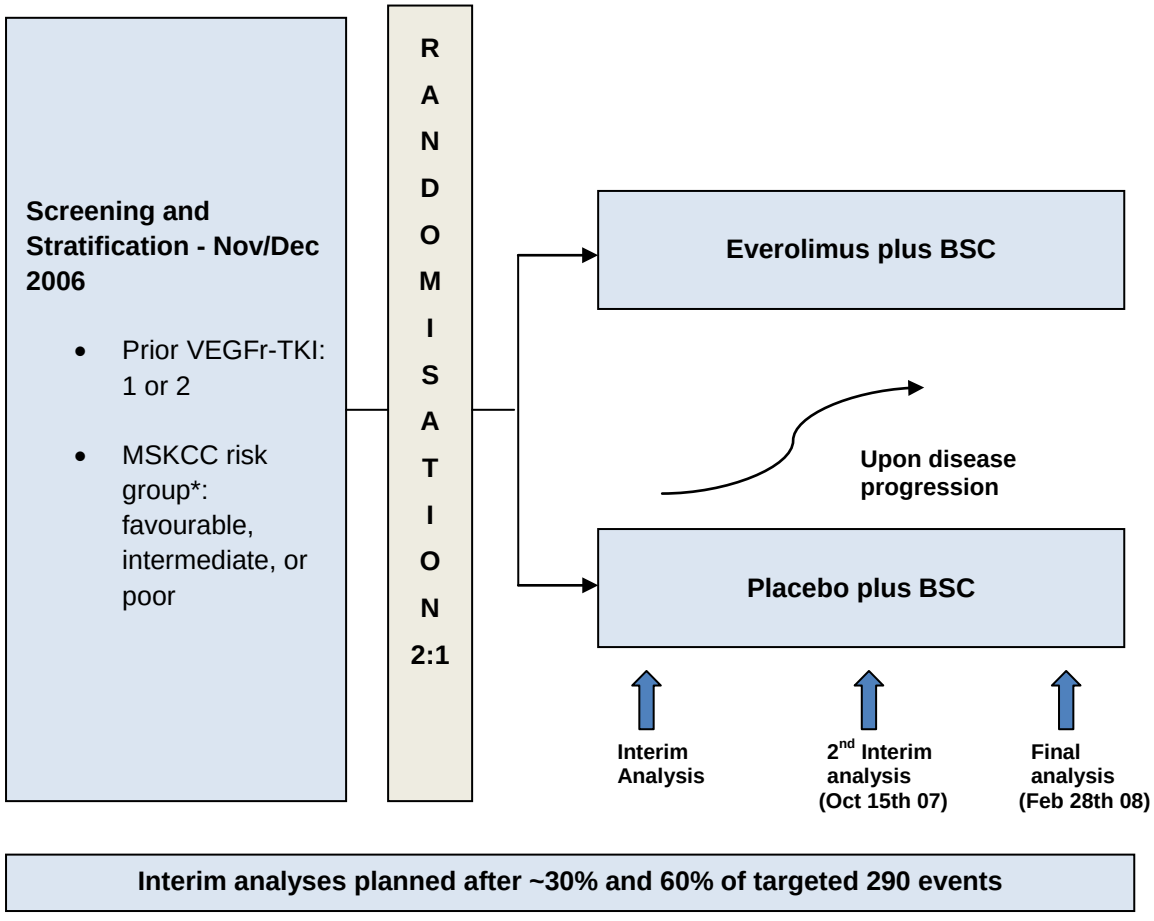
assessment was performed to provide baseline reference data to measure disease progression whilst on blinded treatment [40].

Blinded treatment: Patients meeting inclusion/exclusion criteria were randomised to the study drug or placebo with the first day of treatment representing day 1 of cycle 1, with each treatment cycle defined as 28 days for evaluation purposes. The duration of treatment was not fixed but continued until disease progression (with tumour progression confirmed by RECIST criteria), or discontinuation for other reasons including death or unacceptable toxicity [40].

Open-label provision of everolimus: Once disease progression was confirmed, patients who previously received placebo plus BSC could be offered open-label everolimus if the treating clinician thought this in the best interests of the patient [40].

Figure 6.2 provides an overview of the study conduct with the planned two interim and final analysis time points marked [40].

Figure 6.2 RECORD-1 study design



* Motzer et al., 2004 [18]

6.3.1.4 Intervention and comparator

Adults diagnosed with aRCC with a clear cell component who experienced disease progression on or within six months of treatment on one or more VEGFr-TKI therapies (sorafenib and sunitinib) were randomly assigned to one of the two treatment groups:

a) Everolimus plus BSC. This consisted of a continuous, once daily, oral dose of 10mg/day everolimus administered at the same time each day with or without food. Treatment was continued until documented radiological disease progression, unacceptable toxicity, discontinuation for other reasons, or death. The dose could be reduced to 5mg/day if patients experienced clinically significant haematological or other AEs that according to a nomogram[a] were felt by the site investigator to be related to the drug [44].

b) Placebo plus BSC. This consisted of a continuous, once daily, oral dose of 10mg/day placebo administered at the same time each day with or without food. Treatment was continued until documented radiological disease progression, unacceptable toxicity, discontinuation for other reasons, or death. Patients found to be on placebo when unblinded were allowed to be crossed-over by the investigator to receive open-label everolimus 10mg/day [44].

As BSC was assigned to both treatment arms, the phase III trial can be considered to contain an appropriate comparator as BSC alone represents current clinical practice in the UK for patients who have failed on previous active therapy. Sorafenib and sunitinib are licensed for the second-line treatment of aRCC (after cytokine failure) [69,70] but have not been recommended for use in this context by either NICE or the Scottish Medicines Consortium (SMC) [66,93-95]. In addition, the restrictions dictated by their licences means that neither drug would be considered an appropriate

[a] A nomogram is a graphical calculating device. A nomogram typically has three scales: two scales represent known values and one scale is the scale where the result is read off. The known scales are placed on the outside; i.e. the result scale is in the centre. Each known value of the calculation is marked on the outer scales and a line is drawn between each mark. Where the line and the inside scale intersects is the result.

treatment for aRCC patients who have failed on an initial VEGF-targeted therapy which is the relevant patient population for the decision problem being considered in this appraisal.

In the RECORD-1 trial BSC consisted of the use of both drug and non-drug therapy including the following: ongoing bisphosphonate therapy for treatment of bone metastases, pain medication, localised radiotherapy, nutritional support, oxygen therapy and blood transfusions, use of leukocyte growth factors, and megestrol acetate as an appetite stimulant (except for Japanese patients). The use of other investigational agents was not permitted, nor was the use of other anti-cancer agents whilst the patient was on study drug [40].

6.3.1.5 Participants

Eligible patients were adults aged ≥18 years with aRCC who had progressed on or within six months of stopping treatment with sunitinib, sorafenib or both drugs. Previous therapy with a cytokine (IFN-α or IL-2) or bevacizumab was permitted. Prior vaccine therapy in the adjuvant setting was also permitted. Women of childbearing potential must have had a negative serum or urine pregnancy test within seven days prior to the administration of the first study treatment. Patients were required to provide a written informed consent, obtained according to local guidelines [44].

Specific inclusion criteria were as follows:

- Aged ≥18 years with aRCC and a histologically or cytologically confirmed clear cell component
- Presence of progressive disease as evaluated by RECIST criteria (at least one measurable lesion either in physical examination or determined by CT scan or MRI) on or within six months of treatment with sorafenib, sunitinib or both
- Karnofsky Performance Score of ≥ 70%
- Life expectancy of >3 months (assessed in relation to performance status and other factors)
- Adequate bone marrow function (ANC≥1.5 x 10^9/L, platelets≥100 x 10^9/L, Hb>9g/dl); adequate liver function (serum bilirubin≤1.5 x ULN, ALT and AST ≤2.5 x ULN, patients with known liver metastases AST and ALT ≤5 x ULN), and adequate renal function (serum creatinine ≤1.5 x ULN).

Patients were not eligible for the study for the following reasons:

- Previously been treated with another mTOR inhibitor
- Receiving chemotherapy, immunotherapy or radiotherapy within four weeks prior to visit one. The wash out period for sunitinib and/or sorafenib was two weeks prior to first study dose
- Receiving chronic treatment with corticosteroids or other immunosuppressant therapy
- Active bleeding or on an oral anti-vitamin K medication
- HIV seropositivity history
- Known hypersensitivity to everolimus or other rapamycins
- Untreated CNS metastases or received treatment within 6 months of study entry
- Other severe/uncontrolled medical conditions (e.g. unstable angina pectoris, symptomatic congestive heart failure, recent MI, cardiac arrhythmia, within six months of study entry; diabetes, severe infection, cirrhosis, chronic active hepatitis, chronic persistent hepatitis, severely impaired lung function)
- History of another primary malignancy within the last three years (except non-melanoma skin cancer, and carcinoma *in situ* of uterine cervix)
- Female patients who are pregnant or breast-feeding, or adults not using effective birth control methods
- Patients using other investigational drugs, within four weeks prior to visit one.

Patients could only be enrolled into the study at sites that had received Institutional Review Board approval for the study protocol and was performed in accordance with usual international standards of good clinical practice [40].

6.3.2 Patient numbers and characteristics

The number of patients at the final analysis time point (28th February 2008) randomised to the everolimus treatment arm was 277 (272 at the second interim analysis cut-off, 15th October 2007 reported in the Lancet publication) and in the placebo plus BSC arm was 139 patients (138 at the second interim analysis cut-off, 15th October 2007 reported in the Lancet publication) [44] [40]. This represents the RCT full analysis set (FAS). Although the final analysis is unpublished, as the final clinical study report exists [40] for this together with an ESMO slide presentation [74], this is used as the primary source for the data and results presented in this

submission as it represents the full double-blind period for the trial and the longest duration of patient follow-up.

The baseline characteristics for the patients included at the final analysis cut-off are presented in Table 6.3 below. This shows the two patient groups had very similar baseline characteristics. There were more patients aged ≥65 in the placebo group, although the mean age and range was similar. All patients bar one in placebo had the kidney as the primary site of cancer, all patients across both arms had received prior drug therapy, most had undergone prior surgery (primarily nephrectomy), and all had received prior medication for their cancer. Only a very few patients did not demonstrate a clear cell component. The majority of patients in both arms were Caucasian. The prognosis of most patients in both arms was classified using MSKCC criteria as intermediate, although patients entering the trial still had relatively good performance scores (entry criteria). The characteristics of patients recruited to the trial were similar to the RCC patient population in England and Wales in that there were more males than females and predominantly Caucasian (although males may be slightly over-represented in the trial compared to in England and Wales and overall patients may be slightly younger in the trial). Due to the lack of alternative NICE recommended second-line treatments, patients in the trial may be more heavily pre-treated than would be expected in actual clinical practice if everolimus is used following failure of sunitinib.

Table 6.3 RECORD-1 patient baseline characteristics (final analysis cut-off)*

Patient characteristic	Everolimus (10mg/day) plus BSC	Placebo plus BSC
Number of patients	277	139
Mean Age (range)	61 (27-85)	59 (29-79)
Age ≥65 years - n (%)	112 (40.4)	98 (70.5)
Gender Male: - n (%)	216 (78.0)	106 (76.3)
Race: % Caucasian - n (%)	246 (88.8)	121 (87.1)
BMI (kg/m2) – mean (range)**	26.31 (16-48)	26.22 (18-40)
KPS Score:		
% ≥90 - n (%)	176 (63.5)	94 (67.6)
MSKCC risk		
Favourable - n (%)	81 (29.2)	39 (28.1)
Intermediate - n (%)	156 (56.3)	79 (56.8)
Poor- n (%)	40 (14.4)	21(15.1)
Secondary metastases site (>30%)		

Patient characteristic	Everolimus (10mg/day) plus BSC	Placebo plus BSC
Lung - n (%)	216 (78.0)	110 (79.1)
Lymph node - n (%)	154 (55.6)	83 (59.7)
Bone - n (%)	105 (37.9)	47 (33.8)
Liver - n (%)	99 (35.7)	48 (34.5)
Number of disease sites		
1-2 sites - n (%)	92 (33.2)	49 (35.2)
≥3 sites - n (%)	182 (65.7)	88 (63.3)
Non-clear cell histology - n (%)	11 (4.0)	6 (4.3)
Stage at initial diagnosis		
Stage III - n (%)	108 (38.9)	50 (35.9)
Stage IV - n (%)	88 (31.7)	43 (30.9)
Prior VEGFr-TKI therapy		
Sunitinib - n (%)	124 (44.8)	60 (43.2)
Sorafenib - n (%)	81 (29.2)	43 (30.9)
Sunitinib and Sorafenib - n (%)	72 (26.0)	36 (25.9)
Prior systemic therapy		
Interferon - n (%)	139 (50.2)	70 (50.4)
Interleukin 2 - n (%)	61 (22.0)	33 (23.7)
Chemotherapy - n (%)	37 (13.4)	22 (15.8)
Bevacizumab - n (%)	25 (9.0)	14 (10.1)
Non-drug treatment		
Radiotherapy - n (%)	85 (30.7)	38 (27.3)
Any prior surgery - n (%)	269 (97.1)	133 (95.7)
Number progressed whilst on previous therapy (%)* **	197 (71.1)	110 (79.1)
Region		
USA and Canada - n (%)	77 (27.8)	53 (38.1)
Europe - n (%)	180 (64.9)	71 (51.1)
Japan and Australia - n (%)	20 (7.2)	15 (10.8)

*Source: CSR-addendum, [40] Escudier et al., 2008 [74]

**Some missing cases hence N=268 for everolimus plus BSC, N=136 for placebo plus BSC

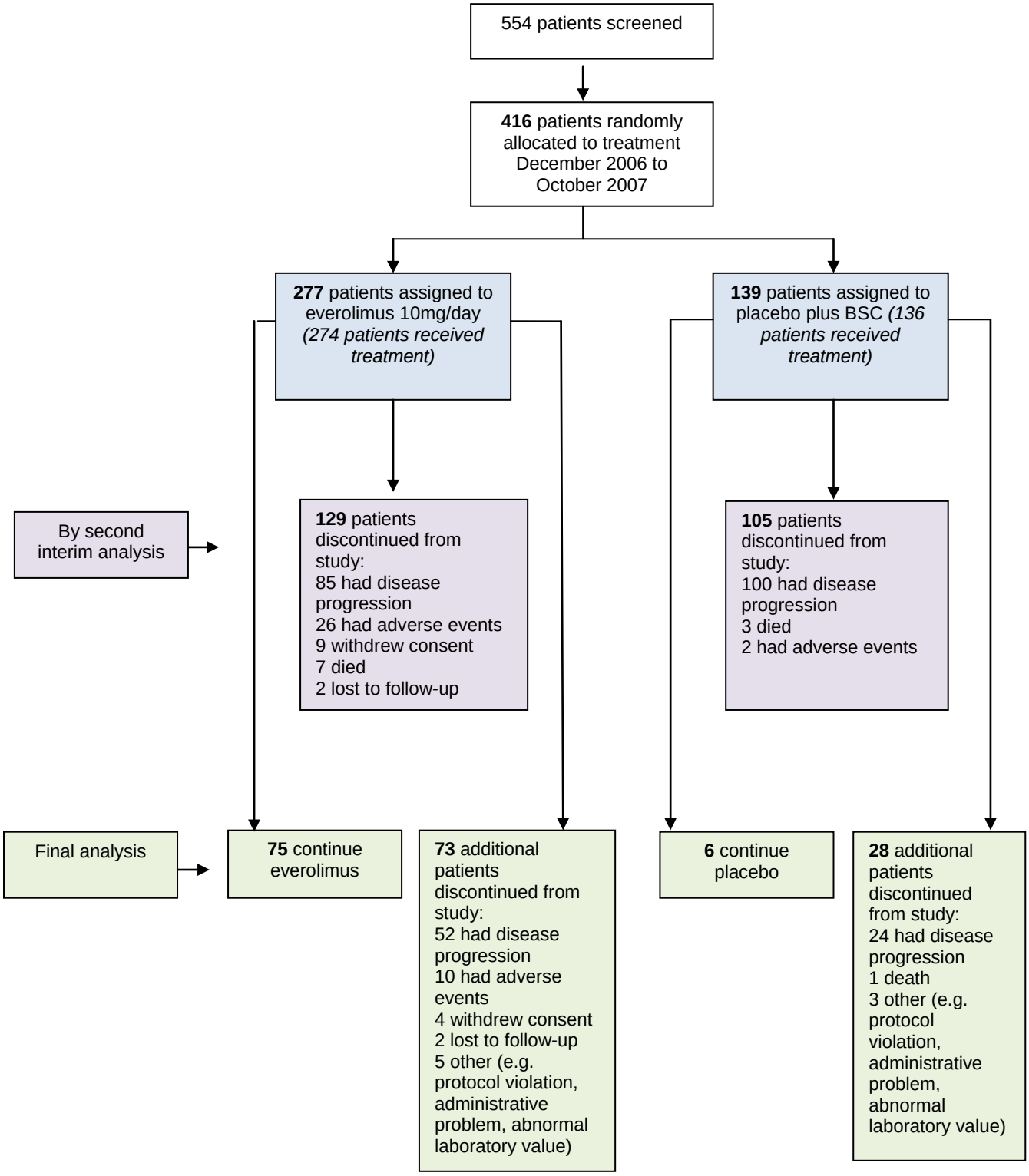
***i.e. progressed before drug discontinuation or within 1 week of discontinuation

Figure 6.3 shows the patient flow through the trial up to the final analysis, and includes information on patient discontinuations at the second interim analysis stage which was published in the Lancet paper [44]. Only five randomised patients did not receive everolimus plus BSC or placebo plus BSC treatment for various reasons primarily including use of prohibited medications, and one placebo patient had no baseline safety assessment so was excluded from further safety analysis [40].

By the final analysis cut-off date, 75 (27%) everolimus plus BSC patients and 6 (4%) placebo plus BSC patients were still continuing treatment. The reasons for patient discontinuation at the final and second interim analysis time points are shown in Figure 6.3**.** At the time of the end of double-blind analyses, 106 of 121 patients[b] in the placebo plus BSC group had crossed over [40] (not shown in Figure 6.3). At the time of the second interim analysis, 79 of 98 (81%) placebo-treated patients who had locally assessed radiological progression were unblinded and crossed over to receive open-label everolimus. Sixty of the 79 placebo-treated patients (80%) had progressed within eight weeks of enrolment [44].

[b] In total there were 124 patients who discontinued placebo due to disease progression, although 3 of these patients did not have radiological reported disease progression and were mistakenly crossed-over to open-label everolimus).

Figure 6.3 RECORD-1 patient participation flow diagram



6.3.3 Outcomes

6.3.3.1 Outcome measures

The primary outcome measure in the trial was progression free survival (PFS)

The secondary outcome measures included in the trial were:

- Objective tumour response rate
- Duration of response
- Overall survival
- Health related quality of life (HRQoL) and related patient reported outcomes (PROs)
- Safety outcomes (frequency of adverse events, laboratory summaries and central radiology assessments of pneumonitis).

6.3.3.2 Progression Free Survival (PFS)

PFS was defined as the time from randomisation to documented radiological confirmed disease progression or death. Tumour response and progression was assessed independently using RECIST criteria [40] [44] at the study site (see Table 4.3 for classification). Confirmation of disease progression was based on central radiology review which was independent of site investigators evaluations. CT or MRI scans were used to evaluate tumour dimensions.

These methods of assessing disease progression and PFS are standard in clinical trials and accepted by regulatory bodies (FDA and EMEA). The measurement of disease progression was performed rigorously and with high accuracy. RECIST criteria and CT/MRI scans are standard measures used in clinical practice for assessing disease progression and aiding treatment decisions in clinical practice [25].

The use of PFS as the primary outcome measure was based on this being considered a reliable predictor of overall survival in many cancers and specifically in aRCC [26,36,37,96,97]. Also, it is considered unethical in clinical trial research to continue to give end stage cancer patients placebo therapy once efficacy has been established via PFS endpoints [31,92]. Hence, PFS and the use of cross-over trials is

increasingly becoming the standard to be accepted by regulatory agencies e.g. FDA in pre-registration advanced cancer trials [32]. As cross-over trials have limitations for assessing final outcomes such as overall survival, comparisons of relative efficacy of new cancer drugs in clinical practice are increasingly being made on their relative PFS performance [26] (see also discussion in Section 4.1.7).

6.3.3.3 Response rate

The data on assessment of tumour response was also to be used to determine objective tumour response rate (at the central investigator defined target lesion sites) measured as the proportion of patients with complete response (CR), partial response (PR), disease progression (DP), stable disease (SD) or unknown (UKN). From this the best overall response during the trial was recorded. Overall objective response rate (ORR) consisted of the proportion of patients who achieved a best overall response of CR or PR, along with duration of response (from documented first response to disease progression) for these patients [40].

6.3.3.4 Overall survival

Overall survival was measured from the date of randomisation to death. Survival status was evaluated on a monthly basis for up to two years after study drug discontinuation. The last possible survival assessment is November 5th 2009, which is two years after the last patient was randomised into the study.

However, due to the cross-over design of the trial post-disease progression, evaluation of survival was confounded by the placebo arm patients also being able to receive everolimus. Hence, statistical methods were necessary in order to more reliably estimate the survival outcomes associated with everolimus plus BSC. This was particularly important in order to generate life years gained estimates for the economic evaluation (see Section 7). The statistical methods used are reported in Section 6.3.4.6.

6.3.3.5 Patient Reported Outcomes

In addition to the KPS to measure performance status (which is on a 0-100 scale) over the course of the study, patients also received the following PRO instruments:

- The Functional Assessment of Cancer-Kidney Symptom Index, Disease Related Symptoms (FKSI-DRS) score [47,48]. This instrument measures a 9-item index of the most important disease related symptoms associated with

kidney cancer and is scored by showing patients a list of statements and asking them to indicate (by circling one number per line) how true each statement has been for them during the past seven days [48].

- European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC-QLQ-C30) [45]. The EORTC QLQ-C30 is a 30-item self-reporting questionnaire developed to assess the quality of life of cancer patients and is composed of both multi-item scales and single-item measures. These include five functional scales that evaluate physical, emotional role, cognitive and social functioning; three symptom scales (fatigue, pain, and nausea and vomiting); a global health status/HRQoL scale; and six individual questions concerning common symptoms in cancer patients [46,98].

These are standard, validated and robust instruments for assessing PRO's. The FKSI-DRS is a disease specific measure that has been previously been used in aRCC trials [50,99]. The EORTC QLQ-C30 is a generic cancer instrument that has been used in many cancer clinical trials, including aRCC [100,101]. The data has been used for both regulatory and HTA submissions, and in publications.

The changes from baseline in EORTC QLQ-C30 and FKSI-DSR scores were assessed. For the QLQ-C30 the analysis was performed using the global health/QoL scale. This dimension provides an important overall measure of the impact of aRCC and treatments such as everolimus on patient health outcomes. Attention was paid to ensuring compliance to completion of the questionnaires as typically in cancer trials there are many missing observations for these instruments [102]. Study investigators were encouraged to ensure the instruments were completed.

6.3.3.6 Treatment compliance

Treatment compliance was assessed by the investigator or his/her designee at each office visit as follows:

- Patients were requested to bring their unused medication including empty packaging to the clinic at each visit;

- All doses taken by the patient and all dose changes during the study were recorded on the Dosage Administration Record CRF;

- The investigator maintained drug accountability records for each patient including tablets administered, tablets used, dose changes, dates dispensed and intervals between visits;

- Drug accountability was routinely monitored by the Novartis monitor.

At the end of the study or when feasible, the Novartis monitor performed a final drug accountability review. In all participating sites bar the US, all used or unused study medication was destroyed according to the sites local regulatory procedures [40].

6.3.3.7 Safety measures

Safety assessments consisted of monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs) to assess frequency. Laboratory data was classified into AE Grades according to the NCI Common terminology Criteria for Adverse Events v3.0 [103].

In addition, special attention was given to two potential sets of adverse event:

- Assessment of non-infectious pneumonitis, a known risk for all mTOR inhibitors [55]. For this, a central radiology review of chest CT scans and chest X-rays was performed.

- Assessment of hyperlipidaemia and hyperglycaemia, which have been linked to mTOR inhibitors including everolimus [55].

6.3.3.8 Timings of assessments

In terms of assessment timings patients were followed up until death or 28 days after study drug discontinuation, primarily for a final safety assessment. Efficacy evaluations were performed every eight weeks and safety assessments every four weeks. Table 6.4 summarises the assessment methods used for the outcomes considered and assessment timings.

Table 6.4 Outcome assessment methods and timings in RECORD-1

Assessments and outcomes	Methods	Timings
Tumour measurement (for evaluation of disease free progression, tumour response, duration of response outcomes).	• Assessed by CT scan or MRI by central independent review (with disease progression confirmed by RECIST criteria)	• Baseline assessment: Assessed 5 weeks prior to first study dose • Next assessment within 1 week of 1st study dose • Then assessment every 8 weeks (+/-1 week) for 1st year and every 12 weeks (+/-1 week) in 2nd year and at drug discontinuation • Additional scans could be performed 4-6 weeks after initial observation to confirm response or disease progression. • Final evaluation at 28 day post drug discontinuation follow-up visit
Overall Survival		• Survival assessment at 28 day post drug discontinuation follow-up visit and followed up monthly for 2 years
HRQoL and PRO (for evaluation of time to clinically meaningful or definitive deterioration in HRQoL/PRO outcome)	• EORTC QLQ-C30 • Karnofsky performance scale • Functional Assessment of cancer therapy Kidney Symptom Index – Disease Related Symptoms (FKSI-DRS) questionnaire (disease related symptoms)	• Baseline assessment: Assessed 5 weeks prior to first study dose • Next assessment within 1 week of 1st study dose • Then assessment every 4 weeks and at drug discontinuation (within 1 week)
Adverse events (for frequency of Grade 1-4 AEs)	• AEs were graded 1-4 according to the National Cancer Institute's common Terminology Criteria for adverse events [103] • Safety assessments included analysis of haematology and blood biochemistry, lipid profile, physical examination, vital signs, chest X ray (for signs of pneumonitis)	• Haematology assessed every 14 days for first 3 cycles (of 28 days each) of study drug • Then every 28 days, and at 28 days following the last dose of study drug. • Other tests and investigations performed every 28 days • AE assessment at 28 day post drug discontinuation follow-up visit

In addition, in the extension phase to the study, patients who were not experiencing disease progression on everolimus were allowed to continue to receive open-label everolimus until disease progression or discontinuation for other reasons. These

patients continued to have routine safety and efficacy evaluations as in Table 6.4 to end of study treatment (start of new anti-cancer therapy) or death, with a final follow-up visit 28 days post discontinuation.

6.3.4 Statistical analysis and definition of study groups

6.3.4.1 Study hypothesis

The primary study hypothesis was that everolimus plus BSC could improve clinical outcomes for late stage aRCC patients who had already experienced disease progression on or following VEGF-targeted treatment. The null hypothesis was that there was no difference in PFS between the treatment arms. The rationale for the study hypothesis was derived from small single-arm studies showing a high proportion of durable disease stabilization or shrinkage in previously treated aRCC patients [39,59], but which needed further investigation in a robustly designed RCT.

6.3.4.2 Planned sample size

The RECORD-1 trial sample size was planned on the basis of the number of disease progression events observed. The sample size calculations were based on numbers needed to demonstrate a clinically meaningful improvement in the risk of disease progression events, which was defined as a risk reduction of 33% HR 0.67 corresponding to a 50% improvement in median PFS from 3.0 months on placebo to 4.5 months on everolimus . A total of 290 progression free survival events were required for final analysis. Sample size calculations were based on an unstratified one-sided sequential log rank score test with cumulative significance level of 0.025 and cumulative 90% power for a 3-look group sequential plan. Based on 21 months scheduled follow-up (16 months recruitment time and 5 months further follow-up), 362 patients would need to be enrolled to observe 290 progression free survival events, assuming 10% of patients lost to follow-up [44].

6.3.4.3 Planned statistical analysis

The 416 patients randomised to everolimus plus BSC or placebo plus BSC represented the final full analysis dataset. These patients were eligible for efficacy assessment by ITT analysis according to the treatment and strata they were assigned to at randomisation. A per protocol population was not defined for analysis. In addition, a safety population consisted of all patients who received at least one study drug dose and had at least one post-baseline safety assessment (274 and 137 patients in the everolimus plus BSC and placebo plus BSC arms, respectively) [40].

Pre-specified statistical analysis for the primary endpoint consisted of the following [40]:

- Median PFS with 95% confidence intervals was measured using Kaplan-Meier time to event of interest methods, with the statistical significance of the difference between treatment arms assessed using the stratified log-rank test, adjusting for strata defined by MSKCC prognostic score.

- Hazard ratios of the treatment effect were estimated using a stratified Cox proportional hazards model for the difference between the treatment arms in PFS outcomes, with two-sided 95% confidence intervals.

Analysis was based on tumour assessments performed by the independent central radiology review. However, PFS comparisons based on site investigator review were also performed [40].

In terms of secondary endpoints, overall survival (OS) was analysed using the same statistical methods. Overall response rate (ORR) was defined as the proportion of patients who attained a CR (complete response) or PR (partial response) during the trial. ORR was compared between treatment arms using exact Mantel-Haenszel test, stratified by MSKCC criteria. Duration of response (defined as CR or PR) was analysed descriptively as no responders were expected in the placebo plus BSC arm [40].

For PRO outcomes, mean FKSI-DRS and EORTC QLQ-C30 global health/QoL scores were evaluated over time (from baseline to patient disease progression). An assessment of median time to deterioration in PRO was performed. Time to clinically meaningful deterioration was defined as a decrease from baseline of at least 3 points for FKSI-DRS, at least 10% for EORTC physical function (PF) and global quality of life (QL) scales, and at least 10 points for KPS. Comparisons were made using Cox proportional hazards ratios and stratified log rank tests [40].

Patients who were still alive and had not experienced disease progression as of the analysis cut-off dates were censored at the last date of adequate tumour evaluation prior to the cut-off. Other reasons for PFS analysis censoring were patient lost to follow-up, consent withdrawn, adequate assessment no longer available, receiving new anti-cancer treatment or event documented after missing >2 tumour assessments [40].

Differences in the incidence of grade 3 and 4 AEs between treatment groups were assessed using the Fisher's exact test [40].

6.3.4.4 Sub-group analysis/secondary analysis

Predefined sub-group analysis was performed on differences in PFS based on MSKCC prognostic score category.

Additional exploratory sub-group analyses were performed for median PFS by gender, prior VEGFr-TKI therapy (sorafenib, sunitinib or both), age (<65 years, ≥65 years), geographic region (US and Canada, Europe, Australia and Japan).

Statistical analysis for the sub-groups consisted of hazard ratios using an unstratified Cox proportional hazards model and p values generated by the unstratified log-rank test [40].

6.3.4.5 Interim and final analyses

In recent years more rigorous requirements for data monitoring in cancer trials have been implemented, specifying the need for formal interim analyses [104]. Hence, for the RECORD-1 trial, first and second interim analyses were planned in the study protocol after approximately 30% (about 87 events) and 60% (about 174 events); respectively of the targeted 290 PFS events had been observed. The aim of the interim analyses were to enable the study to be stopped due to safety issues (at first interim analysis) or if the efficacy objectives were met, or due to lack of efficacy ('futility') (at the second interim analysis) [44].

A cut-off date was set for October 15th 2007 for the second interim analysis, by which time 191 PFS events had been observed (66% of the target 290 events) [44]. After analysis of this data the independent data monitoring committee recommended early termination of the study on PFS efficacy grounds due to the pre-specified efficacy stopping boundary of p≤0.057 being reached (according to the Lan and DeMets method (1983) [105] with O'Brien-Fleming type stopping rules (1979) [106]). At the second interim analysis cut-off, 272 patients had been recruited to the everolimus plus BSC arm and 138 to the placebo plus BSC arm. This data was the basis of the Motzer et al., 2008 publication in the Lancet [44].

Notification to terminate the trial was received on 28th February 2008, with this marking the end of the double-blind phase. Hence, as recruitment and data collection had continued beyond the second interim analysis cut-off date of 15th October 2007,

a further final analysis of the primary and secondary endpoints within the double-blind RCT conducted including the additional patients and follow-up to the 28th February 2008. This is the primary data reported in the Clinical Study Report (CSR)-addendum and in this submission [40]. By this time, 266 progression free events had been observed in 416 patients recruited – an additional five in the everolimus plus BSC arm and an additional 1 placebo plus BSC patient (see Figure 6.3). The statistical analysis plan was constructed in order to test the statistical significance of differences in outcomes between the treatment arms when the defined efficacy or futility boundary was crossed. As this was crossed early at the second interim analysis stage, and the null hypothesis rejected, this means that tests of statistical significance (p values) performed for the final analysis are essentially descriptive in nature.

6.3.4.6 Post hoc analysis: estimation of survival outcomes

Due to cross-over from placebo plus BSC after disease progression being allowed in RECORD-1, the ITT analysis of survival in the placebo plus BSC patients was confounded. The likely effect is to have inflated the survival outcomes of these patients due to over three quarters going on to receive everolimus. Therefore, a statistical approach, the Inverse Probability of Censoring Weight (IPCW) model, was used to address this issue [107]. IPCW has been used extensively in correcting time-varying non-compliance with randomisation (i.e. the same issue as in the RECORD-1 trial post progression) and in observational studies, primarily in HIV survival research [108].

The main steps in applying the IPCW method to the placebo plus BSC data followed those described by Hernán et al., 2006 [109].

1. Firstly, data from RECORD-1 was divided into 4 week segments (‘months’) corresponding to the frequency of visits in the RECORD-1 trial. Information on baseline characteristics and time varying assessments such as disease progression status was obtained.

2. The placebo plus BSC patients were artificially censored in the month in which they crossed-over to receive everolimus (known as cross-over or IPCW censoring).

3. However, this informative censoring is likely to introduce time dependent selection bias due to the patients crossing-over not being the same as those

not crossing over e.g. none of the patients who did not cross over had disease progression. Inverse probability of censoring weights were generated to correct for the potential selection bias due to this cross-over censoring. Therefore, pooled logistic regression analysis was performed to estimate the probability of remaining IPCW uncensored (i.e. not crossing-over to receive everolimus). To develop the weights the logistic regressions were performed for a set of patient baseline characteristics (e.g. age, race, MSKCC category, prior treatments) and adjusted for monthly time varying assessments (e.g. progression status, grade 3 or 4 AEs, death, cross-over status). The final variable selection was based on the best fitting model determined using goodness of fit statistics.

4. A stabilised weight per patient-month (SW_i) of follow-up was generated. Time periods following cross-over were excluded from analysis. Overall, there was data for 523 uncensored placebo plus BSC patient-months with an average of 3.8 months of uncensored follow-up per patient. From this analysis the mean SW was 0.7912 (Std. Dev 0.4231).

5. Everolimus plus BSC patient months were assigned SWi = 1, the placebo plus BSC patient months that were IPCW censored were assigned SWi = 0. The uncensored placebo plus BSC patient-months were assigned the weights generated by the pooled logistic regression analysis. A Cox proportional hazards model was applied to all patients in RECORD-1 (including the treatment indicator and all baseline characteristics), weighted by SW_i to estimate the monthly risk of mortality in the 'hypothetical' absence of cross-over in the placebo plus BSC arm.

6. An IPCW adjusted Cox hazard ratio for risk of death per patient month for everolimus plus BSC versus placebo plus BSC was generated. This hazard ratio was used to generate the transition probabilities for stable and disease progression states leading to death in the Markov model for BSC. This was essential for estimating life years gained and QALYs associated with everolimus (see Section 7).

As with all regression techniques the IPCW method is subject to standard statistical assumptions which include correct model specification and assumption of no

unmeasured confounding (i.e. key covariates/characteristics have been included). As the method essentially discards data for months after patients cross-over there is a risk of wide confidence intervals related to relatively small numbers who did not cross-over [109]. The method was however preferred to the use of other possible methods to deal with bias, such as the rank preserving structure failure time (RPSFT) model, in order to limit as much as possible the risks from model misspecification for measuring survival outcomes. In addition, the resulting hazard ratio for mortality was relatively simple to apply to the transition probabilities for the everolimus arm in the economic model in order to generate the survival time estimates for the placebo arm (see Section 7). All of the transition probabilities for everolimus were based on data taken directly from RECORD-1.

Further details on the IPCW approach used are presented in Section 10.4 Appendix 4.

6.3.5 Critical appraisal of relevant RCTs

An assessment of the methodological quality of the RECORD-1 study was performed. Two reviewers independently evaluated the included studies for methodological quality which used criteria reported by the Centre for Reviews and Dissemination (CRD) [110].

The review of RECORD-1 was primarily based on information from the unpublished Clinical Study Report – addendum for RECORD-1 [40] and the Motzer et al., 2008 Lancet publication [44]. The assessment utilises the same questions used in the PenTAG assessment report for the advanced/mRCC drugs covered by the recent NICE multiple technology appraisal [19] but also incorporates a few supplementary questions to enable application of the Jadad scoring system, which scores key aspects of RCT design and quality [111]. Details of the Jadad quality scoring system can be found in the everolimus systematic review report [81].

The results of the quality assessment of the RECORD-1 trial are presented in Table 6.5 below.

Table 6.5 Quality assessment of the RECORD-1 RCT for everolimus

Assessment question	STUDY, Author : RECORD-1 (CSR-addendum [40] and Motzer et al., 2008 [44])	Jadad score
Study design [Jadad score 1 = 0/1]	*RCT*	1
Is a power calculation provided?	*Yes*	
Is the sample size adequate?	*Yes*	
Was ethical approval obtained?	*Yes*	
Were the study eligibility criteria specified?	*Yes*	
Were the eligibility criteria appropriate?	*Yes*	
Were patients recruited prospectively?	*Yes*	
Was assignment to the treatment groups really random? [Jadad score 2 = 0/1, -1 if inappropriate]	*Partial Yes**	0.5
Was the treatment allocation concealed?	*Yes*	
Were adequate baseline details presented?	*Yes*	
Were the participant's representative of the population in question?	*Yes*	
Were the groups similar at baseline?	*Yes*	
Were baseline differences adequately adjusted for in the analysis?	*NA***	
Was the study described as double blind? [Jadad score 3=0/1]	*Partial Yes****	0.5
Were the outcome assessors blind?	*Partial Yes****	
Was the care provider blind?	*Partial Yes****	
Were participants blinded?	*Partial Yes****	
Was the method of blinding described and appropriate? [Jadad score 4=0/1, -1 if inappropriate [7]]	*Yes*	1
Are the outcome measures relevant to the research question?	*Yes*	
Is compliance with treatment adequate?	*Yes*	
Are withdrawals/dropouts adequately described? [Jadad score 5=0/1]	*Yes*	1
Are all patients accounted for?	*Yes*	
Is the number randomised reported?	*Yes*	
Are protocol violations specified?	*No*	
Are data analyses appropriate?	*Yes*	
Is analysis conducted on an ITT basis?	*Yes*	
Are missing data appropriately accounted for?	*Yes*	
Were any sub-group analyses justified?	*Yes*	
Are the conclusions supported by the results?	*Yes*	
Jadad score		4.00

Supplementary questions to those used in the PenTAG HTA report are in red/bold

*True randomisation for primary endpoint of PFS, but cross-over design enabled patients progressing on placebo to receive everolimus

**No strong need to adjust due to very similar baseline characteristics

***Partial Yes - blinding was the case for the primary endpoint of PFS, but was lifted on disease progression when placebo patients could cross over to everolimus (for ethical reasons)

Overall, the methodological quality of the RECORD-1 study was high, with an estimated score of 4 out of 5 on the Jadad system, which assesses the most critical aspects of trial design relating to potential for bias. RECORD-1 was performed to very high trial conduct standards. The trial was a multicentre, double-blind RCT where enrolled patients had very similar baseline characteristics across the two treatment arms [40]. In addition to the investigators and the patients being blinded to the treatment arm, assessment of outcomes was performed by an independent central review which was also blinded. Randomisation was performed robustly using a validated block approach with treatment allocation concealed. In terms of sample size, power calculations to identify the number of patients required to achieve a clinically meaningful 33% reduction in risk of disease progression for everolimus plus BSC versus placebo plus BSC were performed and clearly reported. The range of primary and secondary outcomes were relevant for assessing clinical/patient benefit and in line with the technology appraisal decision problem, with PFS as the primary outcome, supported by assessment of overall survival, tumour response rate and a number of validated standard cancer specific HRQoL and PRO measures included [40].

The everolimus plus BSC treatment regimen of 10mg/day is that specified in the product SPC (Section 10.1, Appendix 1) and conforms to the expected dosing regimen in UK clinical practice. The RCT participants were comparable to patients who would receive the intervention in the UK. The demographics of UK aRCC patients are largely consistent with the demographics and eligibility criteria in the RECORD-1 trial. The patients included in the trial have measurable disease progression based on RECIST criteria (which is commonly used in UK clinical practice). In addition, to be eligible for the trial, patients had to have a KPS score ≥70% indicating good performance status, without major co-morbidities. This is appropriate for trials and is likely to correspond to clinical practice whereby active treatment for patients with late stage RCC tends to be offered to those with best status and prognosis (e.g. with ECOG 0-1, or high KPS) [66]. The patient withdrawals and discontinuations were clearly presented in a flow chart in the Lancet publication [44], and have been supplemented in this submission by information from the Clinical Study Report for the final analysis [40]. There were very few randomised patients who did not receive at least one dose of everolimus plus BSC or placebo plus BSC.

The phase III, Motzer et al., 2008 study has been published in a high quality journal (The Lancet) [44] and extended by a number of presentations at ASCO including an

updated final analysis (CSR-addendum [40] and presented by Escudier et al., 2008 [74]). The study had the advantage of a comparison arm (i.e. placebo plus BSC) that represents current UK practice for heavily pre-treated aRCC where a VEGF-targeted therapy has already been used (in line with the appraisal decision problem). Another quality included the high patient numbers recruited, and the achievement of highly statistically significant differences in median PFS for everolimus plus BSC versus placebo plus BSC before the intended end of recruitment (i.e. early cut-off at the second interim analysis point) [40].

Analysis was performed robustly; all efficacy analyses were performed using ITT methods, with appropriate and standard statistical analysis [40]. Point estimates and measures of variability (HRs estimated using stratified Cox proportional hazards model, with 95% confidence intervals) were presented for the primary outcome measure of PFS for both the whole trial population and sub-groups analysed. Hazard ratios were also generated for survival outcomes. In addition, p values using stratified log rank tests for the difference in effect of everolimus plus BSC and placebo plus BSC were measured and presented for these variables. Standard statistical tests were also performed for differences in grade 3 or 4 AEs between everolimus plus BSC and placebo plus BSC [40].

In the context of the decision problem for this appraisal, the study achieved a Jadad score of 4 rather than 5 due to the limitation that whilst the study was randomised and double-blinded at the start of the trial, the cross-over element meant that randomisation and blinding were dropped at disease progression, with placebo patients being able to receive everolimus plus BSC. This did not affect the primary endpoint, but confounded the overall survival results for everolimus plus BSC versus placebo plus BSC; hence benefit in median survival could not be adequately demonstrated. There has been an increasing focus on PFS outcomes for regulatory purposes, with commentators supporting the credibility of this outcome measure [26] and use of cross-over trials in cancer for ethical reasons [31,92]. Hence, the trial uses a pragmatic and measurable endpoint whilst retaining the strong elements of a straightforward two arm RCT design. It is not considered ethical to retain blinding and keep patients on placebo when efficacy of the active treatment is demonstrated. This becomes even more important for patients with advanced disease and limited life expectancy and can hinder recruitment to clinical trials in the oncology setting [44].

6.4 Results of the relevant comparative RCTs

6.4.1 Overview

An ITT population was used for all efficacy analyses in the RECORD-1 study. The main results presented here relate to the full data set used for the final analysis [40] as this represents a larger number of patients with greater follow-up duration compared to the second interim analysis cut-off. However, as the latter data is published in the Lancet [44] and statistical analysis of differences was based on PFS efficacy outcomes achieved at this cut-off, reference to these results will be made to complement those from the final analysis.

6.4.2 Duration of dosing

Based on the safety data set (i.e. patients that had received at least one dose of study drug) patients receiving everolimus plus BSC were treated with study drug for more than double the duration of placebo plus BSC patients. The median and mean duration of treatment exposure up to the 28th February 2008 cut-off is shown in Table 6.6. based on the safety dataset (i.e. those patients actually treated). Due to dose interruptions and adjustments for AEs (see 6.7.3), the mean dose of everolimus per patient per day was 9.18mg [40].

Table 6.6 Duration of treatment and mean dosage (final analysis safety population)

	Everolimus plus BSC (N=274)	**Placebo plus BSC (N=137)**
Median duration (range)	141 days (19-451)	60 days (21-295)
Mean duration (SD)	156.1 days (+/-94.3)	90.8 (+/-62.5)
Mean daily dose	9.18mg (SD:+/-1.5)	10mg (SD:+/-1.33)

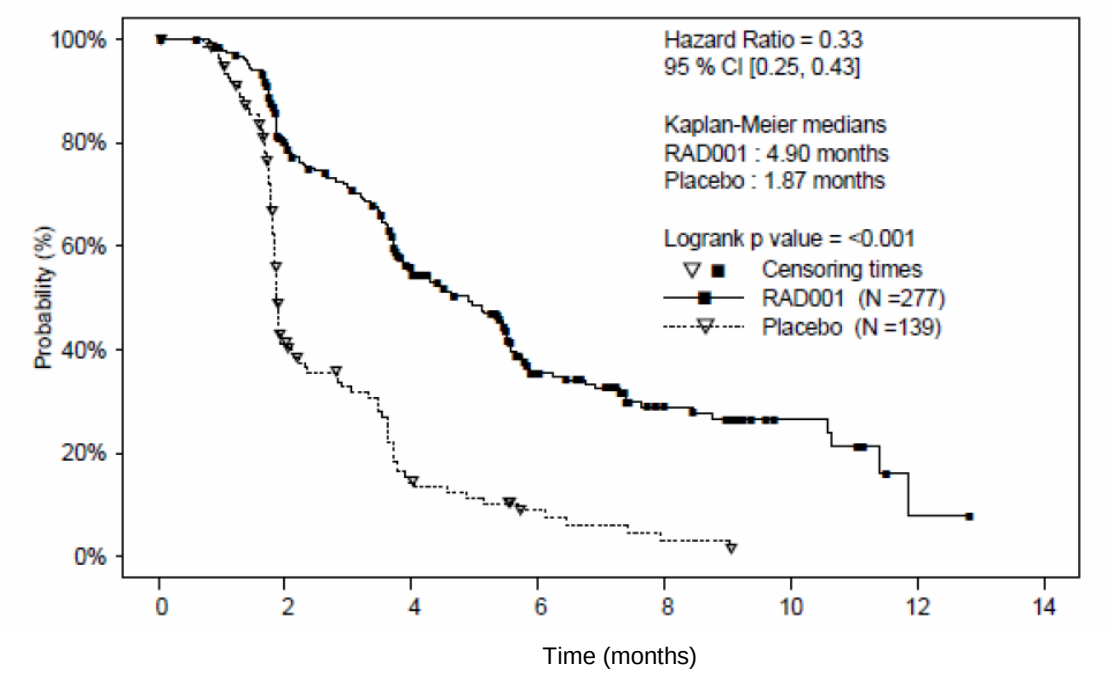
Source: CSR-addendum [40]

6.4.3 Progression free survival in the overall population

Based on the independent central radiology review, there was a 67% reduction in risk of progression associated with everolimus plus BSC compared to placebo plus BSC (HR=0.33, 95%CI: 0.25-0.43) at final analysis cut-off. The everolimus plus BSC arm showed a statistically significant difference in median PFS of 3.03 months compared to placebo plus BSC ($p<0.001$). Median PFS for everolimus plus BSC was 4.90

months (95%CI: 3.98-5.52) and for placebo plus BSC was 1.87 months (95%CI: 1.84-1.94) [40,74]. The Kaplan-Meier plot for median PFS is presented in Figure 6.4.

Figure 6.4 Progression free survival everolimus plus BSC versus placebo plus BSC: Final analysis

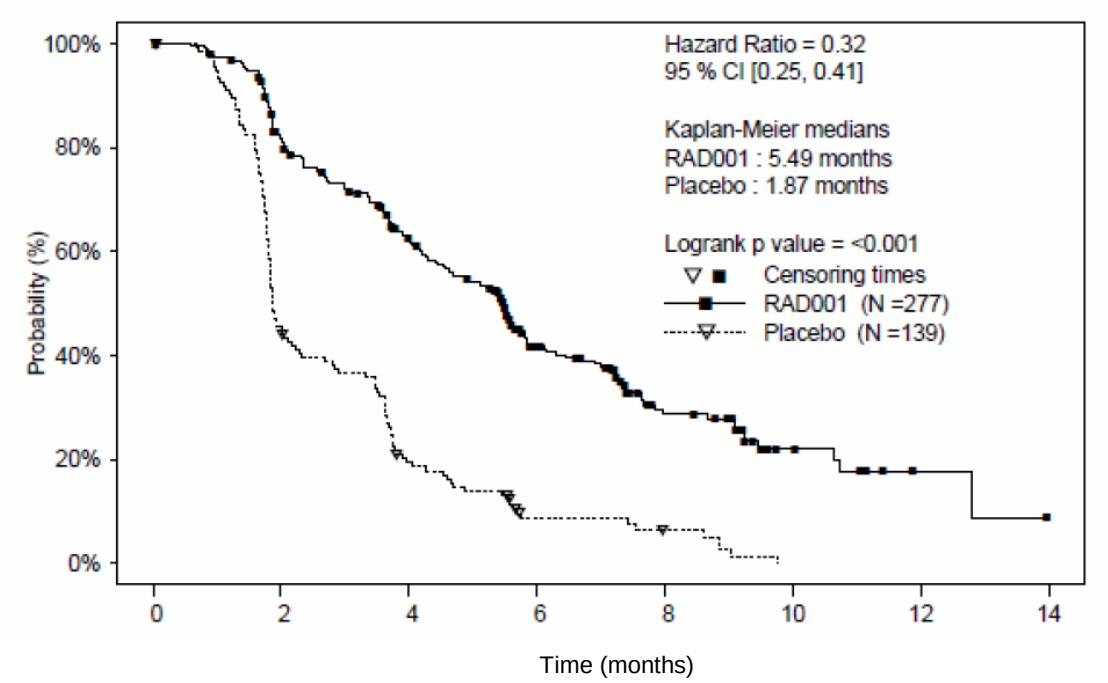


Source: CSR-addendum [40], Escudier et al., 2008 [74]

The K-M plot was based on 266 PFS events defined by the time each patient experienced progression or death (prior to progression). In the everolimus plus BSC arm there were 155 PFS events (56% of patients) consisting of 134 disease progression events and 21 deaths. In the placebo plus BSC arm there were 111 PFS events (80% of patients) consisting of 103 progression and 8 death events. Therefore, 122 patients (44%) and 28 patients (20%) in the everolimus plus BSC and placebo plus BSC groups, respectively, had not progressed or died [40].

The disease progression events determined by local site investigators were similar (N=152, 55% of patients, and N=121, 87% of patients, for everolimus plus BSC and placebo plus BSC, respectively). The results based on local site investigation were consistent with those from the central radiological review with a 68% reduction in risk of disease progression or death (HR=0.32 with 95%CI: 0.25-0.41) and the difference in median PFS statistically significant in favour of everolimus (p<0.001,). Median PFS was 5.49 months in the everolimus plus BSC group and 1.87 in the placebo plus BSC group [40].

Figure 6.5 Progression free survival everolimus plus BSC versus placebo plus BSC using site investigator review: Final analysis



Source: CSR-addendum [40], Escudier et al., 2008 [74]

A pre-defined analysis of PFS based on central radiology review using a multivariate Cox model stratified by MSKCC risk criteria and adjusted for age, gender and prior therapy, and all other multivariate analyses using stratified or unstratified Cox models, produced very similar PFS hazard ratio results as the main analysis [40].

The second interim analysis cut-off also demonstrated a clear reduction in risk of disease progression or death and a statistically significant difference in median PFS between everolimus plus BSC and placebo plus BSC (HR=0.30; 95%CI: 0.22 to 0.40, p<0.001), supporting the outcomes demonstrated at the final analysis [44].

6.4.4 Progression Free Survival by sub-groups

6.4.4.1 PFS by MSKCC prognostic category

Sub-group analysis by MSKCC prognostic category was pre-specified. This demonstrated a statistically significant difference in PFS for all three categories. There was a 69%, 68% and 56% reduction in disease progression or death risk for the everolimus plus BSC group versus placebo plus BSC for favourable, intermediate and poor risk categories, respectively (Table 6.7 below). A statistically significant difference was found for the poor risk patients despite small patient numbers. As can

be seen in Table 6.7 the confidence intervals overlap for each of the MSKCC categories with the lower 95% CI similar for each category. Therefore, there is no evidence suggesting any difference in risk of disease progression or death between favourable, intermediate or poor MSKCC prognostic group.

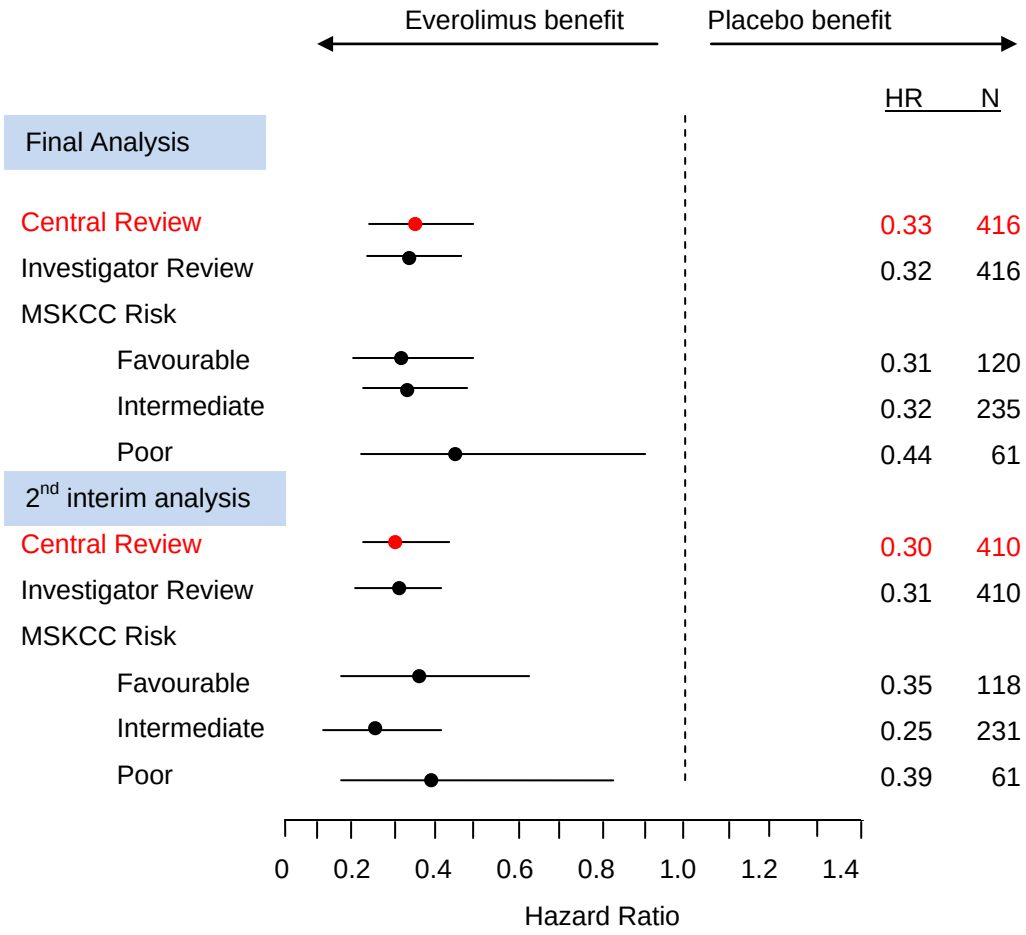
Table 6.7 Progression free survival by MSKCC prognostic category

MSKCC category	Everolimus plus BSC	Placebo plus BSC	hazard ratio* (95%CI)	p-value**
Favourable risk (N)	81	39		
Median PFS (months)	5.8	1.9	0.31 (0.19-0.50)	<0.001
Intermediate risk (N)	156	79		
Median PFS (months)	4.5	1.8	0.32 (0.22-0.44)	<0.001
Poor risk (N)	40	21		
Median PFS (months)	3.6	1.8	0.44 (0.22-0.85)	0.007

Source: CSR-addendum [40]
N = number of patients
* Unstratified Cox proportional hazards model
** Stratified 1 sided log-rank test

The results in Table 6.7 are supported by the analysis performed at the second interim analysis cut-off, with similar HR's of 0.35 (95%CI: 0.20-0.61), 0.29 (95%CI: 0.16-0.37) and 0.39 (95%CI: 0.19-0.81) for the favourable, intermediate and poor risk sub-groups respectively [82] (Figure 6.6). The differences in median PFS between the everolimus plus BSC and placebo plus BSC groups were also statistically significant across the three prognostic categories (p <0.001 for favourable and intermediate risk categories and p=0.009 for the poor risk category) [44].

Figure 6.6 Sub-group analysis of PFS by MSKCC sub-group comparing final and second interim analyses



Source: CSR [82], CSR-addendum [40], Escudier et al., 2008 [74]

6.4.4.2 PFS by other sub-groups

Table 6.8 presents the hazard ratios for other sub-groups at final analysis based on central radiology review. This shows the consistency in differences of PFS results across sub-groups. For all sub-groups the differences in median PFS between everolimus plus BSC and placebo plus BSC were statistically significant at the $p<0.001$ level. Given the recent NICE guidance recommending sunitinib as first line treatment for aRCC, a sub-group of potential interest to NICE is the post sunitinib failure patients. However, there was no difference in outcomes for these patients compared to the total trial population with a hazard ratio of 0.34 and 0.33 respectively.

Table 6.8 Everolimus plus BSC versus placebo plus BSC treatment effect by sub-group

Sub-group	No. of patients		HR (95%CI)* everolimus plus BSC versus placebo plus BSC	Log-rank p value**
	Everolimus plus BSC	Placebo plus BSC		
Age				
<65 years	165	98	0.34 [0.25, 0.47]	<0.001
≥65 years	112	41	0.33 [0.21, 0.51]	<0.001
Gender				
Male	216	106	0.32 [0.24, 0.42]	<0.001
Female	61	33	0.39 [0.23, 0.67]	<0.001
Prior VEGFr-TKIs				
Sorafenib only	81	43	0.25 [0.16, 0.42]	<0.001
Sunitinib only	124	60	0.34 [0.23, 0.51]	<0.001
Both	72	36	0.32 [0.19, 0.54]	<0.001
Region				
US and Canada	77	53	0.29 [0.19, 0.46]	<0.001
Europe	180	71	0.38 [0.27, 0.53]	<0.001
Australia and Japan	20	15	0.18 [0.07, 0.49]	<0.001

Source: CSR-addendum [40]
*Unstratified Cox proportional hazards model
**Unstratified 1 sided log- rank test

6.4.4.3 Probability of PFS

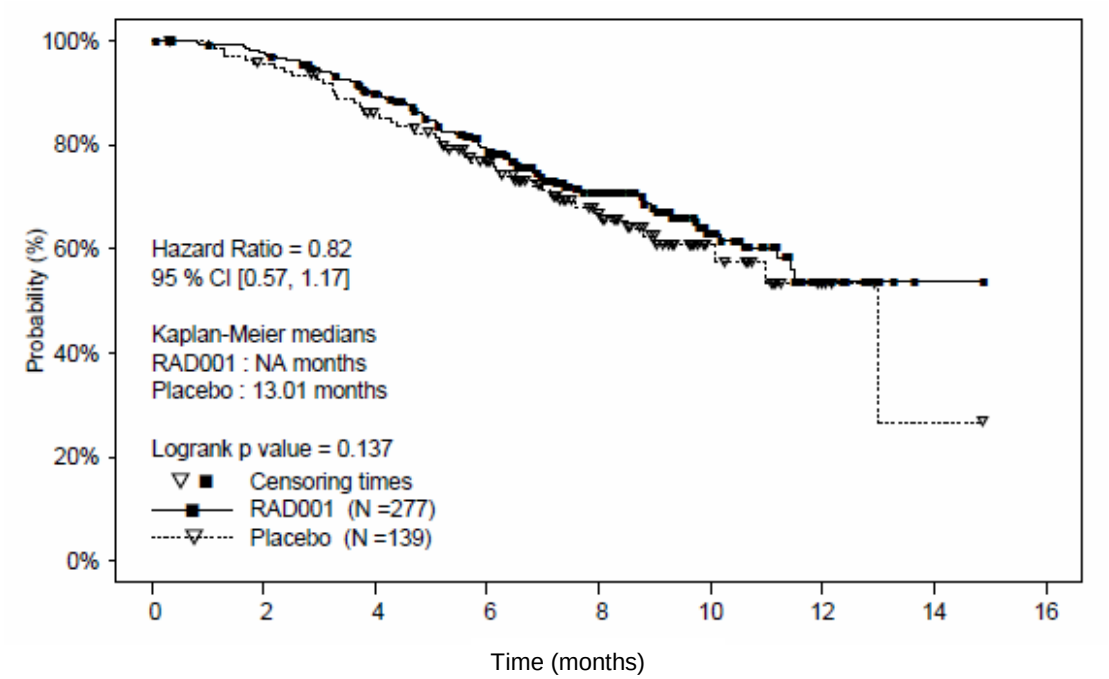
The probability of PFS was also evaluated at the second interim [86] and final analysis [74]. At the second interim analysis for the everolimus plus BSC arm there was a 26% probability of still being in PFS six months post measurable disease progression on or after a prior therapy (95%CI: 14-37%), compared to 2% for placebo plus BSC (95%CI: 0-6%) [44]. At final analysis the probability of being progression free at six months was 35.6% compared to 9% for placebo plus BSC and at 10 months the probability for everolimus plus BSC was still 25% demonstrating long run benefits for a significant proportion of these aRCC patients [83].

6.4.5 Overall survival

6.4.5.1 Overall Survival results in RECORD-1

Due to the cross-over trial design, overall survival (OS) was not a primary endpoint in the trial, as it is highly likely that the placebo plus BSC group will have inflated survival estimates as they were allowed to receive open-label everolimus upon disease progression. Median overall survival had not been reached for the everolimus plus BSC patients at either the second interim or final analysis cut-off points [44,74], and was 8.8 months and 13.01 months for placebo plus BSC at the two time points, respectively. However, the median survival for the placebo plus BSC arm is an overestimate as 76% of placebo plus BSC patients crossed-over. Hence, a statistically significant difference in median survival was not found by the final analysis stage (HR=0.82, 95%CI: 0.57-1.17, p=0.137) [40]. This was consistent with the HR found for the second interim analysis (HR=0.83, 95%CI: 0.50-1.37, p=0.23) [44]. The Kaplan-Meier plot for OS by treatment group for the final analysis is presented in Figure 6.7. Overall, in the everolimus plus BSC group there were 85 OS events (31%) and 48 (35%) in the placebo plus BSC arm, with 192 patients (69%) and 91 patients (65.5%) still alive or lost to follow up in each arm, respectively [40].

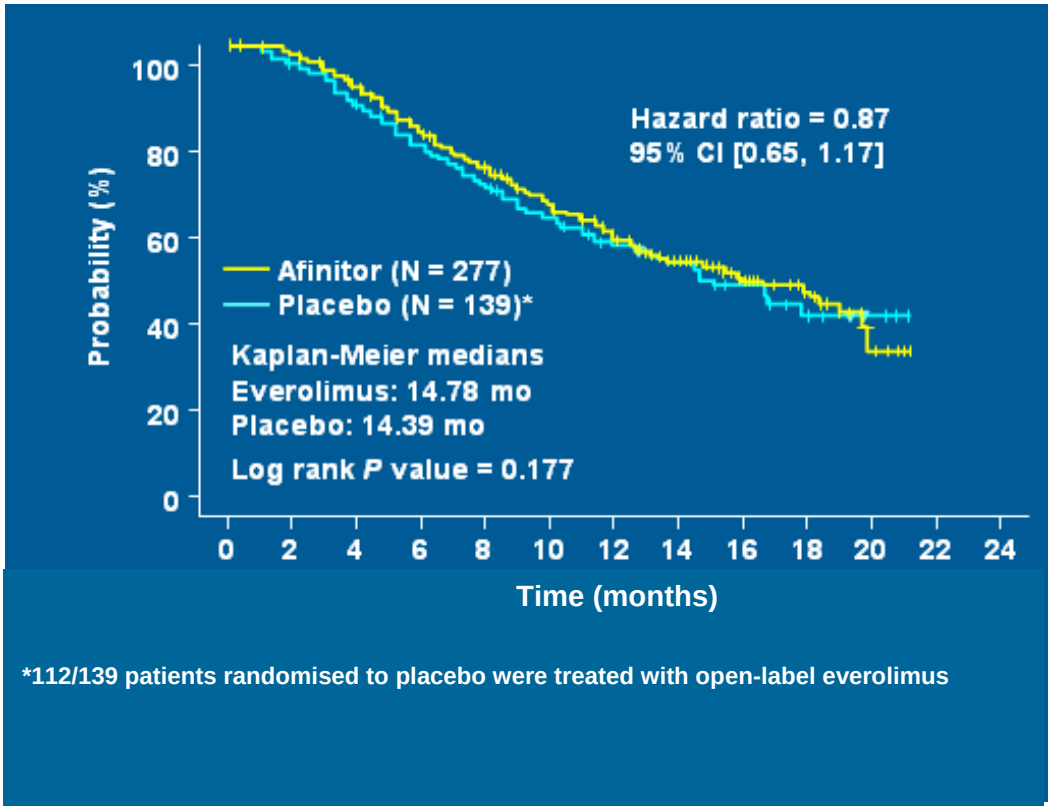
Figure 6.7 Overall survival outcomes by treatment at final analysis



Source: CSR-addendum [40]

A further analysis of OS was performed at a November 2008 cut-off date [112]. At this time point a median OS for the everolimus plus BSC treatment arm had been established at 14.78 months [112]. The median survival for the placebo plus BSC arm was 14.39 months – a statistically significant difference in OS was not observed (HR=0.87, 95%CI: 0.65-1.17, p=0.177). The K-M curves were similar for both treatment groups (Figure 6.8). The lack of significant difference by this stage, based on ITT analysis, was not surprising due to the high cross-over of placebo plus BSC patients (112 out of 139 (81%) by November 2008) to receive everolimus plus BSC [112].

Figure 6.8 Overall survival outcomes (Nov 2008 cut-off)



Source: Motzer et al., 2009 [112]

6.4.5.2 Overall survival comparisons and relationship with PFS outcomes

Due to high cross-over from placebo to everolimus upon disease progression the relationship between PFS and OS based on ITT analysis in RECORD-1 is confounded. However, as discussed in Section 4.1.7, PFS can be considered a clinically relevant surrogate for OS. The RECORD-1 trial shows a highly statistically

significant benefit with respect to PFS for everolimus plus BSC versus placebo plus BSC, and is indicative of the likelihood of an OS benefit versus BSC. The median PFS results for everolimus plus BSC of greater than 3 months versus placebo plus BSC at final analysis in a heavily pre-treated patient population [40] compares favourably with those reported for sorafenib versus BSC in patients who had failed cytokine therapy (for sorafenib a median PFS of 5.5 months compared to 2.8 months for placebo plus BSC, which is a 2.7 month difference) [26,41]. Results from this phase III, RCT for sorafenib in aRCC patients, demonstrated a reduction in risk of PFS events of 56% [41]. This is compared to a 67% risk reduction associated with everolimus after VEGFr-TKI therapy failure in the RECORD-1 trial [40].

There is robust evidence supporting a correlation between the treatment effect on improving PFS and the subsequent impact on overall survival. A recent meta-analysis covering 28 studies and 8,770 patients explored the relationship between median time to disease progression and median OS in controlled trials in aRCC [36]. Using OLS (Ordinary Least Squares) regression, the analysis found that a 1.0 month difference between active treatment and comparator in time to disease progression was associated with a 1.23 month difference in OS ($p<0.0001$) [36]. The analysis included cross-over trials which due to bias underestimate the overall survival outcomes in ITT analysis. Importantly for the context in which everolimus has been evaluated, in sub-group analysis the meta-analysis found a 1.61 difference in overall survival per 1 month gain in time to disease progression (95%CI: 0.70-2.52, $p=0.0014$) based on only including studies without cross-over from placebo to active therapy (n=24 studies). Also a 1.42 OS gain (95%CI: 0.34-2.51, $p=0.0137$) was found when including only studies where patients had received prior therapy (n=16 studies). This study concluded that in patients receiving treatment for aRCC, treatment effects on disease progression are predictive of treatment effects on OS. This conclusion is supported by similar findings of a relationship between PFS as a surrogate and survival outcomes in a range of cancers [26,37,96,97].

Based on the meta-analysis a 3 month benefit in PFS for everolimus can be hypothesised to be associated with at least a 1.23 times improvement in OS but more probably a 1.61 times improvement (4.8 months) based on studies without cross-over [36]. This survival benefit (although approximate) is similar to that estimated from application of the IPCW method to adjust for cross-over bias in the economic model of 4.97 months (see below).

6.4.5.3 Survival estimation using IPCW to address cross-over confounding

To estimate OS outcomes from the RECORD-1 trial data (primarily for use in the economic evaluation reported in Section 7), an additional post hoc analysis using the Inverse Probability of Censoring Weight (IPCW) model was performed to control for confounding in the placebo plus BSC arm associated with 76% cross over to receive everolimus [107]. Applying an IPCW adjusted Cox proportional hazards model produced an estimate that treatment with everolimus plus BSC reduces the risk of mortality by 45% (HR=0.55, 95%CI: 0.32-0.97) [107]. This hazard ratio was applied in the economic model for everolimus to produce a mean life years gained estimate of 4.97 months for everolimus compared to BSC alone (see Section 7).

The survival outcome estimated for everolimus is obtained from a trial in which patients were very heavily pre-treated; many having received several prior therapies (see Table 6.3). Hence, this benefit is significant given the advanced stage of aRCC of patients in the trial, and may be conservative compared to that which could be obtained if in practice everolimus is used earlier as second line treatment after sunitinib.

6.4.6 Objective tumour response rate

Based on RECIST criteria, everolimus plus BSC demonstrated a greater proportion of target lesion response rates that were classified as partial or stable disease, and lower rates of progressive disease as compared to placebo plus BSC. At the final analysis there were 190 patients whose best overall response was classified as partial or stable (69%) compared to only 45 (32%) placebo plus BSC patients. In contrast, progressive disease (as the 'best overall response') was recorded for 57 (21%) everolimus plus BSC patients compared to 74 (53%) for placebo plus BSC patients at final analysis [40]. Table 6.9 below presents the data from the final analysis, and also the second interim analysis which demonstrates an improved outcome in terms of response rate by the final cut-off. Due to small numbers the difference in outcomes for best overall response rate (i.e. considering only CR and PR) was not statistically significant (p=0.131). Also due to too few numbers it was not possible to enable meaningful analysis of duration of CR plus PR response.

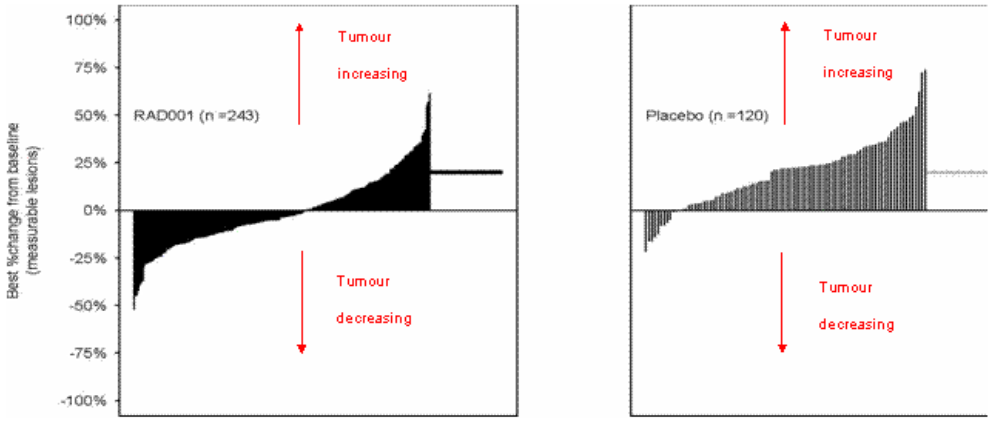
Table 6.9 Tumour response rate: RECIST criteria*

	Second interim analysis (Motzer et al., 2008) [44] (CSR [82])		Final analysis (CSR-addendum [40], Escudier et al., 2008) [74]	
	Everolimus plus BSC (N=272)	Placebo plus BSC (N=139)	Everolimus plus BSC (N=277)	Placebo plus BSC (N=139)
Objective Response	**number (%)**	**number (%)**	**number (%)**	**number (%)**
Complete response (CR)	0 (0)	0 (0)	0 (0)	0 (0)
Partial Response (PR)	3 (1)	0 (0)	5 (2)	0 (0)
Stable Disease (SD)	171 (63)	44 (32)	185 (67)	45 (32)
Progressive Disease (PD)	53 (19)	63 (46)	57 (21)	74 (53)
Unknown	45 (17)	31 (22)	30 (11)	20 (14)

* Park et al., 2003 [25]

Individual patient data from central radiology review are displayed in a waterfall plot in Figure 6.9. The data are presented by best percentage change of the sum of the longest diameters of all target lesions since baseline. Each patient is represented by one line. Minus values indicate tumour shrinkage; positive values indicate tumour growth. Patients with a missing percentage change or those where the overall lesion response at the same assessment, contradicts the measurements obtained on target lesions are flagged. The analysis demonstrates 46.9% of the everolimus treated patients presented with maximum tumour shrinkage of between 1% and less than 50% versus only 10% of placebo treated patients [40].

Figure 6.9 Best percentage change from baseline in sum of longest diameters based on central radiology review



	Everolimus	Placebo
Decrease in best percentage change from baseline	46.9%	10.0%
Increase/zero change in best percentage change from baseline	33.7%	66.7%
* % change in target lesion contradicted by overall lesion response = PD	19.3%	23.3%

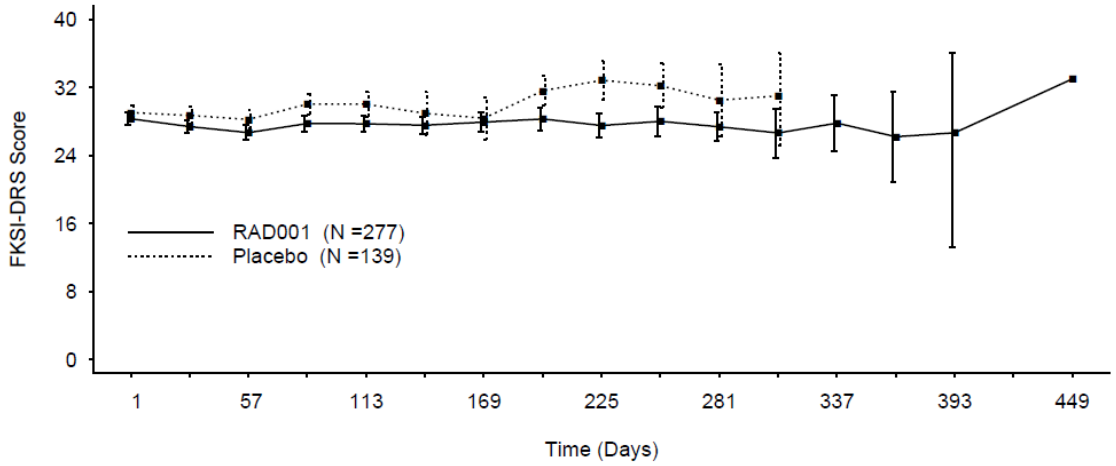
Patients for whom the best % change in target lesions was not available and patients for whom the best % change in target lesions was contradicted by overall lesion response = UNK were excluded from the analysis, percentages above use n as denominator.

Source: CSR addendum [40]

6.4.7 Patient Reported Outcomes and HRQoL

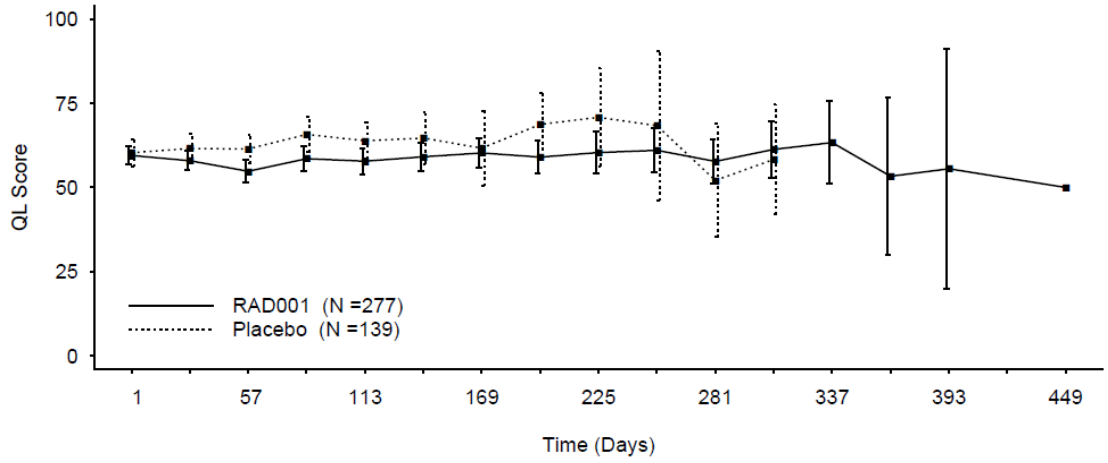
Data from the full analysis set for the mean scores over time for each of the PRO instruments in the RECORD-1 trial revealed similar HRQoL/PRO and functioning/symptom results for everolimus plus BSC and placebo plus BSC patients [40] (Figure 6.10 and Figure 6.11). This indicates that there were no tolerability issues associated with everolimus that had an adverse impact on patient health related quality of life. This low HRQoL impact may also be related to the convenience of everolimus oral once daily administration.

Figure 6.10 Longitudinal mean FKSI-DRS scores by treatment: Full Analysis Set



Source: CSR-addendum [40]

Figure 6.11 Longitudinal mean scores of the Global health status/HRQoL scale (QL) of the EORTC QLQ-C30 questionnaire by treatment: Full Analysis Set



Source: CSR-addendum [40]

The assessment of time to PRO deterioration found that compared to placebo plus BSC, everolimus plus BSC delayed deterioration of disease related symptoms by 3.5 months (median time to deterioration for FKSI-DSR was 7.4 months for everolimus plus BSC and 3.9 months for placebo plus BSC, HR=0.72, 1 sided p value = 0.044) and performance score (median time 5.8 months versus 3.8 months for everolimus plus BSC and placebo plus BSC respectively, HR=0.66, p=0.004) [40,84]. The median time to deterioration in the global quality of life (QL) and physical functioning

(PF) components of the QLQ-C30 was longer in the everolimus plus BSC group, but was not a statistically significant difference (for PF: 5.1 months versus 4.6 months for everolimus plus BSC and placebo plus BSC, respectively, HR = 0.94, p=0.385; for QL: 4.8 and 3.9 months, respectively; HR = 0.97, p=0.444) [84].

PRO/HRQoL questionnaires are often reported in cancer clinical trials as being poorly completed with many missing questionnaires and missing data [102,113]. However, in RECORD-1 compliance was reasonably good given the advanced nature of the RCC. Compliance at baseline was between 86%-92% for the FKSI-DRS and EORTC QLQ-C30 instruments in both treatment arms and despite the requirement to be completed monthly there was still at least 65% compliance by day 113 (post baseline visit 4). Hence, sufficient data was available to assess the health related quality of life impact associated with treatment [40].

6.5 Meta-analysis

A meta-analysis was not considered appropriate for this submission because there is one RCT and no active comparators to everolimus.

6.6 Indirect/mixed treatment comparisons

An indirect/mixed treatment comparison was not carried out because everolimus is the only active treatment approved for patients with aRCC whose disease has progressed following prior VEGF-targeted therapy. Everolimus plus BSC is only compared with placebo plus BSC.

6.7 Safety

6.7.1 Overview

The safety profile of everolimus as a single agent in patients with advanced solid tumours, including patients with aRCC who have failed a previous VEGF-targeted therapy, has been established through observation in two phase I (O'Donnell et al., 2008 [90]; Tabernero et al., 2008 [89]), two phase II (Amato et al., 2009 [59]; Jac et al., 2008 [39]), and one randomised phase III study [44] in patients with aRCC who have failed a previous VEGF-targeted therapy. As a result, everolimus has been investigated in over 550 patients with advanced solid tumours, including 416 patients with aRCC from the pivotal phase III randomised study (RECORD-1, also known as study C2240) [40]. Common adverse events (AEs) at all severity grades (1-4) were recorded for all the above trials with grades 3 and 4 also being reported separately.

The severity of the events was modest when compared to that observed with traditional cytotoxic chemotherapy as reports associated with everolimus were predominantly grade 1 and grade 2 events. The majority of events were reversible, transient and manageable and resolved either spontaneously or following appropriate medical management [40].

6.7.2 Safety of everolimus in conjunction with best supportive care (BSC)

The pivotal phase III RECORD-1 trial [40,44] is the only study that allows direct comparison with placebo plus BSC and hence has an ability to discriminate between drug and disease related toxicities. In the final analysis, 274 and 137 patients with aRCC received at least one dose of everolimus (10mg/day) or placebo, respectively, in conjunction with BSC. In total, 165 patients were exposed to everolimus (10mg/day) for ≥4 months [40,74]. In the everolimus plus BSC group there were 21 (7.6%) on-treatment deaths versus 7 (5.1%) deaths in the placebo plus BSC arm. Three of the everolimus group deaths were due to infectious causes and deemed drug related [40].

Table 6.10 shows the treatment-related AEs that occurred in at least 5% of patients in the everolimus plus BSC group compared with placebo plus BSC. This is based on final analysis safety data [40]. The greater incidence of AEs (and SAEs) in the everolimus plus BSC arm, reported in 40.1% of everolimus plus BSC patients versus 22.6% for placebo plus BSC patients, is related to the much longer duration of exposure for the former (as shown in Table 6.6) [40].

Everolimus was generally well-tolerated and safety findings were consistent with the smaller phase II studies. The most frequent treatment-related AEs of any grade (incidence ≥5%) were anaemia, stomatitis, asthenia, fatigue, cough, diarrhoea, rash, nausea, anorexia, and peripheral oedema, hypercholestrelaemia, pyrexia, headache, mucosal inflammation, epistaxis, hypertryglyceridaemia, pruritis, dry skin, hyperglycaemia, pnemonitis, asthenia, and blood creatinine increase (Table 6.10) [40].

The severity reports with everolimus were predominantly grade 1 and grade 2 events. Grade 3 and 4 events were often reversible, transient, and manageable. The most common grade 3 or 4 adverse events suspected to be related to treatment (incidence ≥3%) were anaemia, hyperglycaemia, stomatitis, fatigue,

hypercholesterolaemia, and dyspnoea (Table 6.10). The majority of these events resolved either spontaneously or following appropriate medical management.

Non-infectious pneumonitis which is a known risk for all mTOR inhibitors was identified early in the program and management guidelines (including CT scans and pulmonary function tests) were implemented. Grade 3 pneumonitis was reported in only 2.6% of the patients receiving everolimus plus BSC treatment in the RECORD-1 study and there were no cases of grade 4 pneumonitis reported (Table 6.10) [40].

Table 6.10 All grades adverse events (≥5% in any treatment group) and grade 3 and 4 adverse events in RECORD-1 safety population (final analysis) *

	Everolimus plus BSC (N=274)**			Placebo plus BSC (N=137)**		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
System organ/Class/AEs						
Blood and lymphatic system disorders						
Anaemia	103 (37.6)	26 (9.5)	2 (0.7)	20 (14.6)	6 (4.4)	1 (0.7)
Gastrointestinal disorders						
Stomatitis	103 (37.6)	11 (4.0)	1 (0.4)	9 (6.6)	0 (0.0)	0 (0.0)
Diarrhoea	81 (29.6)	4 (1.5)	0 (0.0)	9 (6.6)	0 (0.0)	0 (0.0)
Nausea	72 (26.3)	4 (1.5)	0 (0.0)	26 (19.0)	0 (0.0)	0 (0.0)
Mucosal inflammation	51 (18.6)	4 (1.5)	0 (0.0)	2 (1.5)	0 (0.0)	0 (0.0)
Vomiting	56 (20.4)	6 (2.2)	0 (0.0)	16 (11.7)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders						
Rash	80 (29.2)	3 (1.1)	0 (0.0)	9 (6.6)	0 (0.0)	0 (0.0)
Dry skin	35 (12.8)	1 (0.4)	0 (0.0)	7 (5.1)	0 (0.0)	0 (0.0)
Pruritis	37 (13.5)	2 (0.7)	0 (0.0)	9 (6.6)	0 (0.0)	0 (0.0)
General disorders and administration site conditions						
Asthenia	91 (33.2)	7 (2.6)	2 (0.7)	31 (22.6)	6 (4.4)	0 (0.0)

	Everolimus plus BSC (N=274)**			Placebo plus BSC (N=137)**		
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Fatigue	84 (30.7)	15 (5.5)	0 (0.0)	37 (27.0)	4 (2.9)	1 (0.7)
Oedema peripheral	68 (24.8)	2 (0.7)	0 (0.0)	11 (8.0)	1 (0.7)	0 (0.0)
Metabolism and nutrition disorders						
Anorexia	69 (25.2)	4 (1.5)	0 (0.0)	19 (13.9)	1 (0.7)	0 (0.0)
Hypercholesterolaemia	55 (20.1)	9 (3.3)	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)
Hypertriglyceridaemia	40 (14.6)	3 (1.1)	0 (0.0)	3 (2.2)	0 (0.0)	0 (0.0)
Hyperglycaemia	33 (12.0)	17 (6.2)	0 (0.0)	3 (2.2)	2 (1.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders						
Cough	82 (29.9)	2 (0.7)	0 (0.0)	22 (16.1)	0 (0.0)	0 (0.0)
Dyspnoea	65 (23.7)	17 (6.2)	4 (1.5)	20 (14.6)	4 (2.9)	0 (0.0)
Pneumonitis	27 (9.9)	7 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*Source: CSR-addendum [40]

**Safety dataset at final analysis

Some further points relating to the adverse event profile of everolimus are:

- The sum of grade 3 and 4 AEs were significantly different (2 sides Fisher exact test) between everolimus plus BSC and placebo plus BSC groups for stomatitis, hypercholesterolaemia, and hyperglycaemia.

- mTOR inhibitors as a class are responsible for regulating glucose and lipid metabolism, hence there is a risk of occurrence of AEs such as hyperglycaemia, hypercholesterolaemia, and hypertriglyceridaemia. However, in RECORD-1, no grade 4 metabolic disorder events were seen in patients receiving everolimus plus BSC; and only a small percentage of grade 3 metabolic disorder events (6.2% hyperglycaemia, 3.3% hypercholesterolaemia, and 1.1% hypertriglyceridaemia) were observed (Table 6.10) [40].

- A possible concern with mTOR inhibitor therapies is the risk of cardiovascular events. There was evidence of a greater incidence of congestive heart failure in everolimus patients than in placebo patients, although this was uncommon at less than 1% [40].

6.7.3 Discontinuations and dose reductions/interruptions due to adverse events

The RECORD-1 trial had a low rate of adverse drug reactions which were generally easy to treat leading to low levels of discontinuation due to AEs among patients who took everolimus. In total at final analysis, 38 patients in the everolimus safety population (13.9% of patients) had discontinued due to AEs, compared to 4 (2.9%) placebo patients). A similar proportion of patients (N=14, 12.8%) discontinued everolimus during the open-label extension phase due to an AE. Only 7% of patients discontinued due to AE related to the study drug however. [40].

In addition, there were 122 patients (45%) in the everolimus plus BSC group and 17 (12%) in the placebo plus BSC arm with an AE that resulted in a dose reduction and/or interruption of study drug. The following AEs were reported for more than 2% of patients, resulting in dose reduction or interruption of study drug in the everolimus plus BSC group; thrombocytopenia (2.2% versus 0% placebo), stomatitis (4.7% versus 0.7% placebo), asthenia (2.6% versus 0.7% placebo), mucosal inflammation (3.3% versus 0% placebo), pneumonia (2.2% versus 0.7% placebo), dyspnoea (2.9% versus 0% placebo), anaemia (2.6% versus 0% placebo), diarrhoea (2.6% versus 0%

placebo), nausea (2.2% versus 0.7% placebo), vomiting (2.6% versus 2.2% placebo) and pneumonitis (4.4% versus 0% placebo). Serious adverse events that were suspected to be related to study drug were reported for 44 (16%) everolimus treated patients and 1 (0.7%) placebo treated patients. The only serious adverse events suspected to be related to everolimus and reported for >2% of patients were pneumonia 2.2%, dyspnea 2.6% and pneumonitis 2.9% [40].

During the open-label phase, 43 (39.4%) of the patients treated with open-label everolimus required a study drug dose reduction and/or interruption due to an AE. AEs reported for more than 2% of patients were: dyspnoea (5.5%), stomatitis (3.7%), thrombocytopenia (2.8%), asthenia (3.7%) and mucosal inflammation (2.5%) [40].

6.7.4 Safety Conclusion

Overall, the evidence from RECORD-1 and the open-label extension shows everolimus to be generally well tolerated, with a low rate of grade 3 or 4 AEs, and a low rate of related discontinuations, which compares favourably with other therapies in aRCC.

The adverse events observed at the end of the double blind analysis are consistent with those observed at the second interim analysis; the safety profile of everolimus is unchanged with a further 4.5 months of additional data collection [40].

6.7.5 Adverse events in the single-arm phase II studies of everolimus

Although limited data is available from the abstracts, the small phase II trials demonstrated no different or unusual AEs relative to those identified in RECORD-1.

6.8 Non-RCT evidence

6.8.1 Details of how the relevant non-RCTs have been identified and selected

Publications from two related phase II single arm everolimus studies were identified by the systematic search [39,59,87,88]. The steps involved in the identification and selection of these publications are reported in Sections 6.1, 6.2.2 and 6.2.4 and study characteristics in Table 6.3. The first study by Amato et al., 2009 [59], supported by abstracts from Jac et al., 2007 [88] and Amato et al., 2006 [87], was in aRCC patients with good performance status, with the majority of patients experiencing disease progression after previous therapy failure, including VEGF-targeted therapy. The second study by Jac et al., 2008 [39] represents an extension of the first but

focused on enrolment of additional patients whose disease had progressed on or following prior VEGF-TKI therapy. This therefore represents a similar patient population as those eligible for the RECORD-1 trial. Due to the single-arm non-blinded design, there is uncertainty concerning confounding factors influencing the results and the sample size is small in both studies. However, the main aim for including these studies is to provide additional support for the absolute estimates for tumour response and disease progression/PFS outcomes found in the RECORD-1 trial. They also provide supplementary evidence for the relationship between PFS and overall survival outcomes. The results therefore complement the findings from the much larger RECORD-1 RCT.

6.8.2 Summary of methodology of relevant non-RCTs

Both phase II studies had the primary objective of exploring the anti-tumour activity and determination of PFS of everolimus in patients with progressive, measurable aRCC. Information on the methods for the two phase II studies are reported in one full publication (Amato et al., 2009 [59]) and three published abstracts (Amato et al., 2006 [87]; Jac et al., 2007 [88]; and Jac et al., 2008 [39]) presented at ASCO meetings, and summarised in Table 6.11 below.

Table 6.11 Study design for the phase II everolimus studies

	Study A **Amato et al., 2009 [59]†; Amato et al., 2006 [87]; Jac et al., 2007 [88]**	**Study B** **Jac et al., 2008 [39]**
Objective	To determine the progression free survival of patients with aRCC who were receiving daily treatment with everolimus.	To explore efficacy of everolimus in patients with aRCC who have failed on no more than 2 previous therapies one of which was a VEGFr-TKI (sunitinib or sorafenib).
Design	Two-stage, Single arm trial	Single arm trial
Total number allocated to treatment	41	22
Evaluable patients	37	19
Reasons for exclusions from analysis	2 withdrew due to screening failure 2 withdrew due to toxicity	2 patients withdrew within 4 weeks (reasons unclear)
Eligibility/Inclusion criteria	• Adults aged ≥18 years. • Presence of progressive disease • Zubrod performance status* (ZPS) = ≤2	• Presence of progressive disease • Good Performance status (Zubrod performance Status* = 0-1)

	Study A Amato et al., 2009 [59]†; Amato et al., 2006 [87]; Jac et al., 2007 [88]	Study B Jac et al., 2008 [39]
Exclusion criteria	• More than 1 prior therapy • Active CNS involvement	• More than 2 prior therapies, one of which had to be a TKI • Active CNS involvement
Study duration	• Continuous until death or treatment discontinuation	• Continuous until death or treatment discontinuation
Assessment timings	Tumour assessments every 2 cycles (1 cycle = 28 days)	Tumour assessments every 2 cycles (1 cycle = 28 days)
Outcome measures	• Tumour response rate • Time to disease progression • Overall Survival • Adverse events/toxicity Changes in metabolic imaging	• Progression Free Survival • Overall Survival • Adverse events/toxicity
Analysis	• Evaluable patients analysed	• Evaluable patients analysed

†Results taken from this reference as this is the full publication (Amato et al., 2009 [59])
*ZPS is otherwise known as ECOG, with 0-1 representing good performance and corresponding to >70 on the Karnofsky Performance Score (KPS) [114].

Details on the intervention and the baseline characteristics of the patients included in the two studies are presented in Table 6.12 below.

Table 6.12 Intervention and baseline patient characteristics for the phase II everolimus studies

	Study A Amato et al., 2009 [59]† Amato et al., 2006 [87]; Jac et al. 2007 [88]	Study B Jac et al., 2008 [39]
<u>Intervention details</u>		
Everolimus dose	10mg/day oral (dose adjustments if toxicity)	10mg/day oral (dose adjustments if toxicity)
Duration of dose Median (range)	Not specified	Not specified
<u>Patient characteristics</u>		
Age years – median (range)	60 year (38-80 yrs)	57 years
Gender- number Male (%)*	32 (78%)	15 (68%)
ZPS (performance status) 0-1	38 (93%)	22 (100%)
No. of disease sites number ≥3 sites (%)*	14 (34%)	Not specified
Number of patients who received previous systemic therapies (%)*	34 (83%)	Not specified

†Results taken from this reference as this is the full publication (Amato et al., 2009 [59])
* %'s are percentage of number allocated to treatment

6.8.3 Results of the relevant non- RCTs

The results for the main outcome measures from the two phase II studies are specified in Table 6.13 below. This shows that pre-treated patients receiving everolimus plus BSC who have progressed and therefore have very limited life expectancy, experience a PFS of up to 11.2 months, and median overall survival of up to 22.1 months. This is supportive of the PFS finding for everolimus plus BSC in RECORD-1.

Table 6.13 Results from the phase II everolimus studies

	Study A **Amato et al., 2009 [59]†** **Amato et al., 2006 [87];** **Jac et al. 2007 [88]**	**Study B** **Jac et al., 2008 [39]**
Progression Free Survival Median	11.2 months [95% CI, 1.7-36.2]	5.5 months (1-12 months)
Overall survival Median	22.1 months [95% CI, 1.4-36.4]	8 months (1-14+ months)
Tumour response (RECIST) number (%) – by investigator assesment	Partial response = 5 (14%) Disease stable > = 3 mnths = 27 (73%) *Response for ≥6 months:* Disease stable = 21 (57%) **Overall, 70% of patients had either a response or stable disease for ≥6 months.**	Partial response = 3 (16%) Disease stabilisation for >3 months = 14 (74%)

†Results taken from this reference as this is the full publication (Amato et al., 2009 [59])

6.9 Interpretation of clinical evidence

6.9.1 Relevance of the evidence base to the decision problem

The RECORD-1 double-blind randomised, controlled trial represents the primary evidence base demonstrating the clinical efficacy and safety of everolimus for the treatment of aRCC following failure on a VEGF-targeted therapy, supported by the findings from two smaller independent phase II trials (See Section 6.8). Both studies were relevant for the decision problem as they were conducted in patients whose disease had progressed on at least one prior therapy (including VEGF-TKI therapy).

Thus, both studies are important in providing initial evidence of the anti-tumour activity of everolimus plus BSC in aRCC, resulting in the RECORD-1 study.

Although RECORD-1 was a placebo-controlled trial, placebo and everolimus patients received BSC [40]. As the patient population that would be treated with everolimus in clinical practice are those who have already failed following treatment with a VEGF-targeted therapy, the main alternative remaining for these patients would also be BSC. In addition, there are no NICE recommended treatments for aRCC patients who have progressed following first line sunitinib [66]. Hence, BSC represents the appropriate comparator and reflects actual clinical practice. The type of BSC provided in RECORD-1 study centres appears consistent with that expected to be provided in cancer centres in England and Wales.

Relevant outcomes to demonstrate clinical benefits in actual practice as specified in the decision problem for this appraisal were covered by the RECORD-1 trial. These outcomes were:

- A two-thirds (67%) reduction in the risk of disease progression or death associated with a highly statistically significant improvement in median PFS of over 3 months when everolimus is administered alongside BSC compared to placebo plus BSC in patients who have failed on or following VEGF-targeted therapy. Although the patients eligible for everolimus represent a different group of post first-line treatment failure patients than those eligible for sorafenib, the results compare well with the RCT evidence for sorafenib. The improvement over placebo in median PFS for sorafenib plus BSC patients post cytokine failure was 2.7 months with a 56% reduction in risk of disease progression and this trial had earlier demonstrated a statistically significant survival benefit [41]. As VEGF-targeted therapy is viewed as an advance on cytokine therapy in terms of efficacy (see Section 4.4), it is likely that additional PFS benefits with treatment post VEGF-targeted therapy will be harder to achieve than post-cytokine therapy. Such patients are likely to be a relatively difficult-to-treat group of cancer patients in the end stage of life, and so any new active treatment that provides the potential for improved health outcomes for this recently established pre-treated population [44] is likely to be highly valued by patients, carers and treating clinicians.

- For aRCC patients who have failed on other treatments the main aim of further treatment is to stabilise the cancer in order to provide the opportunity

for patients to experience anticipated improvement in overall survival but with no detriment to health related quality of life. In terms of tumour response measured by RECIST criteria, stable disease (SD) or partial response (PR) had been achieved in 69% of everolimus plus BSC patients compared to only 32% of placebo plus BSC patients [40].

- The evidence on HRQoL from the trial was that patient functioning and general health status was maintained whilst experiencing PFS on everolimus treatment, despite the additional AEs associated with active treatment. The additional time spent progression free, and associated maintenance of quality of life in such heavily pre-treated aRCC patients is indicative of the clinical benefits that aRCC patients who receive everolimus in practice could experience.

- Assessment of AEs demonstrates that everolimus is well tolerated with a low rate of grade 3 or 4 AE's (no more than 9.5% of any grade 3 or 4 AE experienced). In addition, only 7% of patients treated with everolimus plus BSC discontinued due to the drug toxicity, despite the advanced stage of aRCC [67]. Everolimus dose intensity within RECORD-1 was 91.8% which indicates the low impact of discontinuations or dose reductions. The safety profile was viewed by a lead investigator as an acceptable risk-benefit ratio in the context of life threatening aRCC [44]. The maintained HRQoL outcomes are also indicative of the good tolerability profile of everolimus.

The strength of these results from RECORD-1 is that they are derived from a highly robust RCT design, with minimum bias for assessing the primary efficacy endpoint, secondary tumour response and PRO/HRQoL outcomes. Progression and tumour assessment was evaluated using robust recognised methods (CT/MRI scans) and criteria (RECIST) that are also used in clinical practice. The analysis was carefully planned to enable two interim analyses and a final analysis to examine whether the pre-specified primary efficacy objective had been met (i.e. in terms of a statistically significant difference in PFS compared to placebo plus BSC). The efficacy objectives were met by the time of the second interim analysis, but there was a further five months of follow-up before the trial was terminated. The more mature final analysis data is valuable for demonstrating the clinical benefits likely in actual clinical practice, hence the focus on this dataset from RECORD-1 in this submission. The trial was also managed to the highest standards of ethical clinical research conduct (e.g.

independent data monitoring, independent central radiology review). A full quality assessment of the RECORD-1 trial and evidence available is provided in Section 6.3.5.

A secondary endpoint in the RECORD-1 trial was overall survival. This was also specified in the decision problem as a key relevant outcome. However, this outcome is difficult to evaluate within cancer RCTs, especially for patients with advanced, end stage cancer. Ethical trial design means an emphasis on faster routes to completion with the use of accepted survival surrogates, in particular PFS, allowing cross-over to the active drug on disease progression and interim analyses with pre-specified efficacy stopping rules in place based on the surrogate endpoint are increasingly common practice. Hence, due primarily to the fact that 76% of patients on placebo crossed-over to receive everolimus at the final analysis, the findings for OS in RECORD-1 based on ITT analysis (i.e. a hazard ratio of 0.82 for everolimus plus BSC versus placebo plus BSC at the final analysis) are likely to be confounded and under-estimate the survival benefits expected in practice.

PFS is an acceptable surrogate endpoint for the FDA and EMEA, and there is a body of evidence demonstrating an association between median PFS improvement and survival benefits in advanced cancer. Due to the difficulty in estimating reliable ITT based survival outcomes from the RECORD-1 trial, the Inverse Probability of Censoring Weights (IPCW) model and adjusted Cox proportional hazards modelling was used to correct for bias associated with the placebo patients crossing over to receive everolimus on disease progression [107]. These methods have previously been used with HIV clinical trial data to produce unbiased survival estimates [108,115]. The IPCW adjusted hazard ratio for mortality was used to generate a more reliable estimate of the survival benefit associated with everolimus treatment in the Markov model. The IPCW adjusted hazard ratio for mortality risk was 0.55 for everolimus plus BSC versus placebo plus BSC [107].

This method and estimate has been used in the base case of the economic evaluation reported in Section 7 for the purposes of generating incremental cost per life years gained and QALY's gained estimates for everolimus. A survival benefit of 4.97 months for everolimus plus BSC was estimated from this analysis. The plausibility of this outcome is supported by evidence from a recent meta-analysis of RCTs in aRCC covering over 8 thousand patients where a treatment effect of each 1 month gain in median time to disease progression was associated with a 1.61 month

improvement in overall survival (N=24 studies) [36] (see Section 6.4.5.2). Hence, on this basis the 3 month median benefit in PFS for everolimus would be expected to translate to an approximate 4.8 month gain in overall survival, which is similar to the estimate generated by the everolimus economic model.

6.9.2 Applicability of study results to patients in routine clinical practice

The primary results included in the RECORD-1 trial [40,44] and in the post hoc survival analysis [107] are expected to be broadly applicable to a similar population of aRCC patients in routine clinical practice in England and Wales (despite the lack of UK treatment centres in the trial). The aRCC patients in the trial correspond to the target population in practice and covered by the SPC for everolimus. Patients in the trial had aRCC and a KPS score of greater than 70 (which corresponds to ECOG 0-1). Clear cell histology and performance status are measured in routine clinical practice hence no problems are anticipated identifying the appropriate targeted aRCC patients who have failed on VEGF-targeted therapy.

As recognised in the NICE scope for this appraisal, without treatment aRCC patients have a median survival of 6-12 months. As patients in the RECORD-1 trial are at a more advanced stage of aRCC having already failed on a number of previous therapies including VEGF-targeted treatment, survival with BSC alone would be expected to be at the lower end of this range or even less. The post hoc modelling of the RECORD-1 data produced an estimated 5.1 month mean life expectancy following VEGF-targeted therapy failure for patients on placebo plus BSC compared to 10.1 months for everolimus plus BSC, using IPCW methods to adjust for trial cross-over bias [107] (see also section 7 as the survival time estimates were generated using the economic model). A mean survival of 5-6 months for late stage aRCC patients receiving BSC alone is plausible.

Many patients in the trial received and failed on more than one prior drug treatment. Everolimus is expected to be used as a second-line treatment in aRCC following VEGF-targeted therapy first-line, as recommended by recent UK clinical guidelines [64]. The most likely positioning of everolimus in clinical practice is second-line use following failure with sunitinib as this VEGFr-TKI is recommended by NICE for first-line use [14]. No other drugs have been recommended for use in aRCC by NICE [66]. Therefore, the benefits in PFS (3.03 months) and for overall survival (4.97 months) for everolimus plus BSC over placebo plus BSC from analysis of the

RECORD-1 trial data may be relatively conservative if everolimus is used earlier in clinical practice than was the case for many patients in the trial.

Everolimus is presented as an oral formulation with a recommended dose of 10mg/day (with dose adjustment to 5mg if required) for the management of adverse reactions [67]. This form of administration is convenient for patients and important from a quality of life/compliance perspective as it enables patients to self-administer treatment in the home. The dose and adjustments in the clinical trial are those that would be expected to be applied in clinical practice.

7 Cost effectiveness

7.1 Published cost-effectiveness evaluations

7.1.1 Identification of studies

A systematic search was carried out in order to identify any existing published cost-effectiveness analyses for everolimus in the target patient population (see decision problem, in Section A, submitted previously). No studies were found. The search strategy used was based on that reported in the PenTAG Assessment Report for bevacizumab, sorafenib, sunitinib and temsirolimus, produced as part of the NICE MTA of drug therapies for aRCC [19]. Details of the search strategy are provided in Section 10.3, Appendix 3.

7.1.2 Description of identified studies

No relevant studies relating to everolimus cost-effectiveness were identified from the systematic search. Hence, a *de novo* economic evaluation of the cost-effectiveness of everolimus plus BSC versus BSC alone in aRCC patients who had failed on prior VEGF-targeted therapy was necessary.

7.2 De novo economic evaluation(s)

An economic model was developed to assess the cost-effectiveness of everolimus 10mg/day plus BSC versus best supportive care (BSC) alone in patients with aRCC whose cancer has progressed on or following VEGF-targeted therapy (i.e. sunitinib, sorafenib and/or bevacizumab). Patients were therefore heavily pre-treated having progressed after surgery and at least one drug therapy including a targeted VEGF treatment. The primary data source for clinical effectiveness was the RECORD-1 RCT of everolimus plus BSC versus placebo plus BSC (study C2240) (reported in Section 6). The cost-effectiveness model was developed in Microsoft Excel incorporating both a deterministic Markov cohort model and a probabilistic Markov second order Monte Carlo simulation analysis. The model consisted of four health states: stable without adverse events (the entry state into the model), stable with adverse events, disease progression and death. The analysis was conducted from an NHS and Personal Social Services perspective in England and Wales using a lifetime horizon of 144 weeks. This was less than three years as, due to the late stage of disease, almost all patients were predicted to have died by this time. Life years and QALY's gained were generated for the everolimus plus BSC and BSC

arms in order to estimate the incremental cost per life year gained and QALY gained. The reference case is summarised in Table 7.1 and is consistent with the decision problem and NICE specifications [116].

Table 7.1 Reference Case

Element of reference case	Description
Decision problem	Cost-effectiveness of everolimus plus BSC at a continuous dose of 10mg/day versus BSC alone in aRCC patients whose cancer has progressed on or following VEGF-targeted therapy
Comparators	Best supportive care
Perspective for costs	NHS and Personal Social Services costs in England and Wales
Perspective for benefits	Impact on patient progression free and overall survival, and health related quality of life
Type of economic evaluation	Cost-utility analysis
Synthesis of evidence on outcomes	Based on a systematic review of clinical outcomes for everolimus
Measure of health effects	QALYs
Source of data for measurement of HRQL	Patients with aRCC who have progressed after first- line treatment
Source of preference data for valuation of changes in HRQL	UK public preferences using the EQ5D instrument, with values as reported in the PenTAG health economic model for second-line treatment of aRCC
Discount rate	3.5% for costs and health benefits
Equity weighting	Calculation of weighting applied to QALY to achieve a cost-effectiveness threshold of £30,000 and £20,000

7.2.1 Technology

7.2.1.1 How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use.

The economic evaluation assesses adult patients with aRCC who experienced disease progression on or within six months of treatment on one or more VEGF targeted therapies. This is consistent with the licensed population for everolimus. Everolimus 10mg/day is assumed in the economic evaluation to be given as monotherapy in addition to BSC.

Everolimus treatment constitutes continuous, once daily dosing until disease progression is experienced (as defined by RECIST criteria) or due to unacceptable adverse reactions. In the case of adverse reactions dose adjustments (to 5mg/day) or interruptions are possible – hence it is assumed in the model that the mean dose used is adjusted to 91.8% dose intensity (from RECORD-1 the mean everolimus dose was 9.18mg/day (91.8% of maximal dose) – see Section 6.4.2). The duration of everolimus use varies for each patient depending on the time spent progression free. The model estimated the mean duration of treatment with everolimus as 172.3 treated days assuming 91.8% dose intensity (187.7 days if there were 100% dose intensity). This is a longer mean duration than the 156 days reported in the RECORD-1 Clinical Study Report for exposure to study drug (see Table 6.3 in Section 6). This is because the model extrapolates beyond the clinical trial. Hence patients who were stable at time of censoring in the trial are assumed in the model to still be receiving everolimus (or placebo) until disease progression or death as determined by the model transition probabilities to these states (see Section 7.2.5.8 below).

7.2.1.2 Has a treatment continuation rule been assumed? Where the rule is not stated in the SmPC this should be presented as a separate scenario, by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

- *the costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required)*
- *the robustness and plausibility of the endpoint on which the rule is based*
- *whether the 'response' criteria defined in the rule can be reasonably achieved*
- *the appropriateness and robustness of the time at which response is measured*
- *whether the rule can be incorporated into routine clinical practice*
- *whether the rule is likely to predict those patients for whom the technology is particularly cost effective*
- *issues with respect to withdrawal of treatment from non-responders and other equity considerations.*

There is no specific treatment continuation rule. Everolimus treatment will continue until disease progression is experienced (unless it is halted early due to toxicity).

7.2.2 Patients

7.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

Patients in the economic evaluation are all heavily pre-treated adult (≥18 years) aRCC patients who have experienced disease progression on or following one or more VEGF-targeted therapies (sunitinib, sorafenib and/or bevacizumab). They reflect a range of prognoses according to the MSKCC criteria (i.e. favourable, intermediate and poor) although due to the stage of aRCC all patients have a limited life expectancy. Patients included in the evaluation had a Karnofsky performance score greater than 70 (which is equivalent to ECOG 0-1) [114]. These patients precisely reflect the licensed indication for everolimus (Section 10.1, Appendix 1).

7.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified? If subgroups are based on differences in relative treatment effect, what clinical information is there to support the biological plausibility of this approach? For subgroups based on differences in baseline risk of specific outcomes, how were the data to quantify this identified? How was the statistical analysis undertaken?

The patient population in the model of heavily pre-treated aRCC patients who have failed on VEGF-targeted therapy already represent a distinct population of aRCC patients receiving second-line aRCC therapy. Sub-groups specified in the previous technology appraisals of aRCC drug therapies consisted of patients with clear cell versus non-clear cell histology, and nephrectomy status [19]. However, patients eligible to be treated with everolimus should all have a clear cell component and would also be expected to have undergone prior nephrectomy. This is also consistent with the RECORD-1 trial data in which over 96% of patients had undergone nephrectomy or related surgery (see Table 6.3 in Section 6).

In RECORD-1, sub-group analysis was performed by MSKCC prognostic category; number/type of prior VEGFr-TKI therapy; and other patient baseline characteristics. Only the first of these was specified a priori. Across all sub-groups, including MSKCC prognostic category or type of prior VEGFr-TKI therapy, there was no evidence of any differences in PFS outcomes compared to the overall patient population (see Figure 6.6 and

Table 6.8 in Section 6). Also, in actual clinical practice selection of pre-treated progressed aRCC patients for everolimus treatment on the grounds of prognostic score, type of prior VEGFr-TKI therapy or other characteristics such as age or gender is not expected.

Based on the sub-group analyses for RECORD-1 there is no evidence to suggest that any of the subgroups investigated benefit more than the overall population. Subgroup analyses by MSKCC risk groups; favourable, intermediate and poor demonstrate that the hazard ratios for PFS are similar across the groups with overlapping confidence intervals. In addition, there was no difference in outcomes between patients who failed on sunitinib (hazard ratio = 0.33) compared to the total trial population (hazard ratio = 0.34). Therefore, due to a lack of meaningful differences in outcomes it is not considered relevant to specify any further sub-populations of the specific heavily pre-treated aRCC population considered within the economic evaluation.

7.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Refer to the subgroups identified in the scope.

There were no obvious sub-groups not considered. Although, as stated above, sub-group analyses were performed in the analysis of the RECORD-1 data, no differences in patient outcomes were found compared to the overall trial population. Therefore, any analysis by sub-group would not be expected to produce differences in the cost-effectiveness results compared to the overall patient population (for example, the hazard ratio for risk of disease progression or death for the sub-group who had failed on sunitinib therapy was 0.34 compared to 0.33 for the whole trial population).

7.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

Although patients have progressed following prior drug therapy, they enter the model in a stable disease state without adverse events (i.e. not having progressed any further). They then receive everolimus plus BSC or BSC only. Based on trial data it was assumed that the average age of patients on receipt of the first treatment was 60 years. They may exit at different times within both groups due to variations in the time they experience further disease progression or death.

7.2.3 Comparator technology

There was no active treatment comparator in the economic evaluation as eligible aRCC patients were already heavily pre-treated and had already failed on first-line VEGF-targeted therapy, and potentially other therapies. No treatments have been recommended by NICE or are licensed for second-line treatment of aRCC post-VEGF targeted therapies. Hence, for this late stage aRCC patient population, BSC represents current practice in England and Wales. BSC was defined as the provision of drug and non-drug therapy for the relief of symptoms and general patient management.

In the economic analysis, everolimus (in addition to BSC) was compared with the provision of BSC alone, as specified in the decision problem for the appraisal. Best supportive care was also considered to be the appropriate comparator for second-line sorafenib and sunitinib post cytokine therapy in the recent technology appraisal for the aRCC drugs [19], although neither drug has been recommended for second-line use by NICE [66].

7.2.4 Study perspective

The study perspective is the NHS and PSS for costs, and health effects, in line with the NICE reference case.

7.2.4.1 Time horizon

The time horizon was patient life-time. Due to the short life expectancy of aRCC patients who have failed on first-line drug therapy, this was a relatively short duration of 144 weeks in the economic model. By this time 100% of the BSC cohort patients and 98.5% of the everolimus cohort patients in the model were predicted to have died.

7.2.5 Framework

a) Model-based evaluations

7.2.5.1 Please provide the following.

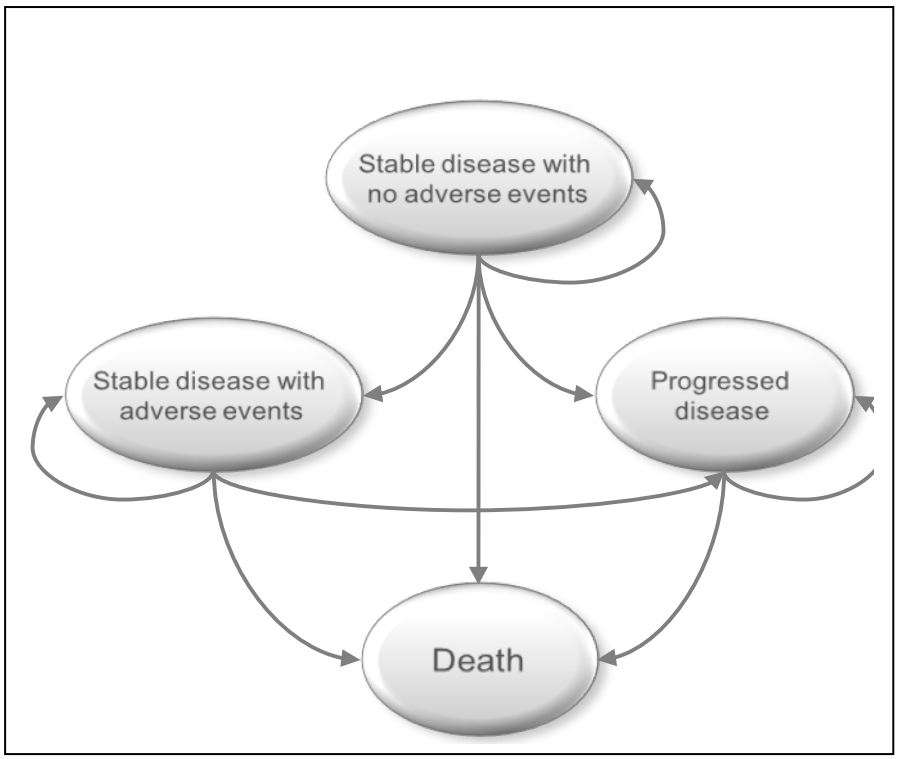
- *A description of the model type.*
- *A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.*
- *A list of all variables that includes their value, range (distribution) and source.*

- *A separate list of all assumptions and a justification for each assumption.*

Model type

The economic model is a state transition model, written in Microsoft Excel and consists of four Markov health states: stable disease (SD) without adverse events (AEs), stable disease with adverse events, progressed disease (PD) and death (Figure 7.1). Patients enter the model in a stable state without AEs (i.e. in PFS), and can either stay in this state or transition from this state to a stable state with AEs, PD, or death. From an SD state with AEs, a patient can remain in this state or transition to PD or death. Once in PD, patients remain in this state until death. The main aim of drug therapy at this stage of aRCC is to maintain patients in a stable disease state and prolong progression free survival (PFS). The majority of patients who responded to everolimus treatment in RECORD-1 were classified as stable response (67%), with a few patients achieving partial response (2%) by the final analysis (Table 6.9 in Section 6). Hence, a stable state in the model corresponds to patients having either a stable or partial tumour response according to RECIST criteria. The definition of PD is also based on RECIST criteria (Table 4.1 in Section 4).

Figure 7.1 Simplified Markov model structure



Model analyses

The economic model consists of two sets of analyses: deterministic and probabilistic. The deterministic analysis runs a cohort of patients through the Markov model health states based on a set of time-dependent transition probabilities. Each health state has a mean utility and cost associated with it. The output is a point estimate of costs and outcomes (life years gained and QALYs), and resulting incremental cost-effectiveness ratios (ICERs). The probabilistic sensitivity analysis assesses the impact of joint parameter uncertainty via a second order Monte Carlo simulation whereby each patient in the Markov cohort is simulated over the model time horizon taking into account the transitions from one health state to another; and estimated costs and utilities for each patient. The deterministic Markov model was used to generate the base case ICERs. The probabilistic analysis enabled generation of a cost-effectiveness acceptability curve (CEAC). Further details are provided in Section 7.2.10.3.

The model was developed within a single Excel workbook. For the deterministic analysis all the formulas and calculations are contained within the spreadsheets. The probabilistic simulation analysis requires additional source code in Visual Basic (VB) to handle multiple iterations, but the functionality is maintained within the Excel spreadsheet.

Variables and assumptions

Table 7.2 summarises the variables and key data utilised within the model.

Table 7.2 Model variables

Variables		Value
Hazard ratio for risk of disease progression: Everolimus plus BSC versus BSC		0.33 [95%CI:0.25-0.43]
Hazard ratio for risk of mortality everolimus versus BSC (IPCW method)		0.55 [95%CI:0.31-0.97]
Mean utilities	Stable disease (SD) with no AEs	0.76 (StdDev:0.03)
	Stable disease (SD) with AEs	0.71 (StdDev:0.04)
	Progressive disease (PD)	0.68 (StdDev:0.04)
	Death	0

Variables		Value
Drug acquisition costs - everolimus	First month – with patient access scheme (PAS)*	£0
	Per 8 weeks – with PAS (after first month)**	£5,266.80
	Without PAS**	£5,544.00
	Per 8 weeks with dose intensity adjustment and PAS	£4,843.92
Dose intensity		91.8%
Drug administration cost	Per 8 week cycle	£0
Mean treatment duration with everolimus (equivalent treated days allowing for dose intensity)		172.27 days
Mean costs of adverse events	Cost for a cycle – everolimus plus BSC	£540.35
	Cost for a cycle – BSC alone	£184.01
Mean costs of resource use (BSC)	Progressive disease state per 8 weeks	£641
	Stable disease – baseline cost (cycle zero)	£237
	Stable disease per 8 weeks – GP/nurse and tests	£110
	Stable disease – CT scan per 6 months	£182
Post disease progression on study drug: drug and non-drug therapy costs	For progressive disease state per 8 weeks	£2,428.78
End of life palliative care costs	One off cost for death state	£3,923.00
Discount rates	For both costs and health outcomes	3.5%

*PAS is a 5% discount on NHS list price (i.e. £2,822 for a pack of 10mg tablets x 30), after first month (first month of everolimus is provided to NHS at £0).

**Cost is before adjustment for dose intensity.

Specific assumptions adopted for the economic modelling are as follows:

- Dose intensity: the cost of 10mg per day everolimus in the model was adjusted by the dose intensity reported in the RECORD-1 final analysis Clinical Study Report (CSR) [40].

- No costs were assumed for drug administration, as everolimus is an oral once daily tablet which can be self-administered.

- Rather than estimate individual disutilities for AEs experienced, it was assumed that when patients started experiencing grade 3 or 4 AEs in an 8 week cycle and moved into the SD with AE state, they would receive the disutility estimated for that state.

- It was assumed that BSC provided in the RECORD-1 trial is consistent with BSC in practice, hence the outcomes experienced by the BSC cohort are those expected in actual clinical practice in England and Wales.

7.2.5.2 Why was this particular type of model used?

Markov cohort models with progressive disease, stable (or PFS) and death health states are frequently used in economic evaluations of cancer interventions, including renal cell carcinoma [117]. A Markov type model with similar health states to our model was also developed by the PenTAG group for the NICE technology appraisal of aRCC drugs [19]. However, the PenTAG model used survival analysis methods to estimate life years gained, whereas the economic model uses the transition probabilities to generate this outcome representing a better fit with the statistical methods used (IPCW adjusted Cox modelling) to correct for cross-over bias in the ITT survival data. The Markov model estimates the costs and outcomes over time for each health state at each cycle for a cohort of aRCC patients. By incorporating time dependency, the model represents an appropriate approach to modelling the patient pathway in terms of time spent based on observed RECORD-1 data by each everolimus and BSC cohort in a stable/progression free state and subsequently in disease progression [118].

7.2.5.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The Markov model states and transitions represent the typical course of disease progression for an aRCC patient cohort. Once patients have experienced disease progression following VEGF-targeted therapy, they enter an initial stable state and start treatment with everolimus monotherapy or receive BSC alone (placebo plus BSC in the RECORD-1 trial). Patients then stay in a stable state with or without experiencing adverse effects until disease progression as defined by RECIST criteria

(with tumour response confirmed by CT or MRI scan), or death. Following disease progression the only other state a patient can enter is death.

The only other possible transition that could happen is from disease progression back to a stable state. Because of the advanced stage of disease and patients having already been heavily pre-treated with limited or no remaining active treatment options, this is unlikely. In addition, the purpose of the evaluation was to explore the cost-effectiveness of everolimus monotherapy, and not a potential sequencing of treatments.

7.2.5.4 What were the sources of information used to develop and inform the structure of the model?

The primary source of information used to develop the structure of the model was the individual patient data from the final analysis of the randomised, controlled, RECORD-1 trial of everolimus plus BSC versus placebo plus BSC (i.e. at 28th February 2008 cut-off) [40]. This informed the starting patient population and health state, and the disease progression pathway adopted. In addition, the use of a Markov model structure was informed by other economic evaluations of cancer interventions, including aRCC [117].

Cross-over of placebo patients to everolimus post disease progression was allowed within the trial protocol for ethical reasons, but resulted in a total of 106 of 139 placebo patients (76%) receiving everolimus by the trial final analysis at February 2008 (and 112/139, 81% of patients, at further follow-up at November 2008). A statistical model, the Inverse Probability of Censoring Weights (IPCW) approach was therefore used to address the problem of estimating survival and life years gained outcomes for everolimus plus BSC versus BSC which was confounded by the high levels of cross-over to everolimus from placebo [107]. The IPCW approach has been established in HIV research to estimate survival outcomes for interventions within observational studies or when there is non-compliance to randomisation within an RCT design e.g. post randomisation open-label follow-up phases when additional treatments may be received in the study arms [108,109,119]. Non-compliance to randomisation tends to lead to an underestimation of the causal effect of the active treatment in ITT analysis. Hence, given the Markov structure of the model, the IPCW approach was applied to multivariate Cox proportional hazards modelling to generate a mortality hazard ratio which could be used to adjust the BSC cohort transition

probabilities relative to the everolimus plus BSC transition probabilities. The steps used in applying the IPCW approach are presented in Section 7.2.5.8 below.

7.2.5.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

Yes. Unlike other models of aRCC a state with AEs was included. This enables the overall costs and HRQoL (utility) impact of everolimus and BSC group related AEs to be captured within the Markov model structure. This provides a more convenient approach than attempting to estimate disutilities for individual AEs.

7.2.5.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

The model cycle length was 8 weeks. This duration was chosen as this represents the time points in the RECORD-1 trial at which tumour response was evaluated. It represents a relevant period for tumour size and symptoms to change to meet RECIST criteria for progressed disease. This is also a clinically relevant period for assessing change in tumour response in aRCC patients in actual clinical practice.

The model consisted of 18 x 8 week cycles, and a baseline cycle state (cycle 0).

7.2.5.7 Was a half-cycle correction used in the model? If not, why not?

A half cycle correction was not applied as it is not expected to have a significant impact on incremental costs and effects due to short cycle length and time horizon.

7.2.5.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

Extrapolation

As reported in Section 6, the RECORD-1 trial was double-blind, randomised up to the time patients experienced disease progression. Beyond this time patients in the placebo plus BSC arm were able to receive open-label everolimus. Patients were followed up for survival outcomes (up to 2 years post randomisation). Transitions between health states to the final death health state were extrapolated to the 144 week time horizon using the Markov model and the double-blind, final analysis patient data from the RECORD-1 trial.

Transition probabilities were calculated using observed patient data up to the time that the patient had died, progressed, or other time points including lost to follow up or withdrawal from the study. There was no patient data remaining by the end of cycle 5 for the BSC only cohort and cycle 7 for the everolimus cohort, . Therefore, constant transition probabilities from these last cycles were then applied to all subsequent cycles.

Bias in ITT survival outcomes associated with patient cross-over

At final analysis of the RECORD-1 trial data, median survival in the everolimus plus BSC group had not been reached, and was 13 months for the placebo plus BSC arm [40]. The mortality HR based on this data was 0.82 (95%CI: 0.57, 1.17, p=0.137) (see Figure 6.7). This result was confirmed at a later survival follow-up at November 2008 where median survival was 14.78 months versus 14.39 for everolimus plus BSC and placebo plus BSC, respectively (HR=0.87, 95%CI: 0.65-1.17, p=0.177) [112]. However, the ITT survival results could not be directly used in the economic model due to the bias associated with 76% of the placebo patients at the final analysis time point (28th February 2008) crossing-over to receive everolimus post disease progression. Fundamentally, the fact that many placebo plus BSC patients subsequently received everolimus means that the ITT survival results are not representative of the survival associated with BSC and is likely to be a significant overestimate due to the impact of active drug.

Applying the IPCW method

The IPCW approach was applied to data from RECORD-1, and broadly followed the steps as described by Hernán et al, 2006. [109].

1. Firstly, data from RECORD-1 was divided into 4 week segments (‘months’) corresponding to the frequency of visits in the RECORD-1 trial. Information on baseline characteristics and time varying assessments such as disease progression status was obtained.

2. The placebo plus BSC patients were artificially censored in the month in which they crossed-over to receive everolimus (known as cross-over or IPCW censoring).

3. This informative censoring is likely to introduce time dependent selection bias due to the patients crossing-over not being the same as those not crossing over e.g. none of the patients who did not cross over had disease progression. Inverse probability of censoring weights were generated to correct for the potential selection bias due to this cross-over censoring. Therefore, pooled logistic regression analysis was performed to estimate the probability of remaining IPCW uncensored (i.e. not crossing-over to receive everolimus). To develop the weights the logistic regressions were performed for a set of patient baseline characteristics (e.g. age, race, MSKCC category, prior treatments) adjusted for monthly time varying assessments (e.g. progression status, grade 3 or 4 AEs, death, cross-over status). The final variable selection was based on the best fitting model determined using goodness of fit statistics.

4. A stabilised weight per patient-month (SW_i) of follow-up was generated. Time periods following cross-over were excluded from analysis. Overall, there was data for 523 uncensored placebo plus BSC patient-months with an average of 3.8 months of uncensored follow-up. From this analysis the mean SW was 0.7912 (Std Dev 0.4231).

5. Everolimus plus BSC patient months were assigned SWi = 1, the placebo plus BSC patient months that were IPCW censored were assigned SWi = 0. The uncensored placebo plus BSC patient-months were assigned the weights generated by the pooled logistic regression analysis. A Cox proportional hazards model was applied to all patients in RECORD-1 (including the treatment indicator and all baseline characteristics), weighted by SW_i to estimate the monthly risk of mortality in the 'hypothetical' absence of cross-over in the placebo plus BSC arm.

6. An IPCW adjusted Cox hazard ratio for risk of death per patient month for everolimus plus BSC versus placebo plus BSC is generated for patients who in any given month could be stable or in disease progression. This hazard ratio was therefore used to generate the transition probabilities for stable and disease progression states leading to death in the Markov model for BSC.

As with all statistical adjustment models, the IPCW method has some standard statistical limitations. In particular it requires assumptions of no model misspecification and of no unmeasured confounding (i.e. all key

covariates/characteristics have been included). Whilst this is somewhat a matter of judgement it was not felt that any important predictors were omitted. As the method essentially discards data for those patients who cross over there is a risk of wide confidence intervals related to relatively small numbers in the placebo plus BSC group (24%, n=33) who did not cross-over [109,109]. Despite these limitations, the expert statistical advisors who were consulted on the use of the IPCW method supported it as a valid and appropriate method for estimating survival outcomes in the presence of cross-over and biased ITT survival data from the RECORD-1 trial.

An alternative approach, the rank preserving structural failure time (RPSFT) model has been adopted to address similar cross-over bias in the economic evaluation of sunitinib for gastrointestinal stromal tumour (GIST) [120]. The approach was also used for sunitinib in GIST within a recent NICE technology appraisal [121]. As with IPCW, accelerated time to failure models such as RPSFT have also been applied to HIV survival research performed largely by the same statistician researchers using the IPCW approach [122]. Although there is not an expectation of majorly different results with the use of either approach, the IPCW was adopted partly because it does not involve the imposition of a structural model for the effect of cross-over and so was anticipated to be relatively more robust to the assumption of no model misspecification [109]. The IPCW approach only utilises data for patients who follow the regime of interest whereas structural models like RPSFT 'borrows' information from subjects who do not follow the regime (e.g. who cross-over). In addition, the RPSFT method models treatment effect in terms of time to event so transition probabilities need to be generated from predicted survival times. In contrast, the hazard ratio for mortality generated by the IPCW Cox model was simple to apply to the everolimus transition probabilities (from RECORD-1) to generate the BSC transition probabilities for states leading to death in the Markov model (see Section 7.2.6.2). All of the everolimus transition probabilities in the model were taken directly from the RECORD-1 trial data.

Further detail on the approach used are presented in Section 10.4, Appendix 4.

b) Non-model-based economic evaluations

7.2.5.9 Was the evaluation based on patient-level economic data from a clinical trial or trials?

The economic model was a Markov cohort model. However, to generate the transition probabilities the model utilised efficacy and adverse event data from the pivotal phase III RCT (RECORD-1) up to the final analysis cut-off date of 28th February 2008 [83].

As reported in section 6 there were two main efficacy analyses of the RECORD-1 data. A second interim analysis was performed at a cut-off date of 15th October 2007 (an earlier first pre-specified interim analysis had been performed for safety assessment) by which time the pre-specified trial stopping criteria for outstanding efficacy in the primary endpoint of progression free survival had been met (demonstrating a 70% reduction in risk of disease progression or death – see Section 6.3.4.5 for details of the interim and final analyses). The results from this second interim analysis have been published in The Lancet [44]. There were 410 patients randomised at this time point that were subsequently followed through to a further updated efficacy analysis at the date of final study termination (end of double blinding) of 28th February 2008. A final analysis was conducted to this time point for the 410 patients at the second interim analysis plus an additional 6 patients recruited post second interim analysis cut-off [40].

Hence, the economic model utilised the following patient data:

- The generation of the (unadjusted) transition probabilities for the transitions from SD to SD with AE's and health states to PD, utilised available efficacy and safety data for the 416 patients (n=277 everolimus plus BSC; n=139 for placebo plus BSC) in the RECORD-1 trial (28th February 2008 analysis) [40].

- The IPCW adjusted Cox regression analysis, performed to enable adjustment of the BSC transition probabilities for states leading to death, was based on the 410 patients in the efficacy population as reported in the Lancet publication (but followed through to February 28th 2008) [44].

The IPCW logistic regression analysis used to address bias associated with cross-over in the placebo plus BSC arm utilised data from 137 patients. Of these 106 patients crossed-over on disease progression (defined as IPCW censored) and 32 patients did not cross over (16 died, 15 had not progressed by study end and one

withdrawal of consent). In total for the placebo plus BSC patients there were 523 patient-months in which cross-over had not occurred, providing an average of 3.8 months of follow-up data per patient. This data was used to generate the weights used in Cox proportional hazards modelling.(see Section 10.4, Appendix 4).

7.2.5.10 Provide details of the clinical trial, including the rationale for its selection.

The RECORD-1 trial has been fully described in Section 6. It was selected because it is the only RCT of everolimus performed in aRCC patients who have failed on or following VEGF-targeted therapy (verified by a systematic search – reported in Section 6).

7.2.5.11 Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Not applicable

7.2.5.12 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup prespecified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

Not applicable.

7.2.5.13 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

Addressed in Section 7.2.5.8.

7.2.6 Clinical evidence

7.2.6.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

The baseline treatment strategy was BSC, and hence the baseline risk of disease progression through the health states in the Markov model were based on the estimated transition probabilities for the BSC cohort. The data and methods used to generate the relative transition probabilities for the BSC alone and everolimus plus BSC cohort are described in section 7.2.6.2 below.

7.2.6.2 How were the relative risks of disease progression estimated?

For the both the everolimus plus BSC and BSC cohort, observed patient data from RECORD-1 was used to calculate the transition probabilities from stable disease to stable disease with AEs, and from both stable disease states to progressive disease:

Transitions from SD to the SD with AE's state were also based on observed data using the rates of adverse events at the level of grade 3 or 4 in the RECORD-1 trial. A lower incidence of AE's were experienced by BSC patients reflected in the lower transition probabilities to this state for this cohort (Table 7.3 below). For each cohort the probability of moving from the SD health state with AE's to the PD health state, and the probabililty of moving from SD health state without AE's to the PD health state were the same in the model. The probability of moving from the two SD health states (with and without AE's) to death were also assumed to be the same. The purpose of the SD with AE state was to assign to this state additional disutility to recognise the quality of life impact of AE's and costs for the treatment of AE's. It was assumed that once AE's were experienced they would be resolved within one cycle, after which patients would be assigned the utility and costs associated with SD (see sections 7.2.7 and 7.2.8 below).

Transition probabilities from PD and SD (with and without AEs) to the death health state for the everolimus plus BSC cohort were based on observed RECORD-1 data. For the BSC cohort the relative transition probabilities for these transitions were adjusted using the mortality hazard ratio for BSC alone versus everolimus plus BSC generated from the IPCW adjusted Cox proportional hazards modelling. The weighted Cox modelling produced an estimate of a 45% reduction in mortality risk for everolimus plus BSC versus placebo plus BSC: HR of 0.55 [95% CI:0.32-0.97, p=0.0389] [107]. This HR relates to patients who in any given month could be stable or in disease progression. The HR of 0.55 equates to a 1.81 times greater risk in any given cycle for placebo plus BSC cohort compared to the everolimus plus BSC cohort arm (i.e. 1/0.55). The transition probabilities between SD and PD states to death for the BSC cohort were generated by multiplying the everolimus transition probabilities (from RECORD-1) by 1.81.

The transition probabilities used in the economic model base case are presented in Table 7.3.

Table 7.3 Transition probabilities used in the economic model for the everolimus and BSC cohorts

Best supportive care																		
Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
AE Risk	0	[redacted]																	
SD w/o AE to PD	0	[redacted]																	
SD w/AE to PD	0	[redacted]																	
PD to Death	0	[redacted]																	
SD w/o AE to Death	0	[redacted]																	
SD w/ AE to Death	0	[redacted]																	

Everolimus																		
Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
AE Risk	0	[redacted]																	
SD w/o AE to PD	0	[redacted]																	
SD w/AE to PD	0	[redacted]																	
PD to Death	0	[redacted]																	
SD w/o AE to Death	0	[redacted]																	
SD w/ AE to Death	0	[redacted]																	

The unadjusted transition probabilities based on data directly obtained from the RECORD-1 trial are presented in Section 10.5, Appendix 5.

7.2.6.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

The primary endpoint in the RECORD-1 trial was progression free survival. As has been demonstrated in Sections 4 and 6, an association exists between PFS (an intermediate outcome) and overall survival. Analyses of data from RCTs in advanced colorectal cancer and advanced breast cancer have found a strong correlation between PFS and overall survival [28,37]. The recent RCTs of cytokine and targeted therapies for aRCC (e.g. VEGF-targeted therapies) have indicated that PFS is associated with overall survival outcomes at least as long as the additional time spent progression free [41]. In addition, a new meta-analysis consisting of 28 RCTs of treatments for aRCC studies covering 8,770 patients has quantified the relationship and estimated that every 1 month median improvement in time to disease progression for active treatment was associated with a median 1.23 month gain in overall survival (95%CI:0.70-1.75, p<0.0001) [36]. In a sub-group analysis a 1.61 difference in overall survival per 1 month gain in time to disease progression (95%CI: 0.70-2.52, p=0.0014) was estimated based on only including studies without cross-over from placebo to active therapy (N=24 studies). In addition, a 1.42 OS gain per month of PFS improvement (95%CI: 0.34-2.51, p=0.0137) was found in a sub-group analysis including the studies where patients had received prior therapy (N=16 studies, which may include studies with a cross-over design). The authors have concluded that in patients receiving treatment for aRCC, treatment effects on disease progression are predictive of treatment effects on OS [36]. PFS is increasingly being used as an outcome for anti-cancer drugs on the grounds that the FDA and EMEA have accepted that it provides a reliable surrogate endpoint for survival [32].

The evidence for an association between PFS and overall survival was not directly used to estimate disease progression and mortality for the base case of the economic model. Instead, use of the IPCW adjusted Cox proportional hazards modelling approach to address bias in the observed RECORD-1 data was preferred as it maintained direct use of the trial data for estimating overall survival for everolimus plus BSC which also formed the basis for generating the placebo plus BSC cohorts. However, evidence demonstrating an association between PFS and

OS supports the view that there is a positive survival benefit associated with everolimus treatment. For example, the 3 month improvement in PFS for everolimus plus BSC from the RECORD-1 trial would be associated with a potential 4.8 month improvement in survival based applying the correlation for aRCC studies without cross-over from the Delea et al., meta-analysis compared to a 4.97 month improvement predicted by the model[36].

7.2.6.4 Were the health effects of adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

The impact of grade 3 and 4 adverse events associated with everolimus treatment and BSC were included in the economic evaluation.

7.2.6.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Expert opinion was not directly used in the model to estimate any of the clinical parameters. However, a number of resource use variables for BSC were from the PenTAG report of other aRCC drugs and it is understood expert opinion was obtained in their assessment [19].

7.2.6.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

No other assumptions not covered above were made regarding the clinical evidence.

7.2.7 Measurement and valuation of health effects

7.2.7.1 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

Health effects were expressed as Life years gained (LYG) and quality adjusted life years gained (QALYs).

7.2.7.2 Which health effects were measured and valued? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

Utilities associated with each of the health states in the model were estimated. Therefore, utilities were generated for the SD without AEs health state, SD with AEs state, PD state, and death. Treatment with everolimus continues whilst the patient is stable or progression free, hence any treatment related AEs will be experienced

during the stable state and are captured within the model. Therefore, both positive and adverse health effects were captured within the health states.

7.2.7.3 How were health effects measured and valued? Consideration should be given to all of the following:

- *State whether the EQ-5D was used to measure HRQL or provide a description of the instrument/s used.*
- *Provide details of the population in which health effects were measured. Include information on recruitment of sample, sample size, patient characteristics and response rates.*
- *Were the data collected as part of a RCT? Refer to section 5.3 as necessary and provide details of respondents.*
- *How were health effects valued? If taken from the published literature, state the source and describe how and why these values were selected. What other values could have been used instead?*
- *Was a mapping mechanism (or 'cross-walk') generated to estimate health-related utilities of patients in the trials? Provide details of the rationale for the analysis, the instruments used, the sample from which the data were derived and the statistical properties of the mapping mechanism.*
- *Were health states directly valued? If so, provide details of the rationale for the analysis, the HRQL measures that were valued, the population who produced the values and full details of the methods used. Explain the rationale for the analysis and the choice of instruments used.*

The RECORD-1 trial did not include the EQ-5D or any other generic preference based measure with which to estimate utilities. However, utility values for health states for patients receiving second-line aRCC treatment were available from the PenTAG Report for the NICE technology appraisal of aRCC drug interventions [19]. The values used in the Assessment Group economic model were based on a manufacturer submission reporting trial based EQ-5D utilities. These were 0.76 for PFS (i.e. SD) (standard error of 0.03), and 0.68 (standard error of 0.04) for PD.

There are a number of limitations in the available utility data, which were also recognised by the PenTAG Assessment Report [19]. In particular, the utilities for health states were not directly derived from patients who had failed first-line treatment, (PenTAG also felt there was insufficient detail to assess the methods used, and the numbers of patients in the trial they were derived from was low [19]). However, there are no utility values available for health states for aRCC patients who

have experienced disease progression following treatment with VEGF-targeted therapies. Hence, the PenTAG model values were applied in the everolimus economic model as the most appropriate and best currently available. The difference in mean utility between the stable/PFS and PD states of 0.08 is likely to be on the conservative side, as recognised by NICE Appraisal Committee reported in the guidance for sunitinib [14]. Due to uncertainty in the state utility values sensitivity and scenario analysis has been performed on mean utilities.

There is limited data available on the disutility for AEs associated with anti-cancer treatment for aRCC. This was not specifically covered within the PenTAG Assessment report. However, in the everolimus economic analysis rather than attempt to identify and aggregate disutility estimates for individual AEs, which could produce a highly inaccurate overall estimate, a single overall disutility for being in the SD with AE state was applied. Therefore, a disutility of -0.05 relative to the SD without AE state was applied to SD with AE state. This value was applied for one cycle when patients entered the SD with AE state as it was assumed the AEs would be resolved within one cycle.

There are no specific available utility estimates for the collection of grade 3 or 4 AEs experienced by aRCC patients in the RECORD-1 trial. Hence, this value is based on published study reporting a disutility for dyspnoea in advanced non-small cell lung cancer [123]. It is therefore reasonable to assume that the utility for the stable with AE state (i.e. 0.71) will be between the mean utilities for the stable without AE (0.76) and PD (0.68) states. The evidence from the HRQoL data in the RECORD-1 trial was that patients maintained a reasonable level of quality of life over time spent in PFS that was similar to that for the placebo plus BSC patients, implying a limited impact of any drug related toxicity/adverse events [40]. Hence, a disutility of 0.05 units for experiencing AEs may be moderately pessimistic. Due to an uncertainty that patients with BSC will experience the same level of disutility once in the SD with AE state, in sensitivity analysis a scenario was explored in which no disutility was applied to this state for the BSC cohort.

Table 7.4 presents a summary of the base case utility values applied in the model.

Table 7.4 Mean utility values for the model health states

	Mean value (St. Dev.) [95%CI]
Stable disease (SD) without adverse events	**0.76** (0.03) [0.70, 0.81]
Stable disease (SD) with adverse events	**0.71** (0.04)
Progressive disease (PD)	**0.68** (0.04) [0.61, 0.76]
Death	**0**

7.2.7.4 Were any other generic or condition-specific preference based measures used in the clinical trials? Provide a description of the data below. The results should be considered in a sensitivity analysis (see Section 6.2.11).

No preference based measures were included in the RECORD-1 trial.

7.2.7.5 Were any health effects excluded from the analysis? If so, why were they excluded?

No relevant health effects were excluded from the analysis.

7.2.8 Resource identification, measurement and valuation

7.2.8.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

The resources included in the economic evaluation covered the following:

- Drug acquisition cost for everolimus. The standard daily dose is 10mg/day, with total cost per patient adjusted for dose intensity.
- No cost was assumed for everolimus drug administration as it is taken orally once a day.
- NHS and PSS resource use associated with stable disease (i.e. progression free survival) and progressive disease for patients with aRCC.
- Costs of drug and non-drug therapies prescribed after patients experience disease progression following everolimus or BSC.
- Treatment for AEs related to everolimus and/or BSC.

7.2.8.2 How were the resources measured?

Everolimus drug acquisition cost

The cost of everolimus was based on patients receiving the standard daily dose of 10mg per day until disease progression. Although the majority of patients in the RECORD-1 trial received the full dose of everolimus 10mg/day, there were some dose adjustments and interruptions primarily due to AEs so that the adjusted average dose was 9.18mg/day (dose intensity of 91.8%).

The list price for everolimus 10mg is £2,970 per pack of 30 tablets (1 month supply) Everolimus drug cost per 8 week cycle adjusted for 91.8% dose intensity was included in the economic model. A patient access scheme (PAS) has been discussed with the Department of Health and is pending Ministerial approval. This scheme offers the first months supply (10mg or 5mg tablets x 30) of everolimus at zero cost to the NHS. Subsequent one month packs (30 x 10mg tablets) will be offered to the NHS at a cost £2,822. This equates to 5% discount on the list price. NB This 5% discount applies to packs of the 10mg tablets only. There are no operational costs assumed for the PAS, as it involves the completion of a short form by the hospital pharmacist regarding the first month at zero cost (see Appendix 8, for the PAS registration form) (see Section 1 for the details of the everolimus patient access scheme). The acquisition cost of everolimus with and without the PAS applied is presented in Table 7.5. using the format provided in the NICE draft patient access scheme submission template [124]. The drug costs in this table are presented with and without dose intensity adjustments. Subsequent base case cost-effectiveness calculations use the dose intensity adjusted cost as that is a closer representation to actual clinical practice. However, the dose intensity estimate was explored in sensitivity analysis including an estimate of cost-effectiveness based on 80% and 100% dose intensity.

Table 7.5 Everolimus drug and patient costs with and without the patient access scheme

	Intervention without PAS		Intervention with PAS		
	Unit cost (30 x 10mg tablet pack) £	**Total cost per 8 week cycle £**	**Unit cost (30 x 10mg tablet pack) £**	**Total cost per 8 week cycle– first cycle* £**	**Total cost per 8 week cycle– subsequent cycles £**
Everolimus acquisition (no dose intensity adjustment)	*2,970*	*5,544.00*	*2,822*	*2,445.30*	*5,266.80*
Everolimus acquisition (with dose intensity adjustment)	2,970	5,089.39	2,822	2,244.79†	4,834.92†
Monitoring tests**	-	-	-	-	-
Diagnostic tests**	-	-	-	-	-
Appointments**	-	-	-	-	-
Other costs**	-	-	-	-	-
Total patient related costs		**5,089.39**		**2,244.79**	**4,843.92**

*First cycle cost based on first month of treatment provided at no cost to NHS.

**No additional costs are anticipated associated with tests or special appointments for everolimus administration. Any additional resource use incurred is routine and associated with the provision of best supportive care and the underlying cancer.

†The 8 week cycle costs are calculated assuming the 91.8% dose intensity adjustment. The unit costs are not DI adjusted in the table.

Resource use and costs associated with aRCC

The estimates of ongoing resource use for the stable (or PFS) and progressive disease states in the economic model were primarily based on those assumed in the PenTAG economic model for BSC resource use [19]. As the PenTAG estimates were estimated per 6 week cycle, these were adjusted to reflect the 8 week cycles in the everolimus economic model. This resource use consisted mainly of resource use associated with patient monitoring (assumed to be GP led), tumour scans, and blood tests. In the everolimus economic model patients are assumed to incur initial resource use post VEGF-targeted therapy disease progression consisting of a GP appointment, a CT scan, and a blood test. This is applied for patients in stable

disease at baseline (cycle 0). Subsequently, as part of patient monitoring, patients are assumed to visit a GP twice and have two blood tests during every 8 week cycle. A CT scan is assumed to be performed less frequently – once every 3 cycles). The resource use estimates and unit costs applied are presented in Table 7.6, resulting in an initial cost of £237, an ongoing cost of £110 per cycle and a CT scan cost of £182 per 3 cycles in stable disease. As BSC was common to the everolimus and comparator cohorts these costs were applied to time spent in stable disease by everolimus plus BSC and BSC alone patients.

Table 7.6 Resource use estimates and costs for the stable disease states

	Resource	Mean Frequency or duration	Unit cost £	Total Cost £
Baseline (initial resource use)	GP visit	1 visit	52[a]	52
	CT scan	1 scan	182[b]	182
	Blood test	1 test	3[c]	3
Cost of baseline resource use				**237**
Follow-up resource use	GP visit	2 visits per 8 weeks	52[a]	104
	Blood test	2 tests per 8 weeks	3[c]	6
	CT scan	1 scan per 3 cycles	182[b]	182
Cost of ongoing resource use – per cycle				**110**
Additional cost of CT scan – per 3 cycles				**182**

Sources for unit costs:

[a:] Curtis, 2008 [125]. PSSRU costs, Table 8.8b – GP visit 17.2 minutes

[b:] Code RA14Z (CT scan, three or more areas). NHS Trust and PCT combined Reference Costs 2007-08 [126]

[c:] Code DAP823 (Haematology-excluding anticoagulant services). NHS Trust and PCT combined Reference Costs 2007-08 [126]

In the economic model the cost of drug therapy with everolimus per cycle was added to the resource use costs of the stable disease health states for patients receiving everolimus.

The PenTAG economic model for aRCC drug therapies estimated resource use for medical management of PD comprising one GP visit per month, 1.5 specialist palliative care community nurse visits per month, and pain medications [19]. These estimates, adjusted for an 8 week cycle, have been applied in the everolimus

economic model as indicated in Table 7.7 below, resulting in an estimated cost for BSC of £641 per cycle.

Table 7.7 Resource use frequency and unit costs in progressive disease

Resource	Mean frequency per 8 week cycle	Unit cost £	Total cost per 8 week cycle £
GP Visits	2 visits	52[a]	104
Specialist community nurse	3 visits	79[b]	237
Supportive therapy	60 vials	5[c]	300
Cost of ongoing resource use – per cycle			**641**

Sources for unit costs:

[a:] Curtis, 2008 [125]. PSSRU costs, table 8.8b – GP visit 17.2 minutes

[b:] Code 202AF- Band 2 Palliative/respite care: adult face-to-face NHS Trust and PCT combined Reference Costs 2007-08

[c:] Morphine sulphate injections. 1 dose per day (1 mg/ml, net price 50-ml vial prefilled syringe £5.00 per pack)

Drug and non-drug therapy in progressive disease

Upon disease progression and following study drug discontinuation, patients in the RECORD-1 trial were given further drug and non-drug therapy, which included surgery, palliative radiotherapy, bisphosphonates and other salvage and investigational drug therapy. In total there was post-trial treatment data available in the follow-up study for 130 patients [127]. The model incorporates the weighted average cost of these post trial treatments for everolimus plus BSC and initial placebo plus BSC patients combined, based on the proportion of patients using each therapy. For drugs administered at this stage a dose intensity of 80% has been assumed (60% and 100% explored in sensitivity analysis). This is lower than for everolimus due to the supportive nature of post study drug discontinuation treatment. Unit costs for the individual treatments have been applied. Table 7.8 presents the drug therapies, frequency of use and unit costs, demonstrating a weighted average cost of £3,373.30 (sum of treatment cost per 8 week cycle x frequency of use for each therapy). Based on the follow-up study it was assumed that 72% of patients received the package of therapy in Table 7.8, which represented the actual proportion of patients in the RECORD-1 trial who after disease progression received an active therapy. Therefore, a cost per 8 week cycle of £2,428.78 (72% of the total weighted cost) was added to the PD health state costs of resource use in Table 7.7.

Table 7.8 Treatments and unit costs for progressive disease supportive therapy (8 weekly cycle cost)

Therapy (Units)	N. of units per 8 weeks (DI adjusted*)	Unit cost £	Frequency of treatment	Total 8 week cost £	Assumptions
Sorafenib - Nexavar® (per day)	44.80	106.45	31.43%	4,768.96	400mg twice daily (total of 800 mg) until no more treatment effect; Unit cost source: BNF 57, Mach 2009 [128]
Sunitinib -Sutent® (per day)	33.60	112	20.95%	3,763.20	One 50-mg tablet taken orally, once daily. Treatment cycles = 6 weeks (4 weeks on active treatment, 2 weeks off treatment) Unit cost source: BNF 57, March 2009 [128]
IFN alfa-2a – Roferon-A® (per week)	6.4	43.44	5.71%	278.02	9 MIU total per week (subcut x 3 per week, max 52 weeks or no more treatment effect; from bevacizumab trial [54]. Unit cost source: BNF 57, March 2009 [128]
Bevacizumab -Avastin® (per 2 weeks -76.5kg patient)	3.20	1,652.00**	14.29%	5,916.80	10 mg/kg administered intravenously once every other week until disease progression; cost includes infusion charge of £197 for each bi-weekly infusion. Drug cost of £924.40 per 400mg vial. Unit cost source: BNF 57, March 2009 [128]
Capecitabine - Xeloda® (per day)	33.60	22.64	0.95%	760.70	BNF-rec dose: mRCC 1.25g/m2 twice daily for 14 days, followed by 7 days off; Average person is 1.829m^2. Drug cost £2.46 per 500mg. Unit cost source: BNF 57, March 2009 [128]
Thoracotomy (per procedure)	1.00	4015.00	1.90%	4,015.00	Code DZ03B NHS Trust and PCT combined Reference Costs 2007-08: Major Thoracic Procedure without complications (CC)
Palliative Radiation Therapy (per day)	5.00	114.00	24.76%	570.00	Code SC22Z NHS Trust and PCT combined Reference Costs 2007-08:: Deliver a fraction of therapy on a megavoltage machine
TOTAL – weighted average cost of all treatments				**£3,373.30**	
Total cost per 8 week cycle (72% uptake of therapy)				**£2,428.78**	

*Dose intensity of 80% was assumed for drug therapies; **Cost includes drug administration cost for bevacizumab only

Adverse events

The costs of adverse events for the everolimus plus BSC and BSC only cohorts were included within the SD with AEs health state, and added to the costs of ongoing resource use for this health state (Table 7.6). The incidence of grade 3 and 4 AEs from the RECORD-1 trial and expected to incur additional treatment costs are presented in Table 7.9 (based on the final analysis safety population). It was assumed that AEs were resolved within one cycle of entering the SD with AEs health state. Therefore, the cost of the AE experienced by a patient in the previous cycle was not reapplied and the general stable disease costs then applied forthwith for that patient. The assumptions and unit costs applied for each AE are presented in Table 7.9. Resource use consisted of drug therapy, procedures such as oxygen therapy for dyspnoea, and hospital stay where required (i.e. dyspnoea and anorexia). Further detail on the treatment schedules and resource use assumed for each AE used in the model are provided in Section 10.6, Appendix 6.

Table 7.9 Adverse events and unit costs included in the model

Adverse Event	Incidence (grade 3 and 4)	Unit Cost £	Cost applied in model (incidence x unit cost) £	Source/assumption
Anaemia	10.2% everolimus 5.1% BSC	1958.00	199.72 99.86	Treatment schedule as reported in Mickisch et al., 2008 [129]
Anorexia/Cachexia	1.5% everolimus	443.13	6.65	Treatment schedules based on: 2009 NCCN Palliative Care Guidelines [130]; Ross et al., 2001 [131]; Yavuzsen et al., 2005 [132] Drug unit costs from BNF 57 March 2009 [128]; Medical costs from NHS reference costs 2007-08 [126]
Nausea / Vomiting	3.7% everolimus	2,200.64	81.42	Treatment schedule as reported in Mickisch et al., 2008 [129]
Dyspnoea	7.7% everolimus 2.9% BSC	2,901.87	223.44 84.15	Treatment schedules based on: 2009 NCCN Palliative Care Guidelines [130]; Ripamonti et al., 1999 [133]; Thomas et al., 2003 [134] Drug unit costs from BNF 57, March 2009 [128]; Medical costs from NHS reference costs 2007-08 [126]
Infections/Infestations	3.0% everolimus	796.45	23.89	Treatment schedules based on: 2009 NCCN Prevention and Treatment of Cancer-Related Infections Guidelines [135]; Reusser et al., 2002 [136]; Vento et al., 2003 [137] Drug unit costs from BNF 57, March 2009 [128]; Medical costs from NHS reference costs 2007-08 [126]
Pneumonitis Single Term	2.6 % everolimus	201.03	5.23	Treatment schedule based on RECORD-1 re: treating non-infectious pneumonitis. Drug unit costs from BNF 57, March 2009 [128]; Medical costs from NHS reference costs 2007-08 [126]

Based on the data in Table 7.9, the weighted average cost of AEs experienced by patients in each cohort and added to the costs for SD for each cohort were as follows:

- £540.35 for everolimus plus BSC
- £184.01 for BSC alone

Hence, these additional costs were applied once when a patient within each cohort entered the SD with AEs health state.

End of life palliative care

Estimates of the cost of end of life palliative care in the UK was identified from two studies [138,139]. The Guest et al., study was a decision analytic model examining the palliative care cost savings from switching patients from a weak to a strong opioid. This was conducted for terminally ill cancer patients using literature, a drug prescription database and expert opinion, and reported a minimum cost of £2,390 (1995/96 costs, or £3,524 inflated to 2008 prices at 3% per annum) for patients surviving less than 50 days [138]). Coyle et al., conducted a study of palliative care in 212 patients in district health authorities in England and Wales. Although this was not cancer specific it was performed for actual patients and was comprehensive in range of resources included. This study was also used in the PenTAG economic model of aRCC drugs where they reported a 2008 cost of £3,923 based on an original cost of £2,701 representing the average hospital and hospice stay cost in Coyle et al., [19,139]. Therefore, a cost of £3,923 was applied in the economic model as a one off cost for the death health state.

As it is uncertain whether this cost will be incurred by all aRCC patients, a scenario is explored in sensitivity analysis whereby it is assumed 0% of patients incur this cost.

Summary of costs for each health state

A summary of the overall cost estimates per 8 week cycle in the Markov model for each health state for the everolimus and BSC arms are presented in Table 7.10.

Table 7.10 Summary of costs per cycle by health state: everolimus and BSC cohorts – including Patient Access Scheme (PAS)

Health state	Everolimus plus BSC cost per cycle £	Cost coverage	BSC Cost per cycle £	Cost coverage
Stable Disease without AEs* *[without PAS]*	4,944.92** † *[5,199.39]*	Everolimus cost plus healthcare resource use	110	Healthcare resource use
Stable Disease with AEs* *[without PAS]*	5,485.27** † *[5,739.74]*	Everolimus cost, healthcare resource use and AE cost	294.01	Healthcare resource use and AE cost
Progressive disease	3,069.78	Healthcare resource use and supportive therapy	3,069.78	Healthcare resource use and supportive therapy
Death	3,923.00	One off end of life palliative care cost	3,923.00	One off end of life palliative care cost

*In addition, there is a baseline cost of £237 for both everolimus plus BSC and BSC cohorts, and the cost of a CT scan every 3 cycles at £182

**The cost per cycle with PAS is after the first month in which everolimus is provided at zero cost to the NHS

†Cost incorporates 91.8% everolimus dose intensity adjustment

7.2.8.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

Resource use was measured using a combination of patient data from the RECORD-1 trial, post trial follow-up data and estimates/assumptions derived from the PenTAG Report on aRCC drug therapies [19].

7.2.8.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

Resource use estimates covered pre-treatment baseline, treatment and resource utilisation during stable states, and resource use associated with progressive disease and end of life palliative care (death). Assumptions and justification for resource use estimates have been covered within Section 7.2.8.2.

7.2.8.5 What source(s) of information were used to value the resources? Were alternative sources of information available? Provide a justification for the preferred source and explain any discrepancies between the alternatives.

The primary source for unit costs to value resources were as follows:

- BNF 57, March 2009 for drug costs [128]
- NHS Trust and PCT combined NHS reference costs 2007-08 [126]
- Curtis, 2008 – PSSRU unit costs [125]
- Published literature and abstract based estimates (in the absence of appropriate NHS reference costs).

7.2.8.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1? If price discounts are presented in sensitivity analyses provide details of formal agreements regarding the discount including the period over which the discount is agreed and confirmation of national organisations with which the discount has been agreed for the whole of the NHS in England and Wales.

Under the terms of the PAS the first month provision (30 days) is free and the acquisition costs for all subsequent packs is £2,822 . (see Table 7.5). The cost applied in the economic analysis base case is adjusted for reported dose intensity in the RECORD-1 trial. The impact of assuming no dose intensity adjustment is explored in sensitivity analysis. There are no operational costs assumed for the PAS, as it involves the completion of a short form by the hospital pharmacist regarding the first month at zero cost (see Appendix 8). Hospitals have the option of a rebate instead of free goods for the first month of therapy.

Does the technology require additional infrastructure to be put in place? Provide details of data sources used to inform resource estimates and values.

It is not anticipated that any additional infrastructure will need to be developed. Everolimus is a convenient oral administration. Cancer centres in England and Wales are already sufficiently set up to support and monitor the administration of everolimus to eligible aRCC patients who have failed on VEGF-targeted therapy.

7.2.8.7 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

Yes, the manner in which resource use was measured and valued was considered consistent with the reference case.

7.2.8.8 Were resource values indexed to the current price year?

Resource use was valued in 2007/08 costs when using NHS reference costs [126] or Curtis 2008 [125], or indexed from the source year to 2008 values if using literature estimates. Drug costs were 2009 based on BNF 57, March 2009 [128].

7.2.8.9 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

All details and justifications for assumptions made in the estimation of resource use and valuation have been included within the resource use sub-sections above.

7.2.9 Time preferences

The base case discount rate of 3.5% was used for both costs and benefits (life years gained and QALYs), in line with the NICE reference case. Discounting was applied after the first year in the model. The impact of 0% discount rates were explored in sensitivity analysis.

7.2.10 Sensitivity analysis

7.2.10.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated including a description of alternative scenarios included in the analysis.

Sensitivity Analysis around time horizon has not been performed as the lifetime time horizon is already a short duration. A number of alternative scenarios have been considered, covered in sensitivity analysis below.

7.2.10.2 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

The base case results have been generated using the deterministic Markov cohort analysis. The following variables that were anticipated to have a potential impact on the ICERs were subject to one way sensitivity analysis and scenario analysis:

- Survival: upper and lower 95% CI's for the mortality HR based on the IPCW adjusted Cox proportional hazards model.
- Utilities: upper and lower 95% CI's for PD and SD utilities.
- Scenario whereby no AE related disutility assumed for BSC cohort (i.e. assumes utility of SD without AEs).
- Scenario whereby utility of SD with AE state for BSC = 0.76, but 0.68 for everolimus.
- Everolimus dose intensity: 100%, 80%.
- Cost of GP visits and blood tests within stable disease per cycle by +/-50%.
- Cost of CT scans within stable disease per cycle by +/-50%.
- Cost of progressive disease: increasing/reducing cost associated with PD (tests, GP and nurse visits and supportive palliative treatment costs) per cycle by +/-50%.
- Disease progression drug and non-drug therapy dose intensity at 60% and 100%.
- Costs of AEs: increasing/reducing cost of AEs for everolimus and BSC cohorts by +/-50%.
- Cost of end of life care (in death state): Cost set to zero (0% use) as per PenTAG report [19].
- Discount rate: 0% for both costs and life years/QALY outcomes.

As was discussed in Section 5, it is anticipated that everolimus satisfies the NICE criteria for end of life treatments [79,80]. The QALY weights that would be required to achieve a cost/QALY, for everolimus versus placebo, of £30,000 and £20,000 were calculated.

7.2.10.3 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

Probabilistic sensitivity analysis was performed using second order Monte Carlo simulation. In this the model parameters are varied simultaneously at the iteration level i.e. the random number generator varies the parameters within their respective distributions for each iteration for the sample size that is simulated. The simulation results presented here used a sample size of 500 patients per cohort, with 200 iterations. Each iteration expresses a point estimate for costs and effects, and the average of all iterations is the resulting ICER. Distributions used were as follows:

- The dirichlet distribution for the transition probabilities.
- Log-normal distribution for the IPCW adjusted hazard ratio for mortality.
- Gamma distribution (0 to infinity) for each resource cost (GP visit cost, community nurse visit cost, blood tests and CT scan costs, adverse event cost, pain killers (morphine) cost, progressive disease drug and non-drug therapy cost).
- A beta distribution was used for utilities (0 to 1).

The outputs generated were in the form of a scatterplot for incremental costs and incremental QALYs, and a CEAC illustrating the probability of everolimus being cost-effective at different thresholds of willingness to pay per QALY gained.

7.2.11 Statistical analysis

7.2.11.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

The transition probabilities for states leading from SD and SD with AEs to disease progression for the everolimus plus BSC and BSC cohorts were based on observed patient data from the RECORD-1 trial. The transition probabilities for everolimus plus BSC for health states leading to disease progression or death are based on the observed patient data from the trial, whilst the transition probabilities for the BSC cohort states leading to death have been adjusted using the IPCW Cox model hazard ratio for mortality [107]. Hence, BSC cohort patients are at a constantly higher relative risk of mortality at any given cycle. The methods used have been described in more detail in Section 7.2.5.8 and in Section 10.4, Appendix 4.

7.2.11.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Time dependent transition probabilities have been built in the model. Hence, the probability of disease progression or death is related to the time the patient has been in the stable or PFS state. Inclusion of time dependency is highly relevant for advanced cancer modelling where the risk increases fairly rapidly over time.

7.2.12 Validity

The model structure was reviewed by clinical and health economic experts. Reviewers agreed with the current structure that the cost-effectiveness model reflects the progression of the disease.

First-order validation (debugging and testing) was extensively performed and all bugs and errors identified were fixed in the calculations in the Markov model, the Visual Basic code, cost-effectiveness calculations, and transition probability calculations. Model cross-testing was performed, where deterministic and probabilistic analyses were compared with each other in several scenarios. Results from both models were similar.

7.3 Results

7.3.1 Base-case analysis

Table 7.11 presents the deterministic base case results with the PAS for the comparison of everolimus plus BSC versus BSC in aRCC patients who have failed previous VEGF-targeted therapy. Mean survival estimated for everolimus plus BSC is estimated to be 0.841 life years (10.1 months) compared to 0.426 life years (5.1 months) for BSC. There is an estimated gain of 0.414 life years (4.97 months) with everolimus plus BSC at an incremental cost of £15,704, the difference in cost primarily driven by the difference in drug cost. The discounted QALY gain is estimated to be 0.304 per patient. The result is an incremental cost-effectiveness ratio of £51,613 per QALY gained (£37,867 per life year gained). Table 7.12 presents the same results without the PAS as requested in the draft NICE template for patient access submission [124], demonstrating an ICER of £61,330 per QALY gained (£45,027 per life year gained).

Table 7.11 Base case cost-effectiveness results per patient (discounted) – with the PAS

	Everolimus plus BSC*	BSC alone*
Drug costs (everolimus)† £	14,045	0
Adverse event costs £	108	8
Resource use costs– GP and nurse £	1,123	742
Resource use costs– Scans/tests £	303	223
Disease progression drug and non-drug costs £	5,156	4,115
Palliative care costs: morphine sulphate plus end of life terminal care £	4,486	4,430
Total costs £	**25,222**	**9,517**
Difference in total costs £	**15,704**	
Life years gained (LYG)	0.841	0.426
Difference in LYG	0.414	
QALYs	0.607	0.302
QALYs difference	**0.304**	
Incremental cost per LYG £	37,893**	
Incremental cost per QALY gained £	**51,613****	

†Dose intensity adjustment of 91.8% has been incorporated

*Costs have been rounded to the nearest £1

** Results are generated from the model so there are some rounding differences in the table.

Table 7.12 Base case cost-effectiveness results per patient (discounted) – without the PAS

	Everolimus plus BSC*	BSC alone*
Drug costs (everolimus)† £	17,001	0
Adverse event costs £	108	8
Resource use costs– GP and nurse £	1,123	742
Resource use costs– Scans/tests £	303	223
Disease progression drug and non-drug costs £	5,156	4,115
Palliative care costs: morphine sulphate + end of life terminal care £	4,486	4,430
Total costs £	**28,178**	**9,517**
Difference in total costs £	**18,661**	
Life years gained (LYG)	0.841	0.426
Difference in LYG	0.414	

	Everolimus plus BSC*	BSC alone*
QALYs	0.607	0.302
QALYs difference	**0.304**	
Incremental cost per LYG £	45,027**	
Incremental cost per QALY gained £	**61,330****	

† Dose intensity adjustment of 91.8% has been incorporated

*Costs have been rounded to the nearest £1

** Results are generated from the model so there are some rounding differences in the table

7.3.1.1 What were the results of the subgroup analysis/analyses if conducted?

No additional sub-group analyses were conducted (see Section 7.2.2.2 for rationale).

7.3.2 Sensitivity analyses

7.3.2.1 What were the main findings of the sensitivity analyses?

The results from the scenario and sensitivity analyses are reported below.

Mortality hazard ratio

The key uncertainty in the clinical data is the estimate of survival benefit which was derived from the RECORD-1 data using IPCW modeling to adjust for the bias in the ITT overall survival results for the placebo plus BSC cohort. Therefore, the 95% CI's for the mortality hazard ratio generated have been applied for estimates of the potential range of survival benefit associated with everolimus. The confidence intervals were wide from 0.31 to 0.97, so applying the upper limit represents a highly pessimistic assumption of survival benefit that is only marginally better than the difference in PFS for everolimus compared to BSC alone. The results are presented in Table 7.13 with/without the PAS applied. In the pessimistic scenario using the upper 95%CI alters the survival benefit estimated for BSC to 0.628 life years (7.53 months), and an estimate of LYG for everolimus plus BSC of 0.212 life years (2.54 months) and 0.165 QALYs. The resulting ICER is £73,605 per QALY gained. Applying the lower 95%CI for the hazard ratio produces an estimated survival outcome with BSC of 0.278 life years (3.3 months), an estimated incremental LYG and QALY for everolimus plus BSC of 0.563 (6.6 months) and 0.408 respectively, and an ICER of £44,298 per QALY gained. The range without the PAS applied is £51,553 to £91,529 per QALY gained.

The impact of the variations in survival assumptions on costs are shown in Table 7.13. The impact of applying the mortality HR of 0.31 is that the cost associated with BSC post disease progression is reduced relative to the base case, but the resulting higher incremental cost for everolimus plus BSC is outweighed by the greater survival benefit in term of impact on the ICER. In contrast, applying the HR of 0.97 increases the cost of BSC and reduces the incremental cost of everolimus plus BSC but this is outweighed by the lower survival benefit, hence resulting in a larger ICER.

Table 7.13 Cost-effectiveness using 95% CIs for the hazard ratio for mortality (discounted)

	Lower 95%CI HR=0.31		**Upper 95%CI HR=0.97**	
	Everolimus plus BSC*	**BSC alone***	**Everolimus plus BSC***	**BSC alone***
WITHOUT PAS:				
Drug costs (everolimus)† £	17,001	0	17,001	0
Adverse event costs £	108	7	108	9
Resource use costs– GP and nurse £	1,123	463	1,123	1,152
Resource use costs– Scans/tests £	303	213	303	231
Disease progression drug and non-drug costs £	5,156	2,282	5,156	6,923
Palliative care costs: morphine sulphate + end of life terminal care £	4,486	4,205	4,486	4,765
Total costs £	**28,178**	**7,170**	**28,178**	**13,081**
Incremental costs £	**21,008**		**15,097**	
Life years gained (LYG)	0.841	0.278	0.841	0.628
Difference in LYG	0.563		0.212	
QALYs	0.607	0.199	0.607	0.442
QALYs difference	**0.408**		**0.165**	
Incremental cost per LYG £	37,334		71,141	
Incremental cost per QALY gained £	**51,553**		**91,529**	
WITH PAS:				
Drug costs (everolimus)† £	14,045	0	14,045	0
Total costs £	25,222	7,170	25,222	13,081
Incremental costs £	**18,052**		**12,141**	
Incremental cost per LYG £	32,080		57,210	
Incremental cost per QALY gained £	**44,298**		**73,605**	

† Dose intensity adjustment of 91.8% has been incorporated

*Costs have been rounded to the nearest £1

NB: Results are generated from the model so there are some rounding differences in the table

One way sensitivity analysis

The results from a series of sensitivity analyses are presented in Table 7.14.

Table 7.14 One way sensitivity and scenario analysis results[†]

Variable	Without PAS			With PAS	
	Incremental cost £*	**Incremental QALY**	**ICER for everolimus plus BSC versus BSC alone £***	**Incremental cost £***	**ICER for everolimus plus BSC versus BSC alone £***
Base Case	**18,661**	**0.304**	**61,330**	**15,704**	**51,613**
Lower 95% CI for mortality HR = 0.31 (see Table 7.13)	21,008	0.408	51,375	18,052	44,298
Upper 95% CI for mortality HR = 0.97 (see Table 7.13)	15,097	0.165	92,074	12,141	73,605
Lower 95% CI for SD utility = 0.70	18,661	0.290	64,376	15,704	54,177
Upper 95% CI for SD utility = 0.81	18,661	0.316	59,003	15,704	49,655
Lower 95% CI for PD utility = 0.61	18,661	0.300	62,275	15,704	52,409
Upper 95% CI for PD utility = 0.76	18,661	0.310	60,284	15,704	50,733
Everolimus DI = 100%	20,179	0.304	66,321	16,959	55,736
Everolimus DI = 80%	16,475	0.304	54,148	13,899	45,680
Utility of SD with AE state for BSC = 0.76, and 0.68 for everolimus	18,661	0.300	62,225	15,704	52,366
Cost of PD health state (inc. post trial costs) +50% per cycle = £4,605	19,319	0.304	63,493	16,363	53,777
Cost of PD health state (inc. post trial costs) -50% per	18,003	0.304	59,167	15,046	49,451

Variable	Without PAS			With PAS	
	Incremental cost £*	Incremental QALY	ICER for everolimus plus BSC versus BSC alone £*	Incremental cost £*	ICER for everolimus plus BSC versus BSC alone £*
cycle = £1,535					
Progressive disease drug and non-drug. DI=100%. Cost = £2,997	18,904	0.304	62,130	15,948	52,414
Progressive disease drug and non-drug. DI=60%. Cost = £1,861	18,417	0.304	60,529	15,461	50,813
Note: the sensitivity analysis for assuming SD with AE utility for BSC = 0.76, costs of GP visits and tests for SD, and costs of CT scan for SD, cost of AEs for everolimus and BSC (all +/-50%), zero cost for end of life palliative care, and 0% discount rate have not been included in the table above due to negligible impact on ICERs. † Dose intensity adjustment of 91.8% has been incorporated *Costs have been rounded to the nearest £1 NB: Results are generated from the model so there are some rounding differences in the table					

The ICER results are most sensitive to the mortality HR (as shown also in Table 7.13), and the dose intensity assumed for everolimus. Variation in the SD and PD utility estimates has some impact on the ICER. Overall, the results are not very sensitive to variations in resource use/cost parameters or discount rate.

Applying end of life QALY weights

As discussed in Section 5, everolimus for aRCC patients who have failed on or following VEGF-targeted treatment meets the criteria for consideration as a life extending, end of life treatment [79,80]:

- The RECORD-1 clinical trial has indicated that the life expectancy of a late stage aRCC patient eligible for everolimus is less than 2 years, and for many patients will be significantly less than one year.

- The standard care option currently is BSC, and with recent NICE guidance there remains no NICE recommended drug therapy for second-line aRCC treatment post first-line sunitinib (a VEGF-targeted therapy) failure [66]. Everolimus is the only mTOR inhibitor available for second-line treatment and given the lack of current options for the heavily pre-treated target population would represent a step-change in the second-line treatment of aRCC.

- The RECORD-1 clinical trial has indicated a median PFS of 3 months which represents the minimum likely survival benefit associated with everolimus plus BSC over BSC alone [40,74]. Analysis of the survival benefit in the economic model has indicated a mean benefit of 4.97 months (0.414 life years gained) or 5.02 months undiscounted (0.418 life years gained) for everolimus over BSC alone.

- Everolimus is indicated for a small sub-population of aRCC patients and it is not expected that any further indications will be licensed for everolimus within the timeframe of this appraisal.

The base case ICER of £51,613 per QALY gained with the PAS was based on a discounted QALY gain of 0.304 for everolimus plus BSC compared to BSC alone. Given the incremental cost of everolimus plus BSC, a QALY gain of 0.528 per patient would be required to achieve a cost-effectiveness threshold of £30,000/QALY gained. Therefore, the QALY weighting that would need to be applied to the base case everolimus QALY gain is 1.72. The weighting required to attain a

£20,000/QALY gained threshold is 2.58. As was noted by the Appraisal Committee for sunitinib, the 0.08 utility difference between PFS states and PD states is likely to be underestimated for aRCC patients. Therefore, as a further scenario if all patients in the economic model with SD are given a utility of 0.80 (the mean UK population EQ-5D utility for age 55-64 [140]), representing a 0.12 difference with PD, the base case ICER becomes £48,525 (with PAS) with a 0.324 QALY gain. The QALY weight then required to achieve a £30,000 threshold is 1.61.

Probabilistic sensitivity analysis

The results generated by the Monte Carlo simulation are presented below for a scenario with an estimated average per cycle cost for everolimus (over all treated cycles) with the PAS applied.

The scatter plot of incremental costs and effects generated by the Monte Carlo simulation is presented in Figure 7.2 below. The resulting CEAC is presented in Figure 7.3. The CEAC demonstrates a high probability (80%) of the ICER being cost-effective at a willingness to pay threshold of £60,000 per QALY gained, and a 40% probability at £50,000 per QALY gained. The main parameter likely to be influencing the shape and uncertainty within the CEAC is the variability in the hazard ratio for mortality applied to the transition probabilities in the model. As the fixed drug cost is the primary cost driver there is relatively low variability associated with incremental costs in the simulation, as can be seen in the scatterplot.

Figure 7.2 Scatter plot of costs and effects

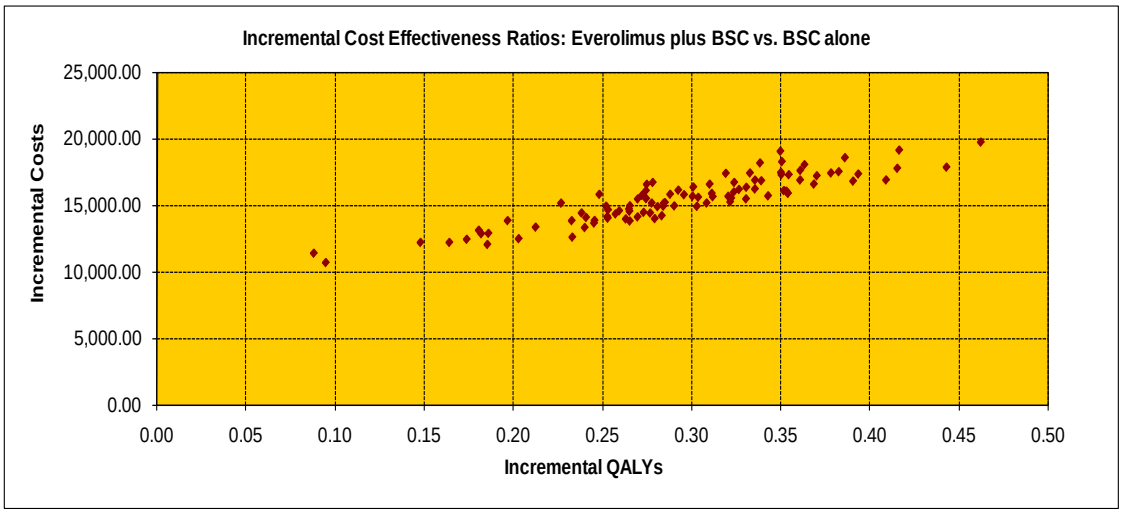
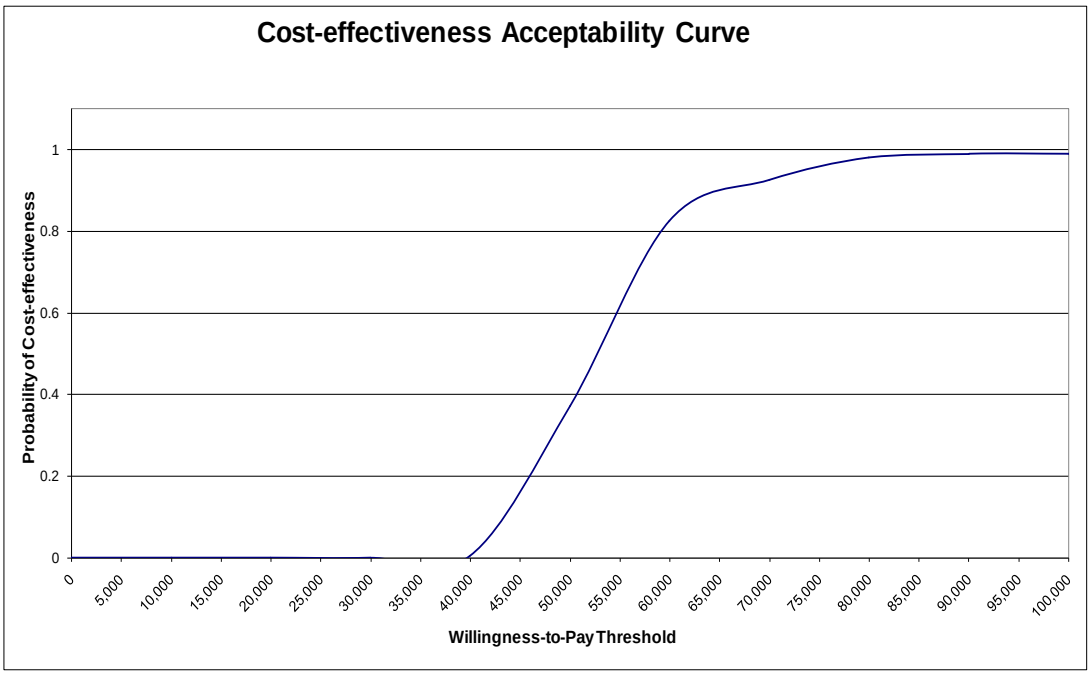


Figure 7.3 Cost-effectiveness acceptability curve



Section 10.7, Appendix 7, presents the scatterplot and CEAC without a PAS adjustment to the cost of everolimus.

7.3.2.2 What are the key drivers of the cost effectiveness results?

The key drivers of the cost-effectiveness results are the cost of the drug, and the survival estimate for everolimus plus BSC compared to BSC alone (see further discussion under Section 7.3.3.1 below). After this the utility difference between stable disease and progressive disease has an influence on cost-effectiveness.

The base case estimates of cost-effectiveness, taking into account the PAS, are comparable to other products for aRCC approved by NICE under the end of life criteria.

7.3.3 Interpretation of economic evidence

7.3.3.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

There are no published estimates of the cost-effectiveness of second-line therapy for aRCC for patients who have failed on or following VEGF-targeted therapy. Hence, it is not possible to provide a direct assessment of the cost-effectiveness results relative to any others for aRCC available. A published assessment of the cost-

effectiveness of sunitinib versus IFN-α for the US setting for the first-line treatment of mRCC is available [117], and for second-line use of sunitinib versus BSC in Finland [141]. However, these studies have low relevance for an England and Wales healthcare setting context. The evidence base for second-line use of sunitinib is very limited as recognised in the NICE guidance covering this use of sunitinib [66]. Everolimus represents a significant step change in aRCC as it targets a patient population that have already failed on a relatively effective first-line treatment (VEGF-targeted therapy, expected to be sunitinib in England and Wales due to positive NICE guidance, in contrast to sorafenib which targets patients failing on a less effective first-line therapy IFN-α).

As noted above, the survival benefit estimated is a key driver of cost-effectiveness. Due to cross-over of over three quarters of placebo patients to everolimus, the RECORD-1 trial ITT survival results do not provide a reliable indicator of survival benefit. The patients who crossed-over may not be comparable to those who did not cross-over so simple censoring of the former patients can introduce selection bias. However, in order to maintain use of the trial data robust statistical methods using IPCW adjusted Cox modelling addressed the bias associated with cross-over in the placebo plus BSC cohort. This produced a mortality hazard ratio of 0.55 for everolimus plus BSC versus BSC alone [107]. As with other methods of addressing the bias associated with cross-over such as the RPSFT, a potential limitation of the approach adopted here is the resulting Cox HR confidence intervals tend to be wide [109]. Therefore, applying the 95% CI's of 0.31 to 0.97 has the greatest impact of the variables considered in sensitivity analysis on the cost-effectiveness ratio (ranging from £44,300 to £73,600 per QALY gained taking the PAS into account). The RPSFT has been accepted as an appropriate method by NICE in an ongoing technology appraisal of sunitinib in GIST for addressing heavy cross-over related bias in ITT survival results (84% of placebo patients had crossed-over to receive sunitinib) [121]. The mortality HR generated by this approach for sunitinib in GIST was 0.505, but with confidence intervals (0.262 – 1.134) that were wider than in the everolimus analysis using IPCW. The IPCW and RPSFT methods are alternative approaches to address the same problem, and originate from the same set of researchers applying the methods primarily to address bias in HIV survival results due to non-compliance to randomisation [109,122]. In our submission the IPCW approach was preferred to other structural model approaches that may have a higher risk from model misspecification for estimating treatment effect on survival outcomes as it essentially uses the data for patients who followed the regimen (i.e. placebo and

BSC) without cross-over as a proxy for those who did (adjusted for selection bias). It was also relatively straightforward to apply to the Markov model as the BSC transition probabilities for transitions to death could simply be adjusted for the IPCW mortality HR, whereas the RPSFT estimates the time to event and so the transition probabilities would need to be generated from the RPSFT predicted survival times.

In terms of sensitivity analysis it was felt that applying the 95% CI's for the IPCW generated mortality HR would provide a reasonable basis for optimistic and pessimistic scenarios of cost-effectiveness. Indeed, application of the upper 95% CI of 0.97 can be interpreted as a highly pessimistic scenario as it assumes only a marginal survival benefit for everolimus post disease progression (likely to be worse than if the ITT survival data alone were used). Recent meta-analysis research has demonstrated that there is a greater than 1:1 relationship between PFS and overall survival in aRCC [36]. This meta-analysis showed in a sub-group of 24 aRCC controlled trials where cross-over was not an issue; a 1 month treatment effect on time to disease progression was associated with a 1.61 month improvement in overall survival. Based on this correlation, for the 3 month improvement in PFS found for everolimus in the RECORD-1 trial this would translate to an expected approximate 4.8 month gain in overall survival, similar to the 4.97 month benefit predicted by the Markov model using the IPCW adjusted HR. Hence, the ICER we have estimated of £51,600 per QALY gained based on a 4.97 month survival benefit appears to represent a plausible and realistic base case estimate.

The meta-analysis estimated a 1.23 month survival improvement per 1 month gain in time to disease progression based on all 28 studies in the study, including cross-over trials. This demonstrates the impact of cross-over on overall survival. Despite the bias this introduces, if we assume this to be a minimum likely correlation a 3 month improvement in PFS would result in a 3.7 month survival benefit (0.308 life years). The impact of this on the ICER was estimated by altering the transition probabilities in the model to obtain the discounted LYG of 0.308. This resulted in an estimate of £60,042 per QALY gained (with the PAS). Although approximate, we have performed this calculation to give a feel for the more likely upper plausible limit to the ICER.

Further support for the plausibility of the base case ICER is provided by the actual estimates of survival outcome generated by the IPCW adjusted Cox analysis applied to the BSC cohort in the Markov model. The base case estimate is a mean survival of 0.426 life years or 5.1 months for BSC, which is clinically plausible for end stage

aRCC patients who have failed on one or more prior therapies including VEGF-targeted therapy. Estimates of survival in aRCC without treatment are in the region of 6-12 months [20,22]. However, this is based on all aRCC patients, so it would be expected that patients who have already failed several therapies, as was the case in the RECORD-1 trial, would have a survival at the lower end of the range or less.

The base case estimate should also be interpreted in the context of everolimus meeting end of life criteria for consideration of the cost-effectiveness ratio. To achieve a target threshold of £30,000 per QALY gained would require a 1.72 weighting to be applied to the average QALY gain (of 0.304) estimated.

Finally, as has been recognised by NICE in the guidance for sunitinib a 0.08 difference in mean utility between stable disease and progressive disease is likely to be an underestimate [14]. A scenario assuming a 0.12 point difference in utility reduces the base case ICER to £48,500 per QALY gained (requiring a 1.61 weighting to attain the £30,000/QALY threshold).

7.3.3.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

Yes.

7.3.3.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The main strengths of the analysis are as follows:

- Markov model using observed patient data from a highly robust RCT for everolimus plus BSC versus BSC alone.
- Robust statistical modelling using a recognised technique to control for bias associated with patient cross-over from placebo to everolimus on disease progression. Robust statistical methodology has been employed to produce plausible base case survival estimates.
- Probabilistic analysis using second order Monte-Carlo simulation.
- Thorough one way sensitivity analysis.

In terms of limitations:

- The primary limitation was due to the ethical study design of the RECORD-1 trial that allowed patients on placebo to cross-over to receive open-label everolimus on disease progression. Based on the final analysis (February 2008) 76% of the BSC patients crossed-over. However, this has been addressed as discussed above.

- Robust utility evidence in aRCC remains limited. Hence, values from the PenTAG report [19] were used which has recognised limitations but represent the best available evidence.

- Similarly, resource use data is limited especially for the costs associated with progressive disease. However, the ICER results are not highly sensitive to this variable.

7.3.3.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Further research into utilities associated with aRCC health states, and resource use associated with BSC would improve the overall robustness of the results, although it is unlikely to make major differences to the base case ICER (expectation is of an improvement in cost-effectiveness with more plausible utility data).

8 Assessment of factors relevant to the NHS and other parties

8.1 What is the estimated annual budget impact for the NHS in England and Wales?

The direct drug budget impact for England and Wales of the uptake of everolimus for the treatment of aRCC in patients who have failed following or on VEGF-targeted therapy is estimated to [redacted]. The annual drug budget impact and number of patients anticipated to receive everolimus is summarised in Table 8.1. The data and assumptions used to provide these estimates are provided in the remainder of this section.

Table 8.1 Estimated drug budget impact of everolimus for aRCC in England and Wales

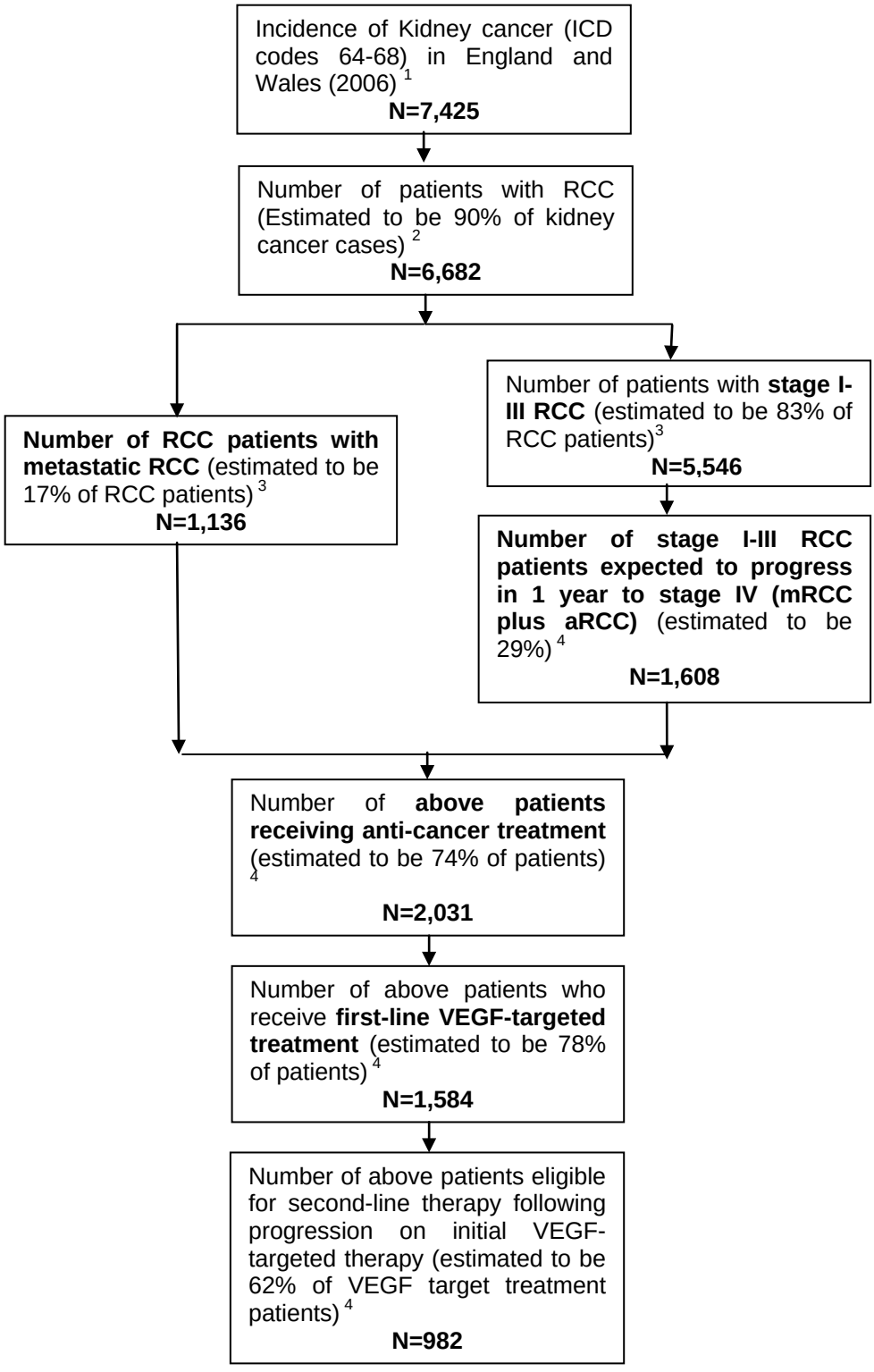
	YEAR				
	One	**Two**	**Three**	**Four**	**Five**
Drug budget impact (with patient access scheme - PAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug budget impact (without PAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eligible numbers of patients	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Forecast uptake	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated Numbers of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug budget impact per 100,000 population (with PAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Drug budget impact per 100,000 population (without PAS)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	YEAR				
	One	**Two**	**Three**	**Four**	**Five**
Estimated Numbers of patients treated per 100,000 population	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

8.2 What number of patients were assumed to be eligible? How was this figure derived?

The costs estimated in Table 8.1 are based on assumptions regarding the number of eligible aRCC patients in England and Wales, combined with forecasts of the uptake rate for everolimus. The calculation of eligible patients is presented in the flow diagram below.

Figure 8.1 Number of patients eligible for everolimus for aRCC in England and Wales



Sources and rationale for estimates:

1. Obtained from Office for National Statistics, Cancer Registrations in 2006 [2] The 2006 estimates have been updated to 2010 based on an estimated growth in kidney cancer incidence.

2. Estimates from McLaughlin et al., 2007 [13] and UK kidney cancer incidence statistics, Cancer Research UK [1]

3. British Association of Urological Surgeons, 2007 [142]

4. Novartis, 2009. Metastatic RCC treatment pathways (4377). Pan European market research of health professionals who see/ treat RCC patients [143].

Figure 8.1 provides an estimate of the eligible patients for everolimus treatment. These are aRCC patients who are either diagnosed with stage IV metastatic RCC or who progress within 1 year to aRCC disease (which contains both locally advanced aRCC and mRCC patients) from an initial diagnosis of stage I-III RCC (according to TNM classification – see Section 4.1.5). Of these patients pan-European market research data covering 11 countries including the UK has been used to estimate the proportion who have received active anti-cancer treatment, have failed on or following first-line VEGF-targeted therapy, and who are eligible for second-line treatment with everolimus [143]. The estimates have been adjusted to allow for a growth in incidence of kidney cancer and aRCC since 2006, the latest year for incidence data for England and Wales. In the UK there has been an estimated growth in incidence of kidney cancer which we have calculated to be 2.2 % and 2.5% per year for males and females, respectively, using incidence data for the period 1975-2006 [1]. Hence, current eligible aRCC patients in England and Wales are estimated to be a total of 982 patients.

The estimates of drug budget impact are based on the number of eligible patients, adjusted for expected uptake of everolimus for the target indication (see Section 8.3 below). Figure 8.1 provides the data to estimate year 1 drug budget impact. There are two assumptions used to estimate annual drug budget impact over years 2-5.

Firstly, the relevant patient population eligible for treatment each year are those newly diagnosed with aRCC and failing on a VEGF-targeted therapy. Treatment with everolimus is not expected to be greater than 1 year. In the double-blind phase of the RECORD-1 trial, only one patient received everolimus for more than 12 months [40] [44]. Hence, it is assumed that the annual incidence estimated represents the eligible patients each year.

Secondly, the annual incidence of aRCC in years 2-5 assumes a continued growth in incidence of 2.2% and 2.5% per year for males and females, respectively. These growth factors have been applied to the year 2 and 5 incidence estimates used to determine eligible patients and budget impact in these years.

There may be some aRCC patients alive in year 1, who were diagnosed in a previous year who could be eligible for everolimus treatment. However, there is a lack of data on prevalence of kidney cancer for England and Wales or UK as a whole. In Scotland, estimates are available for the prevalence of kidney cancer (based on 20 year survival data), estimated to be 75.8 and 48.7 per 100,000 population for males and females, respectively, in 2006 [144]. Applied to England and Wales this would represent a prevalence of kidney cancer of 33,533 patients alive (based on mid-2007 England and Wales population estimates) [145]. The Scottish data demonstrated that half of these patients have survived for up to 5 years – it could be that a small proportion of these patients could have progressed to aRCC and meet the other eligibility criteria for everolimus in year 1. However, in the absence of direct prevalence estimates for England and Wales and the likelihood that oncologists in actual clinical practice will focus treatment with everolimus on newly diagnosed aRCC patients, the latter were assumed to be the relevant patients for the budget impact calculations

8.3 What assumption(s) were made about current treatment options and uptake of technologies?

There are a number of treatment options for patients with kidney cancer depending on the stage of disease. For those patients diagnosed with aRCC the primary first-line option is nephrectomy, followed by first-line drug therapy with a cytokine, or with VEGF-targeted therapy [64], including sunitinib which has recently been recommended for first line use by use by NICE [14]. However, there are no current NICE recommended second-line treatment options for aRCC patients who have failed following or on VEGF-targeted therapy [66]. Therefore, in England and Wales, aRCC patients who are eligible for everolimus would otherwise be expected to receive best supportive care only. The budget impact assessment reported in Table 8.1 is based on this assumption. These estimates may represent an upper estimate of actual budget impact. Anecdotal reports suggest that due to a lack of alternative second line treatment options for aRCC, clinicians may be allowing patients to continue on sunitinib following radiologically confirmed disease progression...If this is

the case, the actual net drug budget impact of everolimus would be lower than that presented in Table 8.1.

Everolimus is not expected to be used in 100% of eligible patients. For example, some patients would not be considered suitable if they had already been treated with an mTOR inhibitor (an exclusion criteria in RECORD-1), or had poor performance status (i.e. KPS below 70 or ECOG >0-1). Nonetheless, uptake would be expected to be reasonably high. Internal Novartis forecasting has predicted an uptake of [redacted]% of eligible patients in year 1, and a [redacted]% uptake in year 2 [146]. The latter rate is also assumed to be the steady state uptake for years 2-5. The resulting patient numbers estimated to be treated with everolimus are presented in Table 8.1 above with [redacted] in year 1, [redacted] in year 2 up to [redacted] due to growth in incidence of aRCC by year 5.

8.4 What assumption(s) were made about market share (where relevant)?

As there are no alternative treatments for the target aRCC population for everolimus, no assumptions were made regarding market share.

8.5 What unit costs were assumed? How were these calculated?

The unit costs of everolimus applied for the budget impact estimates in Table 8.1 are based on the Department of Health agreed patient access scheme (PAS) as follows:

Cost of everolimus 10mg/day (month 1)	£0
Cost of everolimus 10mg/day x 30 tablets after month 1	£2,822
Mean dose everolimus mg (from RECORD-1)	9.18mg
Dose intensity	91.8%
Mean cost of everolimus per patient	£13,613

The economic model estimated a mean duration of treatment of 187.67 days, which if adjusted for 91.8% dose intensity (derived from the RECORD-1 trial as a proportion of patients experienced dose adjustments and interruptions due to adverse reactions) represents 172.27 treated days. With the PAS the first 30 days supply are provided at no cost, followed by the discounted cost of everolimus via the PAS incurred for on average a further 158 days at 91.8% dose intensity (i.e. 145 treated days incurring a drug cost). This produces an everolimus cost of £13,613 per patient treated via the PAS. The estimated mean cost for a patient who adheres to the 10mg daily dose fully is £14,829.

Without the PAS the costs of everolimus is £17,055 based on 172.27 treated days and a 30 x 10mg tablet pack cost of £2,970.

8.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

There are no other significant costs associated with everolimus treatment. The likely observed dose (91.8% dose intensity) has been taken into account in the budget impact calculations above. The economic evaluation in Section 7 demonstrated that the additional BSC resource costs associated with everolimus compared to the provision of BSC alone (other than everolimus drug acquisition cost) are small with an additional cost of £1,660 per patient estimated (derived from Table 7.11). This additional cost is predominantly due to the increased survival time from everolimus plus BSC.

The costs of treating grade 3 or 4 adverse events have been accounted for in the economic analysis in Section 7. The estimated cost for such AEs associated with everolimus was estimated at £108 per patient, compared to £8 for AEs associated with BSC alone (see Table 7.11).

8.7 Were there any estimates of resource savings? If so, what were they?

As everolimus is in addition to best supportive care there are not expected to be any resource savings associated with treatment.

8.7.1 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

No resource savings or redirection of resource use expected.

9 References

(1) Cancer Research UK. UK Kidney Cancer incidence statistics. Last accessed 10th July 2009. http://info.cancerresearchuk.org/cancerstats/types/kidney/incidence/.

(2) The Office for National Statistics. Cancer statistics registrations. Registrations of cancer diagnosed in 2006, England. Series MB1 No. 37.

(3) Welsh Cancer Intelligence and Surveillance Unit. Cancer Incidence in Wales 2003-2007. Annual Publication No. SA901. 23-1-2009.

(4) Cancer Research UK. UK Kidney Cancer mortality statistics. Last accessed 10th July 2009. http://info.cancerresearchuk.org/cancerstats/types/kidney/mortality/?a=5441.

(5) Cohen HT, McGovern FJ. Renal-cell carcinoma. N Engl J Med 2005 Dec 8;353(23):2477-90.

(6) Cancer Research UK. Kidney cancer symptoms and treatment. Last accessed 10th July 2009. http://info.cancerresearchuk.org/cancerstats/types/kidney/symptomsandtreatment/?a=5441.

(7) Chow WH, Gridley G, Fraumeni JF, Jr., Jarvholm B. Obesity, hypertension, and the risk of kidney cancer in men. N Engl J Med 2000 Nov 2;343(18):1305-11.

(8) Bergström A, Hsieh CC, Lindblad P, Lu CM, Cook NR, Wolk A. Obesity and renal cell cancer--a quantitative review. Br J Cancer 2001 Sep 28;85(7):984-90.

(9) Cancer Research UK. Kidney Cancer Risk Factors. Last accessed 10th July 2009. http://info.cancerresearchuk.org/cancerstats/types/kidney/riskfactors/?a=5441 .

(10) Hunt JD, van der Hel OL, McMillan GP, Boffetta P, Brennan P. Renal cell carcinoma in relation to cigarette smoking: meta-analysis of 24 studies. Int J Cancer 2005 Mar 10;114(1):101-8.

(11) Yuan JM, Castelao JE, Gago-Dominguez M, Ross RK, Yu MC. Hypertension, obesity and their medications in relation to renal cell carcinoma. Br J Cancer 1998 May;77(9):1508-13.

(12) Petrella BL, Brinckerhoff CE. Tumor cell invasion of von Hippel Lindau renal cell carcinoma cells is mediated by membrane type-1 matrix metalloproteinase. Mol Cancer 2006;5:66.

(13) McLaughlin J, Lipworth L, Tarone R. Epidemiology of Renal Cancer. Kidney Cancer Journal 5(1) Spring 2007., 10-14. http://www.kidney-cancer-journal.com/.

(14) National Institute for Health and Clinical Excellence (NICE). NICE technology appraisal guidance 169: Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. March 2009.

(15) Cheville JC, Lohse CM, Zincke H, Weaver AL, Blute ML. Comparisons of outcome and prognostic features among histologic subtypes of renal cell carcinoma. Am J Surg Pathol 2003 May;27(5):612-24.

(16) Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. Cancer 1980 Apr 15;45(8):2220-4.

(17) Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982 Dec;5(6):649-55.

(18) Motzer RJ, Bacik J, Schwartz LH, Reuter V, Russo P, Marion S, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 2004 Feb 1;22(3):454-63.

(19) Peninsula Technology Assessment Group (PenTAG). Bevacizumab, sorafenib, tosylate, sunitinib and temsirolimus for renal cell carcinoma: A systematic review and economic evaluation. May 2008. http://www.ncchta.org/project/1711.asp.

(20) Tian GG, Dawson NA. New agents for the treatment of renal cell carcinoma. Expert Rev Anticancer Ther 2001 Dec;1(4):546-54.

(21) Motzer RJ, Bander NH, Nanus DM. Renal-cell carcinoma. N Engl J Med 1996 Sep 19;335(12):865-75.

(22) National Institute for Health and Clinical Excellence (NICE). Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma: Final scope.

(23) Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000 Feb 2;92(3):205-16.

(24) Therasse P, Eisenhauer EA, Verweij J. RECIST revisited: a review of validation studies on tumour assessment. Eur J Cancer 2006 May;42(8):1031-9.

(25) Park JO, Lee SI, Song SY, Kim K, Kim WS, Jung CW, et al. Measuring response in solid tumors: comparison of RECIST and WHO response criteria. Jpn J Clin Oncol 2003 Oct;33(10):533-7.

(26) Knox JJ. Progression-free survival as endpoint in metastatic RCC? Lancet 2008 Aug 9;372(9637):427-9.

(27) Buyse M, Burzykowski T, Carroll K, Michiels S, Sargent DJ, Miller LL, et al. Progression-free survival is a surrogate for survival in advanced colorectal cancer. J Clin Oncol 2007 Nov 20;25(33):5218-24.

(28) Miksad RA, Zietemann V, Gothe R, Schwarzer R, Conrads-Frank A, Schnell-Inderst P, et al. Progression-free survival as a surrogate endpoint in advanced breast cancer. Int J Technol Assess Health Care 2008;24(4):371-83.

(29) Di MM, Bria E, Rossi A, Perrone F. Progression-free survival as primary end point in advanced non-small-cell lung cancer: does the size matter? Ann Oncol 2008 Feb;19(2):402-3.

(30) Gore ME, Escudier B. Emerging efficacy endpoints for targeted therapies in advanced renal cell carcinoma. Oncology (Williston Park) 2006 May;20(6 Suppl 5):19-24.

(31) Daugherty CK, Ratain MJ, Emanuel EJ, Farrell AT, Schilsky RL. Ethical, scientific, and regulatory perspectives regarding the use of placebos in cancer clinical trials. J Clin Oncol 2008 Mar 10;26(8):1371-8.

(32) Johnson JR, Williams G, Pazdur R. End points and United States Food and Drug Administration approval of oncology drugs. J Clin Oncol 2003 Apr 1;21(7):1404-11.

(33) Demetri GD, van Oosterom AT, Garrett CR, Blackstein ME, Shah MH, Verweij J, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006 Oct 14;368(9544):1329-38.

(34) European Medicines Agency. European Public Assessment Report (EPAR) Afinitor. 2009.

(35) Kane RC, Farrell AT, Saber H, Tang S, Williams G, Jee JM, et al. Sorafenib for the treatment of advanced renal cell carcinoma. Clin Cancer Res 2006 Dec 15;12(24):7271-8.

(36) Delea TE, Khuu A, Kay A, Zheng J, Baladi JF. Association between time to disease progression (TDP) endpoints and overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC). Poster 7124. Joint ECCO 15 and 34th ESMO Multidisciplinary Congress, Berlin 20th-24th September 2009.

(37) Sargent DJ, Wieand HS, Haller DG, Gray R, Benedetti JK, Buyse M, et al. Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: individual patient data from 20,898 patients on 18 randomized trials. J Clin Oncol 2005 Dec 1;23(34):8664-70.

(38) Taylor R, Elston J. The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK Health Technology Assessment reports. January 2009. Health Technology Assessment 2009 13[8].

(39) Jac J, Amato RJ, Giessinger S, Saxena S, Willis J. A phase II study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metatstatic renal cell carcinoma which has progressed on tyrosine kinase inhibition therapy. Abstract 5113. 44th American Society of Clinical Oncology Meeting, San Francisco, CA, USA, 14th-16th February, 2008.

(40) Novartis Pharmaceuticals. Full Clinical Study Report - Addendum Report: A randomised, double-blind, placebo-controlled, multicentre phase III study to compare the safety and efficacy of RAD001 plus Best Supportive Care (BSC) versus BSC plus Placebo in patients with metastatic carcinoma of the kidney which has progressed on VEGF receptor tyrosine kinase inhibitor therapy.

(41) Escudier B, Eisen T, Stadler WM, Szczylik C, Oudard S, Siebels M, et al. Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med 2007 Jan 11;356(2):125-34.

(42) Gupta K, Miller JD, Li JZ, Russell MW, Charbonneau C. Epidemiologic and socioeconomic burden of metastatic renal cell carcinoma (mRCC): a literature review. Cancer Treat Rev 2008 May;34(3):193-205.

(43) Harding G, Cella D, Robinson D, Jr., Mahadevia PJ, Clark J, Revicki DA. Symptom burden among patients with renal cell carcinoma (RCC): content for a symptom index. Health Qual Life Outcomes 2007;5:34.

(44) Motzer RJ, Escudier B, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet 2008 Aug 9;372(9637):449-56.

(45) Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 1993 Mar 3;85(5):365-76.

(46) Radiation Therapy Oncology Group. European Organisation for Research and Treatment of Cancer 30-item core quality of life questionnaire (EORTC QLQ C-30). 1-3-2007.

(47) Cella D, Yount S, Du H, Dhanda R, Gondek K, Langefeld K, et al. Development and validation of the Functional Assessment of Cancer Therapy-Kidney Symptom Index (FKSI). J Support Oncol 2006 Apr;4(4):191-9.

(48) Cella D, Yount S, Brucker PS, Du H, Bukowski R, Vogelzang N, et al. Development and validation of a scale to measure disease-related symptoms of kidney cancer. Value Health 2007 Jul;10(4):285-93.

(49) Herrmann E, Gerss J, Bierer S, Kopke T, Bolenz C, Hertle L, et al. Pre-treatment global quality of health predicts progression free survival in metastatic kidney cancer patients treated with sorafenib or sunitinib. J Cancer Res Clin Oncol 2009 Jan;135(1):61-7.

(50) Cella D, Li JZ, Cappelleri JC, Bushmakin A, Charbonneau C, Kim ST, et al. Quality of life in patients with metastatic renal cell carcinoma treated with sunitinib or interferon alfa: results from a phase III randomized trial. J Clin Oncol 2008 Aug 1;26(22):3763-9.

(51) Lang K, Danchenko N, Gondek K, Schwartz B, Thompson D. The burden of illness associated with renal cell carcinoma in the United States. Urol Oncol 2007 Sep;25(5):368-75.

(52) Banks J, Gupta K, Balu S, Chen E, Komatsuzaki Y, Charbonneau C, et al. Epidemiologic, Humanistic, and Economic Burden of Patients with Metastatic Renal Cell Carcinoma (mRCC). Poster PCN3. ISPOR Ninth Annual European Congress.Copenhagen, Denmark.Value in Health. 2006.

(53) Motzer RJ, Hutson TE, Tomczak P, Michaelson MD, Bukowski RM, Rixe O, et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007 Jan 11;356(2):115-24.

(54) Escudier B, Pluzanska A, Koralewski P, Ravaud A, Bracarda S, Szczylik C, et al. Bevacizumab plus interferon alfa-2a for treatment of metastatic renal cell carcinoma: a randomised, double-blind phase III trial. Lancet 2007 Dec 22;370(9605):2103-11.

(55) Sankhala K, Mita A, Kelly K, Mahalinngam D, Giles F, Mita M. The emerging safety profile of mTOR inhibitors, a novel class of anticancer agents. Targ Oncol 4, 135-142. 21-4-2009.

(56) Wullschleger S, Loewith R, Hall MN. TOR signaling in growth and metabolism. Cell 2006 Feb 10;124(3):471-84.

(57) Kim J, Rini BI. Recent advances in molecularly targeted therapy in advanced renal cell carcinoma. Therapy 6(3), 309-320. 2009.

(58) Pouyssegur J, Dayan F, Mazure NM. Hypoxia signalling in cancer and approaches to enforce tumour regression. Nature 2006 May 25;441(7092):437-43.

(59) Amato RJ, Jac J, Giessinger S, Saxena S, Willis JP. A phase 2 study with a daily regimen of the oral mTOR inhibitor RAD001 (everolimus) in patients with metastatic clear cell renal cell cancer. Cancer 2009 Jun 1;115(11):2438-46.

(60) National Institute for Health and Clinical Excellence (NICE). Guidance on Cancer Services: Improving Outcomes in Urological Cancers. 2002.

(61) Amato RJ. Renal cell carcinoma: review of novel single-agent therapeutics and combination regimens. Ann Oncol 2005 Jan;16(1):7-15.

(62) Godley PA, Taylor M. Renal cell carcinoma. Curr Opin Oncol 2001 May;13(3):199-203.

(63) Negrier S, Perol D, Ravaud A, Chevreau C, Bay JO, Delva R, et al. Medroxyprogesterone, interferon alfa-2a, interleukin 2, or combination of both cytokines in patients with metastatic renal carcinoma of intermediate prognosis: results of a randomized controlled trial. Cancer 2007 Dec 1;110(11):2468-77.

(64) Nathan P, Wagstaff J, Porfiri E, Powles T, Eisen T. UK guidelines for the systemic treatment of renal cell carcinoma. Br J Hosp Med (Lond) 2009 May;70(5):284-6.

(65) Jain RK, Duda DG, Clark JW, Loeffler JS. Lessons from phase III clinical trials on anti-VEGF therapy for cancer. Nat Clin Pract Oncol 2006 Jan;3(1):24-40.

(66) National Institute for Health and Clinical Excellence (NICE). NICE Technology Appraisal Guidance TA178: 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. August 2009.

(67) Novartis Pharmaceuticals. Everolimus Summary of Product Characteristics (SPC) [draft]. 2009.

(68) National Institute for Health and Clinical Excellence (NICE). Renal cell carcinoma (second line metastatic) - everolimus. Last accessed 17th July 2009. http://guidance.nice.org.uk/TA/WaveCRS1/48.

(69) Pfizer Limited. Sutent® Summary of Product Characteristics. 2009. http://emc.medicines.org.uk/medicine/18531/SPC/SUTENT+12.5mg%2c+25mg%2c+37.5mg+and+50mg+Hard+Capsules/.

(70) Bayer plc. Nexavar® Summary of Product Characteristics. 2009. http://emc.medicines.org.uk/medicine/18520/SPC/Nexavar+200mg+film-coated+tablets/.

(71) Wyeth Pharmaceuticals. Torisel® Summary of Product Characteristics. 2009. http://emc.medicines.org.uk/medicine/21260/SPC/TORISEL+25+mg+ml+concentrate+and+diluent+for+solution+for+infusion/.

(72) Roche Products Limited. Avastin® Summary of Product Characteristics. 2009. http://emc.medicines.org.uk/medicine/15748/SPC/Avastin+25mg+ml+concentrate+for+solution+for+infusion/.

(73) European Medicines Agency. Committee For Orphan Medicinal Products September 2008 Plenary Meeting Monthly Report. 10-9-2008.

(74) Escudier B, Ravaud A, Oudard S, Hutson TE, Porta C, Bracarda S, et al. Phase-3 randomised trial of everolimus (RAD001) vs Placebo in metastatic renal cell carcinoma. Abstract 720. Ann.Oncol. 19 (Supplement 8) 2008.

(75) Tamaskar I, Garcia JA, Elson P, Wood L, Mekhail T, Dreicer R, et al. Antitumor effects of sunitinib or sorafenib in patients with metastatic renal cell carcinoma who received prior antiangiogenic therapy. J Urol 2008 Jan;179(1):81-6.

(76) Ljungberg B, Hanbury DC, Kuczyk MA, Merseburger AS, Mulders PF, Patard JJ, et al. Guidelines on renal cel carcinoma. Update 3rd March 2009. 1-28.

(77) Bellmunt J, Guix M. The medical management of metastatic renal cell carcinoma: integrating new guidelines and recommendations. BJU Int 2009 Mar;103(5):572-7.

(78) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™. 1-4-2009. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

(79) National Institute for Health and Clinical Excellence (NICE). Appraising life-extending, end of life treatments. 5-1-2009.

(80) National Institute for Health and Clinical Excellence (NICE). Update report on the application of the 'end-of-life' supplementary adivce in health technology appraisals. July 2009.

(81) Tolley Health Economics Ltd. Afinitor® (everolimus) for renal cell carcinoma: A systematic review. September 2009.

(82) Novartis Pharmaceuticals. Full Clinical Study Report: A randomised, double-blind, placebo-controlled, multicentre phase III study to compare the safety and efficacy of RAD001 plus Best Supportive Care (BSC) versus BSC plus Placebo in patients with metastatic carcinoma of the kidney which has progressed on VEGF receptor tyrosine kinase inhibitor therapy.

(83) Kay A, Motzer RJ, Figlin RA, Escudier B, Oudard S, Porta C, et al. Updated data from a phase III randomized trial of everolimus (RAD001) versus PBO in metastatic renal cell carcinoma (mRCC). Abstract 278. 45th American Society of Clinical Oncology Meeting, Orlando, FL, USA, 29th May-2nd June, 2009.

(84) Beaumont J, Cella D, Hutson TE, Bracarda S, Grünwald V, Thompson JA, et al. Patient-reported outcomes in a randomised trial of everolimus with metastatic renal cell carcinoma patients. J.Clin.Oncol. 27 (suppl; abstract e17516). 2009.

(85) Motzer RJ. RAD001 plus best supportive care (BSC) vs BSC plus placebo in patients with metastatic renal cell carcinoma (RCC), which has progressed on VEGFr-TKI therapy: results from a randomized, double-blind, multicenter Phase-3 study (Oral presentation). 44th American Society of Clinical Oncology Meeting, San Francisco, CA, USA, 14th-16th February, 2008.

(86) Motzer RJ, Escudier, Oudard, ., Porta C, Hutson TE, et al. RAD001 vs placebo in patients with metastatic renal cell carcinoma (RCC) after progression on VEGFr-TKI therapy: Results from a randomized, double-blind, multicenter Phase-III study. Abstract LBA5026. 44th American Society of Clinical Oncology Meeting, San Francisco, CA, USA, 14th-16th February, 2008.

(87) Amato RJ, Misellati A, Khan M, Chiang S. A phase II trial of RAD001 in patients (Pts) with metastatic renal cell carcinoma (MRCC). Abstract 4530. 42nd American Society of Clinical Oncology Meeting, Atlanta, GA, USA, 2nd-6th June, 2006.

(88) Jac J, Giessinger S, Khan M, Willis J, Chiang S, Amato RJ. A phase II trial of RAD001 in patients (Pts) with metastatic renal cell carcinoma (MRCC). Abstract 5107. 43rd American Society of Clinical Oncology Meeting, Chicago, IL, USA, 1st-5th June, 2007.

(89) Tabernero J, Rojo F, Calvo E, Burris H, Judson I, Hazell K, et al. Dose- and schedule-dependent inhibition of the mammalian target of rapamycin pathway with everolimus: a phase I tumor pharmacodynamic study in patients with advanced solid tumors. J Clin Oncol 2008 Apr 1;26(10):1603-10.

(90) O'Donnell A, Faivre S, Burris HA, III, Rea D, Papadimitrakopoulou V, Shand N, et al. Phase I pharmacokinetic and pharmacodynamic study of the oral mammalian target of rapamycin inhibitor everolimus in patients with advanced solid tumors. J Clin Oncol 2008 Apr 1;26(10):1588-95.

(91) Porter L, Burris H, Jones S. Summary of results in patients with metastatic renal cell cancer (RCC) from phase I studies of RAD001 (everolimus). J.Clin.Oncol. 2006;24 (Suppl, pt1):644s. Abstract 14599.

(92) Joensuu H. Sunitinib for imatinib-resistant GIST. Lancet 2006 Oct 14;368(9544):1303-4.

(93) Scottish Medicines Consortium (SMC). Sutent® (sunitinib) Advice Page. 9-7-2007. http://www.scottishmedicines.org.uk/smc/5197.html.

(94) Scottish Medicines Consortium (SMC). Nexavar® (sorafenib) Advice Page. 13-11-2006. http://www.scottishmedicines.org.uk/smc/4936.html.

(95) Scottish Medicines Consortium (SMC). Sutent® (sunitinib) Advice Page (second-line treatment). 2009. http://www.scottishmedicines.org.uk/smc/files/sunitinib_Sutent_MRCC_343_07.pdf.

(96) Louvet C, de GA, Tournigand C, Artru P, Maindrault-Goebel F, Krulik M. Correlation between progression free survival and response rate in patients with metastatic colorectal carcinoma. Cancer 2001 Jun 1;91(11):2033-8.

(97) Johnson KR, Ringland C, Stokes BJ, Anthony DM, Freemantle N, Irs A, et al. Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. Lancet Oncol 2006 Sep;7(9):741-6.

(98) Elmqvist MA, Jordhoy MS, Bjordal K, Kaasa S, Jannert M. Health-related quality of life during the last three months of life in patients with advanced cancer. Support Care Cancer 2009 Feb;17(2):191-8.

(99) Bukowski R, Cella D, Gondek K, Escudier B. Effects of sorafenib on symptoms and quality of life: results from a large randomized placebo-controlled study in renal cancer. Am J Clin Oncol 2007 Jun;30(3):220-7.

(100) Poulakis V, Witzsch U, de VR, Moeckel M, Becht E. Quality of life after surgery for localized renal cell carcinoma: comparison between radical nephrectomy and nephron-sparing surgery. Urology 2003 Nov;62(5):814-20.

(101) Shinohara N, Harabayashi T, Sato S, Hioka T, Tsuchiya K, Koyanagi T. Impact of nephron-sparing surgery on quality of life in patients with localized renal cell carcinoma. Eur Urol 2001 Jan;39(1):114-9.

(102) Bernhard J, Cella DF, Coates AS, Fallowfield L, Ganz PA, Moinpour CM, et al. Missing quality of life data in cancer clinical trials: serious problems and challenges. Stat Med 1998 Mar 15;17(5-7):517-32.

(103) Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events v3.0 (CTCAE). 9-8-2006.

(104) National Cancer Institute. Essential Elements of a Data and Safety Monitoring Plan for Clinical Trials Funded by the National Cancer Institute. April 2001.

(105) Lan KK, DeMets D. Discrete sequential boundaries for clinical trials. Biometrika 70[3], 659-663. 1983.

(106) O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979 Sep;35(3):549-56.

(107) Wiederkehr D, Howe C, Casciano R, Motzer RJ, Zheng J, Baladi JF. Overall Survival among Metastatic Renal Cell Carcinoma Patients Corrected for Crossover using Inverse Probability of Censoring Weights: Analyses from the everolimus Phase III Trial. Abstract 7.131. Joint ECCO 15 and 34th ESMO Multidisciplinary Congress, Berlin 20th-24th September 2009.

(108) Cain LE, Cole SR. Inverse probability-of-censoring weights for the correction of time-varying noncompliance in the effect of randomized highly active antiretroviral therapy on incident AIDS or death. Stat Med 2009 May 30;28(12):1725-38.

(109) Hernan MA, Lanoy E, Costagliola D, Robins JM. Comparison of dynamic treatment regimes via inverse probability weighting. Basic Clin Pharmacol Toxicol 2006 Mar;98(3):237-42.

(110) Khan K, Ter Riet G, Glanville J, Sowdon A, Kleijnen J. Undertaking systematic reviews of research on effectiveness: CRDs guidance for carrying out or commissioning reviews. CRD Report No.4. 2nd edition. York: Centre for Reviews and Dissemination, University of York, 2009.

(111) Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 1996 Feb;17(1):1-12.

(112) Motzer RJ, Escudier B, Oudard S, Porta C, Hutson TE, Bracarda S, et al. Updated data from a phase III randomized trial of everolimus (RAD001) versus placebo in metastatic renal cell carcinoma (mRCC) (oral presentation). ASCO 2009 Genitourinary Cancers Symposium.February 26th-28th 2009.Orlando, Florida, USA.

(113) Hahn EA, Webster KA, Cella D, Fairclough DL. Missing data in quality of life research in Eastern Cooperative Oncology Group (ECOG) clinical trials: problems and solutions. Stat Med 1998 Mar 15;17(5-7):547-59.

(114) Buccheri G, Ferrigno D, Tamburini M. Karnofsky and ECOG performance status scoring in lung cancer: a prospective, longitudinal study of 536 patients from a single institution. Eur J Cancer 1996 Jun;32A(7):1135-41.

(115) Cole SR, Hernan MA. Constructing inverse probability weights for marginal structural models. Am J Epidemiol 2008 Sep 15;168(6):656-64.

(116) National Institute for Health and Clinical Excellence (NICE). Guide to the Methods of Technology Appraisal. 1-6-2008.

(117) Remak E, Charbonneau C, Negrier S, Kim ST, Motzer RJ. Economic evaluation of sunitinib malate for the first-line treatment of metastatic renal cell carcinoma. J Clin Oncol 2008 Aug 20;26(24):3995-4000.

(118) Briggs A, Claxton K, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford University Press; 2007.

(119) Cain LE, Cole SR, Greenland S, Brown TT, Chmiel JS, Kingsley L, et al. Effect of highly active antiretroviral therapy on incident AIDS using calendar period as an instrumental variable. Am J Epidemiol 2009 May 1;169(9):1124-32.

(120) Chabot I, LeLorier J, Blackstein ME. The challenge of conducting pharmacoeconomic evaluations in oncology using crossover trials: the example of sunitinib for gastrointestinal stromal tumour. Eur J Cancer 2008 May;44(7):972-7.

(121) National Institute for Health and Clinical Excellence (NICE). Final Appraisal Determination. Sunitinib for the treatment of gastrointestinal stromal tumours.

(122) Hernan MA, Cole SR, Margolick J, Cohen M, Robins JM. Structural accelerated failure time models for survival analysis in studies with time-varying treatments. Pharmacoepidemiol Drug Saf 2005 Jul;14(7):477-91.

(123) Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer 2008 Dec;62(3):374-80.

(124) National Institute for Health and Clinical Excellence (NICE). Patient access scheme submission template for technology appraisals. June 2009.

(125) Curtis L. Unit costs of health and social care. 2008. Personal Social Services Research Unit (PSSRU), The University of Kent.

(126) Department of Health. NHS Reference Costs 2007/08. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_098945.

(127) Wiederkehr D, Casciano R, Stem L, Zheng J, Baladi JF. Therapeutic care in metastatic renal cell carcinoma during the follow-up phase of the RECORD-1 phase III trial. J.Clin.Oncol 27, 2009 (suppl; abstr e17531).

(128) British National Formulary. BNF 57. March 2009. http://www.bnf.org/bnf/.

(129) Mickisch G, Escudier B, Gore M, Walzer S, Sabaté E, Nuijten M. Cost of Managing Side Effects in the Treatment of First-line Metastatic Renal Cell Carcinoma in Germany, France, and the UK: Bevacizumab + Interferon Alpha-2A Compared with Sunitinib.Poster 5110. 44th American Society of Clinical Oncology Meeting, San Francisco, CA, USA, 14th-16th February, 2008.

(130) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™ Palliative Care, V.I.2009.

(131) Ross DD, Alexander CS. Management of common symptoms in terminally ill patients: Part I. Fatigue, anorexia, cachexia, nausea and vomiting. Am Fam Physician 2001 Sep 1;64(5):807-14.

(132) Yavuzsen T, Davis MP, Walsh D, LeGrand S, Lagman R. Systematic review of the treatment of cancer-associated anorexia and weight loss. J Clin Oncol 2005 Nov 20;23(33):8500-11.

(133) Ripamonti C. Management of dyspnea in advanced cancer patients. Support Care Cancer 1999 Jul;7(4):233-43.

(134) Thomas JR, von Gunten CF. Management of dyspnoea. J Support Oncol 2003 May;1(1):23-32.

(135) National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology™ Prevention and Treatment of Cancer-Related Infections. V.I.2009.

(136) Reusser P. Management of viral infections in immunocompromised cancer patients. Swiss Med Wkly 2002 Jul 13;132(27-28):374-8.

(137) Vento S, Cainelli F. Infections in patients with cancer undergoing chemotherapy: aetiology, prevention, and treatment. Lancet Oncol 2003 Oct;4(10):595-604.

(138) Guest JF, Hart WM, Cookson RF. Cost analysis of palliative care for terminally ill cancer patients in the UK after switching from weak to strong opioids. Palliative Care Advisory Committee. Pharmacoeconomics 1998 Sep;14(3):285-97.

(139) Coyle D, Small N, Ashworth A, Hennessy S, Jenkins-Clarke S, Mannion R, et al. Costs of palliative care in the community, in hospitals and in hospices in the UK. Crit Rev Oncol Hematol 1999 Nov;32(2):71-85.

(140) Kind P, Hardman G, Macran S. UK Population Norms for EQ-5D. November 1999. Centre for Health Economics, The University of York.

(141) Purmonen T, Martikainen JA, Soini EJ, Kataja V, Vuorinen RL, Kellokumpu-Lehtinen PL. Economic evaluation of sunitinib malate in second-line treatment of metastatic renal cell carcinoma in Finland. Clin Ther 2008 Feb;30(2):382-92.

(142) British Assocaition of Urological Surgeons. BAUS Cancer Registry: Analyses of Minimum data set for Urological cancers January 1st - 31st December 2006. 2007.

(143) Novartis Pharmaceuticals. Metastatic RCC treatment pathways (4377). Pan European market research of health professionals who see/ treat RCC patients. 2009.

(144) Information and Statistics Division S. Cancer of the kidney: ICD-10 C64-C65. 28-4-2009. http://www.isdscotland.org/isd/1406.html.

(145) The Office for National Statistics. Population estimates for England and Wales - current datasets. 2007. http://www.statistics.gov.uk/statbase/Product.asp?vlnk=15106.

(146) Novartis Pharmaceuticals. Data on File: Forecasting of everolimus uptake in years 1 to 5. 2009.

10 Appendices

10.1 Appendix 1: Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

▼Afinitor 5mg tablets

▼Afinitor 10mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Afinitor 5mg tablets:

Each tablet contains 5 mg everolimus.

Excipients

Each tablet contains 149 mg lactose.

Afinitor 10mg tablets:

Each tablet contains 10 mg everolimus.

Excipients

Each tablet contains 297 mg lactose.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

Afinitor 5mg tablets:

White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “5” on one side and “NVR” on the other.

Afinitor 10mg tablets:

White to slightly yellow, elongated tablets with a bevelled edge and no score, engraved with “UHE” on one side and “NVR” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Afinitor is indicated for the treatment of patients with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

4.2 Posology and method of administration

Treatment with Afinitor should be initiated and supervised by a physician experienced in the use of anticancer therapies.

Posology

The recommended dose is 10 mg everolimus once daily. Treatment should continue as long as clinical benefit is observed or until unacceptable toxicity occurs.

Dose adjustment due to adverse reactions

Management of severe and/or intolerable suspected adverse reactions may require dose alterations. Afinitor may be dose reduced or temporarily withheld (e.g. for one week) followed by reintroduction at 5 mg daily. If dose reduction is required, the suggested dose is 5 mg daily (see also section 4.4).

Special populations

Paediatric patients (<18 years)

Afinitor is not recommended for use in children and adolescents due to lack of data on safety and efficacy.

Elderly patients (≥65 years)

No dose adjustment is required (see section 5.2).

Renal impairment

No dose adjustment is required (see section 5.2).

Hepatic impairment

For patients with moderate hepatic impairment (Child-Pugh class B), the dose should be reduced to 5 mg daily. Everolimus has not been evaluated in patients with severe hepatic impairment (Child-Pugh class C) and is not recommended for use in this patient population (see sections 4.4 and 5.2).

Method of administration

Afinitor should be administered orally once daily at the same time every day, consistently either with or without food (see section 5.2). Afinitor tablets should be swallowed whole with a glass of water. The tablets should not be chewed or crushed.

If a dose is missed, the patient should not take an additional dose, but take the usual prescribed next dose.

4.3 Contraindications

Hypersensitivity to the active substance, to other rapamycin derivatives or to any of the excipients.

4.4 Special warnings and precautions for use

Non-infectious pneumonitis

Non-infectious pneumonitis is a class effect of rapamycin derivatives, including Afinitor. Non-infectious pneumonitis (including interstitial lung disease) was described in 12% of patients taking Afinitor (see section 4.8). Some cases were severe and on rare occasions, a fatal outcome was observed. A diagnosis of non-infectious pneumonitis should be considered in patients presenting with non-specific respiratory signs and symptoms such as hypoxia, pleural effusion, cough or dyspnoea, and in whom infectious, neoplastic and other non-medicinal causes have been excluded by means of appropriate investigations. Patients should be advised to report promptly any new or worsening respiratory symptoms.

Patients who develop radiological changes suggestive of non-infectious pneumonitis and have few or no symptoms may continue Afinitor therapy without dose adjustments If symptoms are moderate, consideration should be given to interruption of therapy until symptoms improve. The use of corticosteroids may be indicated. Afinitor may be re-initiated at 5 mg daily.

For cases where symptoms of non-infectious pneumonitis are severe, Afinitor therapy should be discontinued and the use of corticosteroids may be indicated until clinical symptoms resolve. Therapy with Afinitor may be re-initiated at 5 mg daily depending on the individual clinical circumstances.

Infections

Afinitor has immunosuppressive properties and may predispose patients to infections, especially infections with opportunistic pathogens (see section 4.8). Localised and systemic infections, including pneumonia, other bacterial infections and invasive fungal infections, such as aspergillosis or candidiasis, have been described in patients taking Afinitor. Some of these infections have been severe (e.g. leading to respiratory failure) and occasionally fatal. Physicians and patients should be aware of the increased risk of infection with Afinitor, be vigilant for symptoms and signs of infection, and institute appropriate treatment promptly.

Pre-existing infections should be treated appropriately and have resolved fully before starting treatment with Afinitor. If a diagnosis of invasive systemic fungal infection is made, Afinitor treatment should be promptly and permanently discontinued and the patient treated with appropriate antifungal therapy.

Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, anaphylaxis, dyspnoea, flushing, chest pain or angioedema (e.g. swelling of the airways or tongue, with or without respiratory impairment) have been observed with everolimus (see section 4.3).

Oral ulceration

Mouth ulcers, stomatitis and oral mucositis have been observed in patients treated with Afinitor (see section 4.8). In such cases topical treatments are recommended, but alcohol- or peroxide-containing mouthwashes should be avoided as they may exacerbate the condition. Antifungal agents should not be used unless fungal infection has been diagnosed (see section 4.5).

Laboratory tests and monitoring

Renal function

Elevations of serum creatinine, usually mild, have been reported in clinical trials (see section 4.8). Monitoring of renal function, including measurement of blood urea nitrogen (BUN) or serum creatinine, is recommended prior to the start of Afinitor therapy and periodically thereafter.

Blood glucose and lipids

Hyperglycaemia, hyperlipidaemia and hypertrigylceridaemia have been reported in clinical trials (see section 4.8). The majority of cases of hyperglycaemia occurred in patients who had an abnormal fasting glucose level before taking Afinitor. Monitoring of fasting serum glucose is recommended prior to the start of Afinitor therapy and periodically thereafter. When possible optimal glycaemic control should be achieved before starting a patient on Afinitor.

Haematological parameters

Decreased haemoglobin, lymphocytes, neutrophils and platelets have been reported in clinical trials (see section 4.8). Monitoring of complete blood count is recommended prior to the start of Afinitor therapy and periodically thereafter.

Interactions

Co-administration with inhibitors and inducers of CYP3A4 and/or the multidrug efflux pump P-glycoprotein (PgP) should be avoided. If co-administration of a ***moderate*** CYP3A4 and/or PgP inhibitor or inducer cannot be avoided, dose adjustments of Afinitor can be taken into consideration based on predicted AUC (see section 4.5).

Concomitant treatment with ***potent*** CYP3A4 inhibitors result in dramatically increased plasma concentrations of everolimus (see section 4.5). There are currently not sufficient data to allow dosing recommendations in this situation. Hence, concomitant treatment of Afinitor and ***potent*** inhibitors is not recommended.

Hepatic impairment

Afinitor should not be used in patients with severe hepatic impairment (Child-Pugh class C) (see sections 4.2 and 5.2).

Vaccinations

The use of live vaccines should be avoided during treatment with Afinitor (see section 4.5).

Lactose

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Wound healing complications

Impaired wound healing is a class effect of rapamycin derivatives, including Afinitor. Caution should therefore be exercised with the use of Afinitor in the peri-surgical period.

4.5 Interaction with other medicinal products and other forms of interaction

Everolimus is a substrate of CYP3A4, and also a substrate and moderate inhibitor of PgP. Therefore, absorption and subsequent elimination of everolimus may be influenced by products that affect CYP3A4 and/or PgP. *In vitro*, everolimus is a competitive inhibitor of CYP3A4 and a mixed inhibitor of CYP2D6.

Known and theoretical interactions with selected inhibitors and inducers of CYP3A4 and PgP are listed in Table 1 below.

CYP3A4 and PgP inhibitors increasing everolimus concentrations

Substances that are inhibitors of CYP3A4 or PgP may increase everolimus blood concentrations by decreasing metabolism or the efflux of everolimus from intestinal cells.

CYP3A4 and PgP inducers decreasing everolimus concentrations

Substances that are inducers of CYP3A4 or PgP may decrease everolimus blood concentrations by increasing metabolism or the efflux of everolimus from intestinal cells.

Table 1 Effects of other active substances on everolimus

Active substance by interaction	**Interaction – Change in Everolimus AUC/C_{max}** **Geometric mean ratio (observed range)**	**Recommendations concerning co-administration**
***Potent* CYP3A4/PgP inhibitors**		
Ketoconazole	AUC ↑15.3-fold (range 11.2-22.5) C_{max} ↑4.1-fold (range 2.6-7.0)	Concomitant treatment of Afinitor and potent inhibitors is not recommended.
Itraconazole, posaconazole, voriconazole	Not studied. Large increase in everolimus concentration is expected.	
Telithromycin, clarithromycin		
Nefazodone		

Ritonavir, atazanavir, saquinavir, darunavir, indinavir, nelfinavir		
Moderate CYP3A4/PgP inhibitors		
Erythromycin	AUC ↑4.4-fold (range 2.0-12.6) C_{max} ↑2.0-fold (range 0.9-3.5)	Use caution when co-administration of moderate CYP3A4 inhibitors or PgP inhibitors cannot be avoided. If patients require co-administration of a moderate CYP3A4 or PgP inhibitor, dose reduction to 5 mg daily or 5 mg every other day may be considered. However, there are no clinical data with this dose adjustment. Due to between subject variability the recommended dose adjustments may not be optimal in all individuals, therefore close monitoring of side effects is recommended.
Verapamil	AUC ↑3.5-fold (range 2.2-6.3) C_{max} ↑2.3-fold (range1.3-3.8)	
Ciclosporin oral	AUC ↑2.7-fold (range 1.5-4.7) C_{max} ↑1.8-fold (range 1.3-2.6)	
Fluconazole	Not studied. Increased exposure expected.	
Diltiazem		
Amprenavir, fosamprenavir	Not studied. Increased exposure expected.	
Grapefruit juice or other food affecting CYP3A4/PgP	Not studied. Increased exposure expected (the effect varies widely).	Combination should be avoided.

***Potent* CYP3A4 inducers**		
Rifampicin	AUC ↓63% (range 0-80%) C_{max} ↓58% (range 10-70%)	Avoid the use of concomitant potent CYP3A4 inducers. If patients require co-administration of a potent CYP3A4 inducer, an Afinitor dose increase from 10 mg daily up to 20 mg daily should be considered using 5 mg increments applied on Day 4 and 8 following start of the inducer. This dose of Afinitor is predicted to adjust the AUC to the range observed without inducers. However, there are no clinical data with this dose adjustment. If treatment with the inducer is discontinued, the Afinitor dose should be returned to the dose used prior to initiation of the co-administration.
Carbamazepine, phenobarbital, phenytoin	Not studied. Decreased exposure expected.	
Efavirenz, nevirapine	Not studied. Decreased exposure expected.	
St John's Wort (*Hypericum perforatum*)	Not studied. Large decrease in exposure expected.	Preparations containing St John's Wort should not be used during treatment with everolimus

Agents whose plasma concentration may be altered by everolimus

Based on *in vitro* results, the systemic concentrations obtained after oral daily doses of 10 mg make inhibition of PgP, CYP3A4 and CYP2D6 unlikely. However, inhibition of CYP3A4 and PgP in the gut cannot be excluded; hence everolimus may affect the bioavailability of co-administered drugs which are CYP3A4 and/or PgP substrates.

Vaccinations

The immune response to vaccination may be affected and, therefore, vaccination may be less effective during treatment with Afinitor. The use of live vaccines should be avoided during treatment with Afinitor (see section 4.4). Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, BCG (Bacillus Calmette-Guérin), yellow fever, varicella, and TY21a typhoid vaccines.

4.6 Pregnancy and lactation

Fertility

Based on non-clinical findings, male fertility may be compromised by treatment with everolimus (see section 5.3).

Women of childbearing potential

Women of childbearing potential must use an effective method of contraception while receiving everolimus.

Pregnancy

There are no or limited amount of data from the use of everolimus in pregnant women. Studies in animals have shown reproductive toxicity effects (see section 5.3).

Everolimus is not recommended during pregnancy and in women of childbearing potential not using contraception.

Lactation

It is not known whether everolimus is excreted in breast milk. However, in rats, everolimus and/or its metabolites readily pass into the milk. Therefore, women taking everolimus should not breast-feed.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. Patients should be advised to be cautious when driving or using machines if they experience fatigue during treatment with Afinitor.

4.8 Undesirable effects

The data described below reflect exposure to everolimus (n=274) and placebo (n=137) in a randomised phase III study for the treatment of metastatic renal cell carcinoma. In total, 165 patients were exposed to everolimus 10 mg/day for ≥4 months. The median age of patients was 61 years (range 27-85).

The most frequent grade 3-4 adverse reactions (incidence≥2%) were lymphocytes decreased, glucose increased, haemoglobin decreased, phosphate decreased, cholesterol increased, infections, stomatitis, fatigue, and pneumonitis.

The median duration of blinded study treatment was 141 days (range 19-451) for patients receiving Afinitor and 60 days (range 21-295) for those receiving placebo. The rates of adverse reactions resulting in permanent discontinuation were 7% and 0% for the Afinitor and placebo treatment groups, respectively. Most adverse reactions were grade 1 or 2 in severity.

Table 2 shows the incidence of adverse reactions reported for patients receiving everolimus 10 mg/day. Adverse reactions in Table 2 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2 Adverse reactions

Infections and infestations	
Very common	Infections [a]
Blood and lymphatic system disorders	
Very common	Lymphocytes decreased [b], haemoglobin decreased [b], platelets decreased [b], neutrophils decreased [b]
Immune system disorders	

Not known	Hypersensitivity
Metabolism and nutrition disorders	
Very common	Glucose increased [b], cholesterol increased [b], triglycerides increased [b], phosphate decreased [b], anorexia
Common	Dehydration
Uncommon	New-onset diabetes mellitus
Psychiatric disorders	
Common	Insomnia
Nervous system disorders	
Very common	Abnormal taste
Common	Headache
Eye disorders	
Common	Conjunctivitis, eyelid oedema
Cardiac disorders	
Uncommon	Congestive cardiac failure
Vascular disorders	
Common	Hypertension
Not known	Haemorrhage
Respiratory, thoracic and mediastinal disorders	

Very common	Pneumonitis [c], dyspnoea, epistaxis, cough
Common	Haemoptysis
Gastrointestinal disorders	
Very common	Stomatitis [d], diarrhoea, mucosal inflammation, vomiting, nausea
Common	Dry mouth, abdominal pain, dysphagia, dyspepsia
Hepatobiliary disorders	
Very common	Alanine aminotransferase increased [b], aspartate aminotransferase increased [b]
Common	Bilirubin increased [b]
Skin and subcutaneous tissue disorders	
Very common	Rash, dry skin, pruritus
Common	Palmar-plantar erythrodysaesthesia syndrome, erythema, skin exfoliation, nail disorder, acneiform dermatitis, onychoclasis
Uncommon	Angioedema
Renal and urinary disorders	
Very common	Creatinine increased [b]
General disorders and administration site conditions	
Very common	Fatigue, asthenia, peripheral oedema
Common	Chest pain, pyrexia
Uncommon	Impaired wound healing

Investigations	
Common	Weight decreased

[a] Includes all events within the 'infections and infestations' system organ class (such as pneumonia, sepsis, and opportunistic infections [e.g. aspergillosis and candidiasis (see also section 4.4)])

[b] Frequency based on determination of abnormal laboratory value (as part of routine laboratory assessment)

[c] Includes pneumonitis, interstitial lung disease, lung infiltration, pulmonary alveolar haemorrhage, pulmonary toxicity, and alveolitis

[d] Includes stomatitis and aphthous stomatitis, and mouth and tongue ulceration

4.9 Overdose

Reported experience with overdose in humans is very limited. Single doses of up to 70 mg have been given with acceptable acute tolerability. General supportive measures should be initiated in all cases of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Protein kinase inhibitors, ATC code: L01XE10

Mechanism of action

Everolimus is a selective mTOR (mammalian target of rapamycin) inhibitor. mTOR is a key serine-threonine kinase, the activity of which is known to be upregulated in a number of human cancers. Everolimus binds to the intracellular protein FKBP-12, forming a complex that inhibits mTOR complex-1 (mTORC1) activity. Inhibition of the mTORC1 signalling pathway interferes with the translation and synthesis of proteins by reducing the activity of S6 ribosomal protein kinase (S6K1) and eukaryotic elongation factor 4E-binding protein (4EBP-1) that regulate proteins involved in the

cell cycle, angiogenesis and glycolysis. Everolimus reduces levels of vascular endothelial growth factor (VEGF), which potentiates tumour angiogenic processes. Everolimus is a potent inhibitor of the growth and proliferation of tumour cells, endothelial cells, fibroblasts and blood-vessel-associated smooth muscle cells and has been shown to reduce glycolysis in solid tumours *in vitro* and *in vivo*.

Clinical efficacy

A phase III, international, multicentre, randomised, double-blind study comparing everolimus 10 mg/day and placebo, both in conjunction with best supportive care, was conducted in patients with metastatic renal cell carcinoma whose disease had progressed on or after treatment with VEGFR-TKI (vascular endothelial growth factor receptor tyrosine kinase inhibitor) therapy (sunitinib, sorafenib, or both sunitinib and sorafenib). Prior therapy with bevacizumab and interferon-α was also permitted. Patients were stratified according to Memorial Sloan-Kettering Cancer Center (MSKCC) prognostic score (favourable- *vs.* intermediate- *vs.* poor-risk groups) and prior anticancer therapy (1 *vs.* 2 prior VEGFR-TKIs).

Progression-free survival, documented using RECIST (Response Evaluation Criteria in Solid Tumours) and assessed via a blinded, independent central review, was the primary endpoint. Secondary endpoints included safety, objective tumour response rate, overall survival, disease-related symptoms, and quality of life. After documented radiological progression, patients could be unblinded by the investigator: those randomised to placebo were then able to receive open-label everolimus 10 mg/day. The Independent Data Monitoring Committee recommended termination of this trial at the time of the second interim analysis as the primary endpoint had been met.

In total, 416 patients were randomised 2:1 to receive Afinitor (n=277) or placebo (n=139). Demographics were well balanced (pooled median age [61 years; range 27-85], 78% male, 88% Caucasian, number of prior VEGFR-TKI therapies [1-74%, 2-26%]).

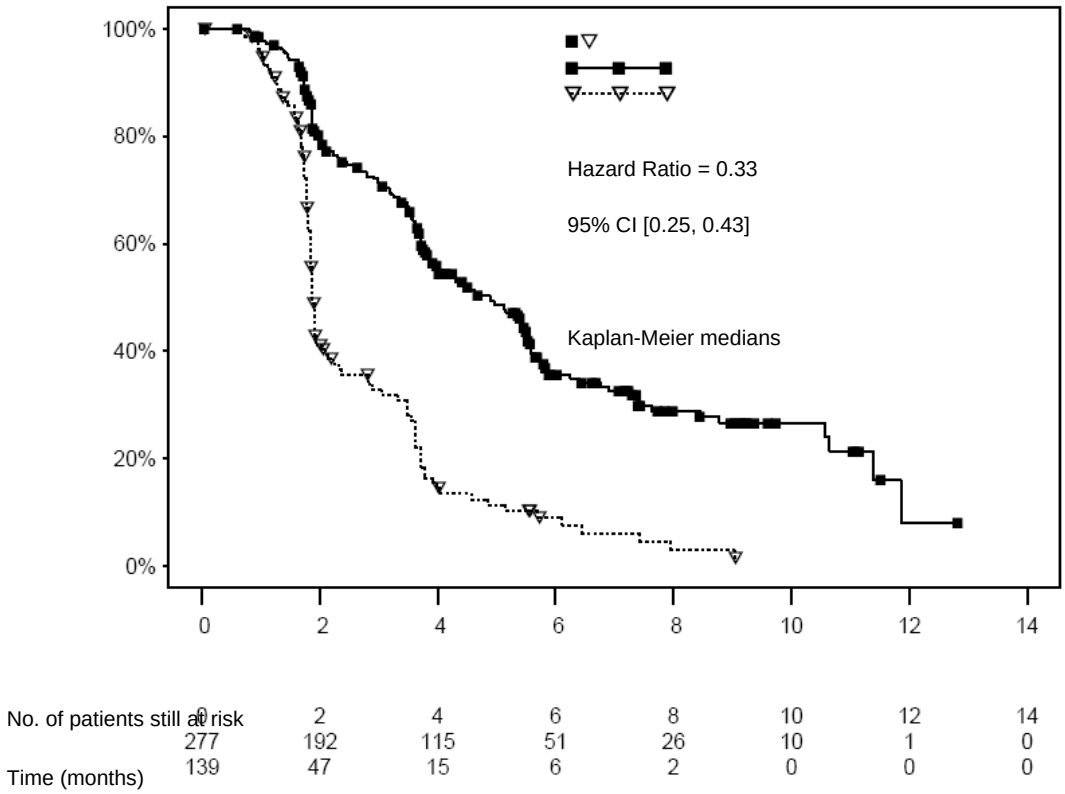
Afinitor was superior to placebo for the primary endpoint of progression-free survival, with a statistically significant 67% reduction in the risk of progression or death (see Table 3 and Figure 1).

Table 3 Progression-free survival results

Population	n	Afinitor n=277	Placebo n=139	Hazard ratio (95%CI)	p-value
		Median progression-free survival (months) (95% CI)			
Primary analysis					
All (blinded independent central review)	416	4.9 (4.0-5.5)	1.9 (1.8-1.9)	0.33 (0.25-0.43)	<0.0001 [a]
Supportive/sensitivity analyses					
All (local review by investigator)	416	5.5 (4.6-5.8)	1.9 (1.8-2.2)	0.32 (0.25-0.41)	<0.0001 [a]
MSKCC prognostic score (blinded independent central review)					
Favourable risk	120	5.8 (4.0-7.4)	1.9 (1.9-2.8)	0.31 (0.19-0.50)	<0.0001
Intermediate risk	235	4.5 (3.8-5.5)	1.8 (1.8-1.9)	0.32 (0.22-0.44)	<0.0001
Poor risk	61	3.6 (1.9-4.6)	1.8 (1.8-3.6)	0.44 (0.22-0.85)	0.007

[a] Stratified log-rank test

Figure 1 KaplanMeier progression-free survival curves



Six-month PFS rates were 36% for Afinitor therapy compared with 9% for placebo.

Confirmed objective tumour responses were observed in 5 patients (2%) receiving Afinitor, while none were observed in patients receiving placebo. Therefore, the progression-free survival advantage primarily reflects the population with disease stabilisation (corresponding to 67% of the Afinitor treatment group).

No statistically significant treatment-related difference in overall survival was noted (hazard ratio 0.87; confidence interval: 0.65-1.17; p=0.177). Crossover to open-label Afinitor following disease progression for patients allocated to placebo confounded the detection of any treatment-related difference in overall survival.

5.2 Pharmacokinetic properties

Absorption

In patients with advanced solid tumours, peak everolimus concentrations (C_{max}) are reached at a median time of 1 hour after daily administration of 5 and 10 mg everolimus under fasting conditions or with a light fat-free snack. C_{max} is dose-proportional between 5 and 10 mg. Everolimus is a substrate and moderate inhibitor of PgP.

Food effect:

In healthy subjects, high fat meals reduced systemic exposure to Afinitor 10 mg (as measured by AUC) by 22% and the peak plasma concentration C_{max} by 54%. Light fat meals reduced AUC by 32% and C_{max} by 42%. Food, however, had no apparent effect on the post absorption phase concentration-time profile.

Distribution

The blood-to-plasma ratio of everolimus, which is concentration-dependent over the range of 5 to 5,000 ng/ml, is 17% to 73%. Approximately 20% of the everolimus concentration in whole blood is confined to plasma of cancer patients given Afinitor 10 mg/day. Plasma protein binding is approximately 74% both in healthy subjects and in patients with moderate hepatic impairment. In patients with advanced solid tumours, V_d was 191 l for the apparent central compartment and 517 l for the apparent peripheral compartment.

Metabolism

Everolimus is a substrate of CYP3A4 and PgP. Following oral administration, everolimus is the main circulating component in human blood. Six main metabolites of everolimus have been detected in human blood, including three monohydroxylated metabolites, two hydrolytic ring-opened products, and a phosphatidylcholine conjugate of everolimus. These metabolites were also identified in animal species used in toxicity studies, and showed approximately 100 times less activity than everolimus itself. Hence, everolimus is considered to contribute the majority of the overall pharmacological activity.

Elimination

Mean CL/F of everolimus after 10 mg daily dose in patients with advanced solid tumours was 24.5 l/h. The mean elimination half-life of everolimus is approximately 30 hours.

No specific excretion studies have been undertaken in cancer patients; however, data are available from the studies in transplant patients. Following the administration of a single dose of radiolabelled everolimus in conjunction with ciclosporin, 80% of the radioactivity was recovered from the faeces, while 5% was excreted in the urine. The parent substance was not detected in urine or faeces.

Steady-state pharmacokinetics

After administration of everolimus in patients with advanced solid tumours, steady-state $AUC_{0-\tau}$ was dose-proportional over the range of 5 to 10 mg daily dose. Steady-state was achieved within two weeks. C_{max} is dose-proportional between 5 and 10 mg. t_{max} occurs at 1 to 2 hours post-dose. There was a significant correlation between $AUC_{0-\tau}$ and pre-dose trough concentration at steady-state.

Special populations

Hepatic impairment

The average AUC of everolimus in 8 subjects with moderate hepatic impairment (Child-Pugh class B) was twice that found in 8 subjects with normal hepatic function. AUC was positively correlated with serum bilirubin concentration and with prolongation of prothrombin time and negatively correlated with serum albumin concentration. The impact of severe hepatic impairment (Child-Pugh class C) on the pharmacokinetics of everolimus has not been assessed (see sections 4.2 and 4.4).

Renal impairment

In a population pharmacokinetic analysis of 170 patients with advanced solid tumours, no significant influence of creatinine clearance (25-178 ml/min) was detected on CL/F of everolimus. Post-transplant renal impairment (creatinine clearance range 11-107 ml/min) did not affect the pharmacokinetics of everolimus in transplant patients.

Elderly patients

In a population pharmacokinetic evaluation in cancer patients, no significant influence of age (27-85 years) on oral clearance of everolimus was detected.

Ethnicity

Oral clearance (CL/F) is similar in Japanese and Caucasian cancer patients with similar liver functions. Based on analysis of population pharmacokinetics, oral clearance (CL/F) is on average 20% higher in black transplant patients.

5.3 Preclinical safety data

The preclinical safety profile of everolimus was assessed in mice, rats, minipigs, monkeys and rabbits. The major target organs were male and female reproductive systems (testicular tubular degeneration, reduced sperm content in epididymides and uterine atrophy) in several species; lungs (increased alveolar macrophages) in rats and mice; pancreas (degranulation and vacuolation of exocrine cells in monkeys and minipigs, respectively, and degeneration of islet cells in monkeys), and eyes (lenticular anterior suture line opacities) in rats only. Minor kidney changes were seen in the rat (exacerbation of age-related lipofuscin in tubular epithelium, increases in hydronephrosis) and mouse (exacerbation of background lesions). There was no indication of kidney toxicity in monkeys or minipigs.

Everolimus appeared to spontaneously exacerbate background diseases (chronic myocarditis in rats, coxsackie virus infection of plasma and heart in monkeys, coccidian infestation of the gastrointestinal tract in minipigs, skin lesions in mice and monkeys). These findings were generally observed at systemic exposure levels within the range of therapeutic exposure or above, with the exception of the findings in rats, which occurred below therapeutic exposure due to a high tissue distribution.

In a male fertility study in rats, testicular morphology was affected at 0.5 mg/kg and above, and sperm motility, sperm head count, and plasma testosterone levels were diminished at 5 mg/kg, which is within the range of therapeutic exposure and which caused a reduction in male fertility. There was evidence of reversibility. Female fertility was not affected, but everolimus crossed the placenta and was toxic to the foetus. In rats, everolimus caused embryo/foetotoxicity at systemic exposure below the therapeutic level. This was manifested as mortality and reduced foetal weight. The incidence of skeletal variations and malformations (e.g. sternal cleft) was increased at 0.3 and 0.9 mg/kg. In rabbits, embryotoxicity was evident in an increase in late resorptions.

Genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of clastogenic or mutagenic activity. Administration of everolimus for up to 2 years did not indicate any oncogenic potential in mice and rats up to the highest doses, corresponding respectively to 4.3 and 0.2 times the estimated clinical exposure.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Butylated hydroxytoluene (E321)

Magnesium stearate

Lactose monohydrate

Hypromellose

Crospovidone type A

Lactose anhydrous

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in the original package in order to protect from light and moisture.

6.5 Nature and contents of container

Aluminium/polyamide/aluminium/PVC blister containing 10 tablets.

Packs containing 30, 60 or 90 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited

Wimblehurst Road

Horsham

West Sussex, RH12 5AB

United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

Afinitor 5mg tablets:

EU/1/09/538/001

EU/1/09/538/002

EU/1/09/538/003

Afinitor 10mg tablets:

EU/1/09/538/004

EU/1/09/538/005

EU/1/09/538/006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03.08.2009

10. DATE OF REVISION OF THE TEXT

10.2 Appendix 2: Search strategy for Section 6

The strategy for the systematic review for everolimus clinical effectiveness reported in Section 6 is presented below. In addition, a systematic review report is available containing further details on methods and the search protocol [81].

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Searches were carried out using DATASTAR.

The computerised bibliographic databases that were searched were:

- MEDLINE [1950 to June 2009], and MEDLINE IN PROCESS
- EMBASE [1980 to June 2009]
- BIOSIS [1985 to June 2009].

A search was carried out to identify relevant conference abstracts for everolimus from selected cancer meetings between 2005 and 2009. The conference websites searched were ASCO (American Society of Clinical Oncology main conferences and satellite symposiums in 2005, 2006, 2007, 2008, 2009); ECCO (European CanCer Organisation) (2006, 2008); and ESMO (European Society for Medical Oncology (2005, 2007).

In addition to the sources above, the following sources were reviewed for additional published or unpublished data on the clinical effectiveness and safety of everolimus:

- HTA database (CRD) website
- Database of abstracts of review effects (DARE) (CRD website)
- NHS Economic Evaluation Database (NHS EED) (CRD website)
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Register of Controlled Trials (CCTR)
- Clinical Trials.gov
- Current Controlled Trials (www.controlled-trials.com)
- NICE and NIHR Health Technology Assessment website
- Hand searching of selected primary study references.

10.2.2 The date on which the search was conducted.

The database and abstract search was conducted on 16th June 2009.

10.2.3 The date span of the search.

Please refer to Section 10.2.1.

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strategy was based directly on that used by the PenTAG (Peninsula Technology Assessment Group) Report; the Assessment Group in their independent systematic review of evidence on clinical effectiveness of drug therapies for aRCC [19]. It was modified to focus the search on articles relating to everolimus in advanced RCC.

The search strategy and terms used are presented below. The search was run in DATASTAR.

No.	Database	Search term	Results
CP		[Clipboard]	0
1	MEZZ	renal ADJ cell ADJ carcinoma$1 OR cell ADJ renal ADJ carcinoma$1 OR renal ADJ carcinoma$1 OR kidney ADJ carcinoma$1 OR kidney ADJ cell ADJ carcinoma$1 OR renal ADJ adenocarcinoma$1 OR kidney ADJ adenocarcinoma$1 OR adenocarcinoma$1 ADJ renal OR adenocarcinoma$1 ADJ kidney$	19664
2	MEZZ	Carcinoma-Renal-Cell#.DE.	15577
3	MEZZ	hypernephroma$1 OR nephroid ADJ carcinoma$1 OR hypernephroid ADJ carcinoma$1 OR kidney ADJ hypernephroma$1 OR kidney ADJ pelvic ADJ carcinoma$1 OR kidney ADJ pyelocarcinoma$1 OR renal ADJ hypernephroma$1 OR grawitz ADJ tumor$1 OR grawitz ADJ tumour$1 OR renal ADJ cell ADJ neoplasm$1 OR renal ADJ cell ADJ cancer$1 OR renal ADJ tumor$1 OR renal ADJ tumour$1 OR carcinoma ADJ chromophobe ADJ cell ADJ kidney$1	7824
4	MEZZ	Kidney-Neoplasms#.DE.	46150
5	MEZZ	(cancer$ NEXT kidney$1).TI,AB.	1215
6	MEZZ	(neoplasm$1 NEXT kidney$1).TI,AB.	345
7	MEZZ	(neoplasm$1 NEXT renal).TI,AB.	354
8	MEZZ	(cancer$ NEXT renal).TI,AB.	1683
9	MEZZ	(tumor$1 NEXT kidney$1).TI,AB.	3608
10	MEZZ	(tumour$1 NEXT kidney$1).TI,AB.	722
11	MEZZ	(tumor$1 NEXT renal).TI,AB.	3791
12	MEZZ	(tumour$1 NEXT renal).TI,AB.	802
13	MEZZ	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12	54668
14	MEZZ	(everolimus OR afinitor OR rad001 OR rad ADJ 001).TI,AB.	650
15	MEZZ	13 AND 14	45
16	MEZZ	limit set 15 H=Y	26
17	MEZZ	PT=EDITORIAL OR PT=LETTER	907263
18	MEZZ	16 NOT 17	26
19	EMZZ	renal ADJ cell ADJ carcinoma$1 OR cell ADJ renal ADJ carcinoma$1 OR renal ADJ carcinoma$1 OR kidney ADJ	25483

		carcinoma$1 OR kidney ADJ cell ADJ carcinoma$1 OR renal ADJ adenocarcinoma$1 OR kidney ADJ adenocarcinoma$1 OR adenocarcinoma$1 ADJ renal OR adenocarcinoma$1 ADJ kidney$	
20	EMZZ	hypernephroma$1 OR nephroid ADJ carcinoma$1 OR hypernephroid ADJ carcinoma$1 OR kidney ADJ hypernephroma$1 OR kidney ADJ pelvic ADJ carcinoma$1 OR kidney ADJ pyelocarcinoma$1 OR renal ADJ hypernephroma$1 OR grawitz ADJ tumor$1 OR grawitz ADJ tumour$1 OR renal ADJ cell ADJ neoplasm$1 OR renal ADJ cell ADJ cancer$1 OR renal ADJ tumor$1 OR renal ADJ tumour$1 OR carcinoma ADJ chromophobe ADJ cell ADJ kidney$1	6481
21	EMZZ	Kidney-Cancer#.DE.	37291
22	EMZZ	(cancer$ NEXT kidney$1).TI,AB.	800
23	EMZZ	(neoplasm$1 NEXT kidney$1).TI,AB.	263
24	EMZZ	(neoplasm$1 NEXT renal).TI,AB.	315
25	EMZZ	(cancer$ NEXT renal).TI,AB.	1501
26	EMZZ	(tumor$1 NEXT kidney$1).TI,AB.	2910
27	EMZZ	(tumour$1 NEXT kidney$1).TI,AB.	597
28	EMZZ	(tumor$1 NEXT renal).TI,AB.	3446
29	EMZZ	(tumour$1 NEXT renal).TI,AB.	669
30	EMZZ	19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29	44346
31	EMZZ	(everolimus OR afinitor OR rad001 OR rad-001).TI,AB.	628
32	EMZZ	30 AND 31	56
33	EMZZ	limit set 32 H=Y	56
34	EMZZ	PT=EDITORIAL OR PT=LETTER	689828
35	EMZZ	33 NOT 34	56
36	BIZZ	renal ADJ cell ADJ carcinoma$1 OR cell ADJ renal ADJ carcinoma$1 OR renal ADJ carcinoma$1 OR kidney ADJ carcinoma$1 OR kidney ADJ cell ADJ carcinoma$1 OR renal ADJ adenocarcinoma$1 OR kidney ADJ adenocarcinoma$1 OR adenocarcinoma$1 ADJ renal OR adenocarcinoma$1 ADJ kidney$	21449
37	BIZZ	hypernephroma$1 OR nephroid ADJ carcinoma$1 OR hypernephroid ADJ carcinoma$1 OR kidney ADJ hypernephroma$1 OR kidney ADJ pelvic ADJ carcinoma$1 OR kidney ADJ pyelocarcinoma$1 OR renal ADJ hypernephroma$1 OR grawitz ADJ tumor$1 OR grawitz ADJ tumour$1 OR renal ADJ cell ADJ neoplasm$1 OR renal ADJ cell ADJ cancer$1 OR renal ADJ tumor$1 OR renal ADJ tumour$1 OR carcinoma ADJ chromophobe ADJ cell ADJ kidney$1	6736
38	BIZZ	(cancer$ NEXT kidney$1).TI,AB.	728
39	BIZZ	(neoplasm$1 NEXT kidney$1).TI,AB.	199
40	BIZZ	(neoplasm$1 NEXT renal).TI,AB.	247
41	BIZZ	(cancer$ NEXT renal).TI,AB.	1246
42	BIZZ	(tumor$1 NEXT kidney$1).TI,AB.	2771
43	BIZZ	(tumour$1 NEXT kidney$1).TI,AB.	341
44	BIZZ	(tumor$1 NEXT renal).TI,AB.	3142
45	BIZZ	(tumour$1 NEXT renal).TI,AB.	411
46	BIZZ	renal ADJ cell ADJ cancer	1616
47	BIZZ	kidney ADJ cancer	1748
48	BIZZ	36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47	31957
49	BIZZ	(everolimus OR afinitor OR rad001 OR rad-001).TI,AB.	654
50	BIZZ	48 AND 49	24
51	BIZZ	HUMANS#	7733619
52	BIZZ	50 AND 51	23
53	BIZZ	PT=EDITORIAL OR PT=LETTER	163502

54	BIZZ	52 NOT 53	22
55	BIZZ EMZZ MEZZ [all]	combined sets 18, 35, 54	104
56	BIZZ EMZZ MEZZ [all]	dropped duplicates from 55	39
57	BIZZ EMZZ MEZZ [all]	unique records from 55	65

The search of conference abstracts and other databases used key terms: everolimus, RAD001, Afinitor and (metastatic) renal cell carcinoma, kidney cancer.

10.2.5 Details of any additional searches, for example searches of company databases (include a description of each database).

The complete search coverage is provided in Section 10.2.1. In addition, Novartis provided unpublished Clinical Study Reports (CSR) for the RECORD-1 trial (and supplementary internal reports consisting of the following:

- CSR relating to the second interim analysis [82]
- CSR-addendum relating to the final analysis [40]
- RECORD-1 Survival update report [112]
- Slide presentations relating to conference abstracts identified [85]

10.2.6 The inclusion and exclusion criteria.

Systematic reviews; randomised clinical trials (RCTs) for everolimus in aRCC with the following outcomes were included:

Efficacy endpoints

- Overall survival
- Progression free survival (PFS)
- Tumour response rate

Health Related Quality of life (HRQoL) related endpoints

- Disease specific HRQoL (e.g. QLQ-C30)
- Generic HRQoL (e.g. SF36)
- Utility based (e.g. EQ 5D, HUI, SF 6D)

Safety endpoints

- Treatment related adverse events (grade 3 and 4, or high frequency grade 1 or 2)

Phase II studies and non-RCTs were considered where there was insufficient evidence from phase III RCTs. Conference abstracts were included to provide supporting evidence if a journal publication was available, or as a primary source if there was no primary publication. However, a primary source of evidence used was the Novartis CSRs for the RECORD-1 trial, in particular the report relating to the final analysis dataset [40].

10.2.7 The data abstraction strategy.

The records identified in the electronic and other searches were assessed for inclusion by two reviewers from Tolley Health Economics Ltd. Each reviewer independently scanned all titles and abstracts identified in the searches to identify reports that might be relevant for clinical and economic review, using the inclusion/exclusion criteria, outcomes/endpoints, and study designs outlined in the sections above. Full details of the included and excluded publications and abstracts can be found in the systematic review report [81]. Disagreements were resolved by discussion and consensus.

Data extraction for the review of clinical effectiveness was also carried out by two reviewers. Standardised data extraction forms (DEF) were used (see the systematic review report [81]). The DEF was based on that used in the PenTAG assessment of aRCC drugs, but with additional fields to obtain a greater depth of study information and data. Data was extracted by one reviewer and then checked by the second. Data extraction forms for each full study and abstract covered are included in the systematic review report [81]. Where there were several publications/abstracts for the same study these have been combined into one DEF. As much quantitative information as possible for the outcomes of interest has been abstracted from the source publications into the DEF's, including hazard ratios and p values for differences in PFS, survival, tumour response and HRQoL parameters. This provides the key source information available on public domain evidence for everolimus for the NICE submission. Data in the actual NICE submission is supplemented by additional data from the unpublished CSR's for the RECORD-1 trial.

The two reviewers independently evaluated the included studies for methodological quality which used criteria based on those specified by CRD [110]. The strategy itself

was directly taken from the PenTAG Report [19], with a few supplementary questions added to enable application of the Jadad quality scoring system.

10.3 Appendix 3: Search strategy for Section 7

A search was also conducted in order to identify any publications or abstracts relating to the economic evaluation (cost-effectiveness, cost analysis) of everolimus in aRCC.

10.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Searches were carried out using DATASTAR.

The specific databases searched were:

- Medline and Medline (R) In-Process
- Embase
- NHS Economic Evaluation Database (NHS EED).

A search was carried out for any conference abstracts relating to the cost or cost-effectiveness of everolimus from selected cancer meetings between 2005 and 2009. The conference websites searched were ASCO main conferences and satellite symposiums in 2005, 2006, 2007, 2008, 2009; ECCO 2006, 2008; and ESMO 2005, 2007. In addition, abstracts to the International Society of Pharmacoeconomics and Outcomes (ISPOR) Journal, Value in Health, were searched from 2005 to June 2009.

The other non-electronic databases accessed for the search of everolimus clinical effectiveness were also searched for any relevant economic evaluations.

10.3.2 The date on which the search was conducted.

June 16th and 17th 2009.

10.3.3 The date span of the search.

The electronic databases and abstracts were searched as per the clinical effectiveness search (see 10.2.1). The search of NHS EED and other sources was for the period 2000-2009.

10.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The electronic search strategy for economic evaluations is provided below. It is directly based on that used by PenTAG [19], with some modifications to focus on everolimus. The search was run in DATASTAR.

No.	Database	Search term	Results
CP		[Clipboard]	0
1	MEZZ	Cost-Benefit-Analysis#.DE.	45168
2	MEZZ	Economics-Pharmaceutical#.DE.	2012
3	MEZZ	Drug-Costs#.DE.	9033
4	MEZZ	Models-Economic#.DE.	6462
5	MEZZ	Fees-and-Charges#.DE.	24024
6	MEZZ	economic$ OR price OR pricing OR pharmaeconomi$	408034
7	MEZZ	cost OR costly OR costing$ OR costed	235790
8	MEZZ	cost$ NEXT (benefit$ OR utilit$ OR utilis$ OR minim$)	50979
9	MEZZ	expenditure$ NOT energy	21836
10	MEZZ	value NEXT (money OR monetary)	658
11	MEZZ	budget$	18261
12	MEZZ	economic NEXT burden$	2448
13	MEZZ	(resource ADJ use).TI,AB.	2718
14	MEZZ	Economics-Dental#.DE. OR Economics-Hospital#.DE. OR Economics-Medical#.DE. OR Economics-Nursing#.DE.	34494
15	MEZZ	Costs-and-Cost-Analysis#.DE.	141977
16	MEZZ	Value-Of-Life#.DE.	5008
17	MEZZ	Cost-Of-Illness#.DE.	11494
18	MEZZ	Economics#.W..DE.	404159
19	MEZZ	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18	677026
20	MEZZ	PT=COMMENT OR PT=EDITORIAL OR PT=LETTER	979189
21	MEZZ	19 NOT 20	627135
22	MEZZ	Carcinoma-Renal-Cell#.DE.	15577
23	MEZZ	(renal ADJ cell ADJ carcinoma$1 OR cell ADJ renal ADJ carcinoma$1 OR renal ADJ carcinoma$1 OR kidney ADJ carcinoma$1 OR kidney ADJ cell ADJ carcinoma$1 OR renal ADJ adenocarcinoma$1 OR kidney ADJ adenocarcinoma$1 OR adenocarcinoma$1 ADJ renal OR adenocarcinoma$1 ADJ kidney$1).TI,AB.	19667
24	MEZZ	(kidney$1 NEXT cancer).TI,AB.	1839
25	MEZZ	(hypernephroma$1 OR nephroid ADJ carcinoma$1 OR hypernephroid ADJ carcinoma$1 OR kidney ADJ hypernephroma$1 OR kidney ADJ pelvic ADJ carcinoma$1 OR kidney ADJ pyelocarcinoma$1 OR renal ADJ hypernephroma$1 OR grawitz ADJ tumor$1 OR renal ADJ cell ADJ cancer$1 OR renal ADJ tumor$1 OR renal ADJ tumour$1 OR carcinoma ADJ chromophobe ADJ cell ADJ kidney$1 OR chromophobe ADJ cell ADJ kidney ADJ carcinoma$).TI,AB.	7759
26	MEZZ	22 OR 23 OR 24 OR 25	28412
27	MEZZ	(everolimus OR afinitor OR rad001 OR rad-001).TI,AB.	650
28	MEZZ	21 AND 26 AND 27	0

29	EMZZ	economic$ OR price OR pricing OR pharmaeconomi$	155175
30	EMZZ	Cost-Benefit-Analysis#.DE.	31352
31	EMZZ	Pharmacoeconomics#.W..DE.	57398
32	EMZZ	Drug-Cost#.DE.	36279
33	EMZZ	Statistical-Model#.DE.	20588
34	EMZZ	Fee#.W..DE.	9455
35	EMZZ	cost OR costly OR costing$ OR costed	259610
36	EMZZ	cost$ NEXT (benefit$ OR utilit$ OR utilis$ OR minim$)	36988
37	EMZZ	expenditure$ NOT energy	10716
38	EMZZ	value NEXT (money OR monetary)	540
39	EMZZ	budget$	15102
40	EMZZ	economic NEXT burden$	2283
41	EMZZ	(resource ADJ use).TI,AB.	2380
42	EMZZ	Economics#.W..DE. OR Health-Economics#.DE. OR Health-Economics#.DE. OR Health-Economics#.DE. OR Health-Economics#.DE.	249852
43	EMZZ	Cost#.W..DE.	131462
44	EMZZ	Socioeconomics#.W..DE.	49349
45	EMZZ	Statistical-Model#.DE.	20588
46	EMZZ	Cost-Of-Illness#.DE.	5036
47	EMZZ	29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46	487626
48	EMZZ	PT=EDITORIAL OR PT=LETTER	689828
49	EMZZ	47 NOT 48	440189
50	EMZZ	Kidney-Carcinoma#.DE.	22987
51	EMZZ	(renal ADJ cell ADJ carcinoma$1 OR cell ADJ renal ADJ carcinoma$1 OR renal ADJ carcinoma$1 OR kidney ADJ carcinoma$1 OR kidney ADJ cell ADJ carcinoma$1 OR renal ADJ adenocarcinoma$1 OR kidney ADJ adenocarcinoma$1 OR adenocarcinoma$1 ADJ renal OR adenocarcinoma$1 ADJ kidney$1).TI,AB.	17758
52	EMZZ	(kidney$1 NEXT cancer).TI,AB.	1404
53	EMZZ	(hypernephroma$1 OR nephroid ADJ carcinoma$1 OR hypernephroid ADJ carcinoma$1 OR kidney ADJ hypernephroma$1 OR kidney ADJ pelvic ADJ carcinoma$1 OR kidney ADJ pyelocarcinoma$1 OR renal ADJ hypernephroma$1 OR grawitz ADJ tumor$1 OR renal ADJ cell ADJ cancer$1 OR renal ADJ tumor$1 OR renal ADJ tumour$1 OR carcinoma ADJ chromophobe ADJ cell ADJ kidney$1 OR chromophobe ADJ cell ADJ kidney ADJ carcinoma$).TI,AB.	6400
54	EMZZ	50 OR 51 OR 52 OR 53	29154
55	EMZZ	(everolimus OR afinitor OR rad001 OR rad-001).TI,AB.	628
56	EMZZ	49 AND 54 AND 55	2
57	BIZZ	economic$ OR price OR pricing OR pharmaeconomi$	404144
58	BIZZ	cost ADJ benefit OR pharmacoeconomics	5338
59	BIZZ	cost$1 OR value	673736
60	BIZZ	cost OR costly OR costing$ OR costed	126318
61	BIZZ	cost$ NEXT (benefit$ OR utilit$ OR utilis$ OR minim$)	6011
62	BIZZ	expenditure$ NOT energy	4197
63	BIZZ	value NEXT (money OR monetary)	207
64	BIZZ	budget$	11332
67	BIZZ	economic NEXT burden$	1101
68	BIZZ	(resource ADJ use).TI,AB.	2953
69	BIZZ	57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 67 OR 68	1063409
70	BIZZ	renal ADJ cell ADJ cancer	1616

71	BIZZ	(renal ADJ cell ADJ carcinoma$1 OR cell ADJ renal ADJ carcinoma$1 OR renal ADJ carcinoma$1 OR kidney ADJ carcinoma$1 OR kidney ADJ cell ADJ carcinoma$1 OR renal ADJ adenocarcinoma$1 OR kidney ADJ adenocarcinoma$1 OR adenocarcinoma$1 ADJ renal OR adenocarcinoma$1 ADJ kidney$1).TI,AB.	18073
72	BIZZ	(kidney$1 NEXT cancer).TI,AB.	1207
73	BIZZ	(hypernephroma$1 OR nephroid ADJ carcinoma$1 OR hypernephroid ADJ carcinoma$1 OR kidney ADJ hypernephroma$1 OR kidney ADJ pelvic ADJ carcinoma$1 OR kidney ADJ pyelocarcinoma$1 OR renal ADJ hypernephroma$1 OR grawitz ADJ tumor$1 OR renal ADJ cell ADJ cancer$1 OR renal ADJ tumor$1 OR renal ADJ tumour$1 OR carcinoma ADJ chromophobe ADJ cell ADJ kidney$1 OR chromophobe ADJ cell ADJ kidney ADJ carcinoma$).TI,AB.	5552
74	BIZZ	70 OR 71 OR 72 OR 73	23133
75	BIZZ	PT=EDITORIAL OR PT=LETTER	163502
76	BIZZ	74 NOT 75	22880
77	BIZZ	(everolimus OR afinitor OR rad001 OR rad-001).TI,AB.	654
78	BIZZ	69 AND 76 AND 77	0

The search of conference abstracts and other databases for economic evaluations used key terms: everolimus, RAD001, Afinitor and cost-effectiveness, cost-utility, cost-benefit, cost, (metastatic) renal cell carcinoma, kidney cancer.

10.3.5 Details of any additional searches, for example searches of company databases (include a description of each database).

No other searches were made.

10.4 Appendix 4: Further details on the IPCW analysis and IPCW Cox modelling

Inverse probability of Censoring Weights (IPCW) was used to account for selection bias associated with cross-over of 76% of placebo plus BSC patients to receive open-label everolimus on disease progression.

The IPCW analysis was carried out in a two-step process:

Step 1: Fit logistic regressions to model the probability of being IPCW-censored and develop stabilised weights from the results of these models.

Step 2: The weights were applied to a Cox proportional hazards model to estimate mortality risk and overall survival.

The IPCW adjusted Cox regression analysis, performed to enable adjustment of the BSC transition probabilities for states leading to death, was based on the 410 patients in the efficacy population as reported in the Lancet publication (but followed through to February 28th 2008).

Step 1: Developing stabilised weights (IPCW)

The observed RECORD-1 data was partitioned into monthly increments from randomisation to either death, cross-over to everolimus or end of study. Each monthly increment was assigned the baseline characteristics, including age in 5-year increments, sex, race, MSKCC prognostic score, prior treatments (nephrectomy, radiation, sunitinib, sorafenib, or both sunitinib and sorafenib), time since RCC diagnosis, and treatment randomisation of the patient, in addition to the time-varying assessments from the prior month, which included progression status, grade 3/4 adverse event occurrence, and Karnofsky performance score. Time-varying factors of 'prior progression' and "adverse events" were defined as the occurrence of progression or a grade 3/4 adverse event during the prior month of follow-up. "Time-varying KPS" was defined as the most recent KPS. Additionally, for each month, current death and cross-over information was assessed. Placebo plus BSC patients who crossed over to everolimus were artificially censored at the month of cross-over and time periods following cross-over were not included in the subsequent analysis.

Of 137 patients randomised to placebo plus BSC and included in the IPCW analysis, 105 (76%) were IPCW censored due to cross-over (i.e. with disease progression),

leaving 32 patients IPCW uncensored (16 had died, 1 had withdrawal of consent, and 15 had not experienced an event by study end (i.e. disease progression or death)).

Because cross-over occurred frequently and early, few patients contributed monthly time periods beyond 7 months (90^{th} percentile). In order to ensure the ability to weight monthly time periods, the occurrence of at least one patient in both the placebo plus BSC and everolimus groups was required. Thus, months beyond 11 were collapsed into a "beyond 11 month" interval.

BSC patients contributed a total of 523 uncensored patient months, with an average of 3.8 months follow-up per patient (Table 10.1).

Table 10.1 Placebo plus BSC patients included in the IPCW analysis

Number of monthly time intervals among placebo plus BSC patients							
N	**Mean**	**Minimum**	**Lower quartile**	**Median**	**Upper quartile**	**Maximum**	**Sum**
137	3.83	0	2	3	5	11	523

The observed differences in patient characteristics are summarised in Table 10.2 below. While observed differences in patient characteristics between patients who were artificially censored at cross-over and those who remained uncensored were not significant (Chi-square statistics). This is likely to be, at least in part, due to the small sample size. If any differences had been found between the groups, further assessment would be required and adjustments made where appropriate.

Table 10.2 Observed differences in baseline characteristics for placebo plus BSC patients in IPCW analysis

Characteristic		Censored (i.e. cross-over patients) N=105 n (%)	Uncensored (i.e. not cross-over) N=32 n (%)	P-value
Race	White	90 (85.7)	30 (93.8)	<0.23
	Other	15 (14.3)	2 (6.3)	
Base KPS	100	32 (30.5)	9 (28.1)	<0.35
	90	44 (41.9)	9 (28.1)	

Characteristic		Censored (i.e. cross-over patients) N=105 n (%)	Uncensored (i.e. not cross-over) N=32 n (%)	P-value
	80	19 (18.1)	9 (28.1)	
	70	10 (9.5)	5 (15.6)	
Prior VEGFr-TKI therapy	Sunitinib only	49 (46.7)	12 (37.5)	<0.37
	Sorafenib only	32 (30.5)	11 (34.4)	<0.68
	Sorafenib and sunitinib	24 (22.9)	9 (28.1)	<0.55
MSKCC risk for second-line treatment	Favourable	34 (32.4)	5 (15.6)	<0.14
	Intermediate	57 (54.3)	20 (62.5)	
	Poor	14 (13.3)	7 (21.2)	
Previous surgery (nephrectomy)		65 (61.9)	17 (53.1)	<0.38
Prior radiotherapy		26 (24.8)	11 (34.3)	<0.29
Age (years)		58.7	61.2	<0.61
Years since initial diagnosis		3.8	5.8	<0.10

The weights generated by the IPCW are quantities that are inversely proportional to an estimate of the conditional probability, given the covariates considered, of having not progressed (remaining uncensored) in any month. The IPCW or stabilised weight SW per month of follow-up is described by the following formula:

$$SW_i = \frac{\text{Probability of remaining uncensored until the given month conditional on baseline factors}}{\text{Probability of remaining uncensored until the given month conditional on baseline factors and a collection of time-varying covariates}}$$

The numerator of the weights, which is an estimate of the probability of remaining uncensored until the given month conditional on the baseline characteristics, stabilises the weights to improve efficiency. The denominator of the weights is an estimate of the probability of remaining uncensored (not progressing and crossing over) until the given month conditional on the baseline factors and a collection of time-varying covariates.

Pooled logistic regressions were used with censoring as the dependent variable in order to estimate SWi per month of follow-up. The choice of baseline and time-varying covariates were based on prior knowledge and data exploration. Literature

within HIV/AIDS research suggest that demographics information (age, gender, race), along with treatment history and disease duration may improve the fit of the logistic models. Interaction terms were tested between prior treatments and MSKCC and KPS. Gender, baseline KPS, time-varying KPS, and prior nephrectomy were dropped from the final logistic models. Final variable selection was based upon goodness-of-fit statistics. Interaction terms were tested between prior treatments and MSKCC and KPS.

Among all uncensored time periods in patients randomised to BSC, the numerator, denominator, and stabilized weights (SW) generated are presented in the following table (Table 10.3).

Table 10.3 Stabilised weights

Number of monthly time intervals among placebo plus BSC patients							
	N	**Mean**	**Lower quartile**	**Median**	**Upper quartile**	**Maximum**	**Sum**
Numerator of SW per month	523	0.5331	0.2879	0.5913	0.0044	0.9818	278.82
Denominator of SW per month	523	0.5474	0.2861	0.6183	0.0032	0.9778	286.27
SW per month	523	0.7912	0.4231	0.9690	0.0000	1.9420	413.80

Step 2: Cox modelling

From the IPCW analysis monthly observations for the placebo plus BSC patients were weighted according to the stabilised weights and monthly observations for everolimus patients were assigned a weight equal to 1. Zero weights were assigned to months during or after which censoring/cross-over occurred.

A Cox proportional hazards model, with death per month as the dependent variable, for the effect of treatment in the absence of crossover was fitted using the estimated stabilised weights per month of follow-up. The dichotomous treatment indicator as well as baseline covariates were included as predictors in the Cox model to adjust for selection bias related to the baseline covariates.

Summary results for the Cox proportional hazards model is summarised in Table 10.4 below.

Table 10.4 Hazard ratios for the IPCW adjusted Cox modelling

Covariate	Hazard Ratio	95%CI
Treatment: everolimus plus BSC versus placebo plus BSC	0.55	0.31-0.97
Age:continuous (5 year groups)	0.98	0.87-0.91
MSKCC: Continuous (poor to good)	1.68	1.10-2.59
Prior radiotherapy: Yes versus No	0.59	0.13-2.70
MSKCC*Prior Radiotherapy	1.51	0.75-3.04
Sunitinib only: Yes versus No	0.66	0.41-1.07
Sorafenib: Yes versus No	0.37	0.21-0.66
Years since diagnosis	0.94	0.88-1.01

The results suggest that treatment with everolimus is associated with significant reduction in the risk of mortality per month of approximately 45% (HR: 0.5518; 95% CI: 0.3138-0.9701; p-value=0.0389).

Conclusions

The results presented are subject to the standard assumptions of an IPCW analysis including no unmeasured confounding and no model misspecification. The strength of the analysis is that it makes use of data for patients who have not crossed over whilst adjusting for selection bias (i.e. it does not 'borrow' information from crossed over patients as might be the case with other methods) [109]. The use of the approach was assessed by independent statisticians who deemed in an appropriate method to use (details on request). A limitation is the relatively wide confidence intervals around the central HR estimate.

The HR of 0.55 was applied to the economic model in order to estimate survival outcomes from Markov states leading to death. The HR was used to generate transition probabilities for the BSC, to reflect the higher risk of mortality in the hypothetical absence of cross-over bias for patient cycles leading to death. The

transition probabilities for all states leading directly to death for the BSC arm were generated by multiplying the corresponding everolimus transition probabilities by 1.81 ie 1 divided by 0.55. All of the everolimus transition probabilities were based on data taken directly from RECORD-1.

10.5 Appendix 5: Unadjusted transition probabilities in the economic model

Best supportive care

Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
AE Risk (State 1 to 2)	0																		
SD w/o AE to PD (State 1 to 3)	0																		
SD w/AE to PD (State 1 to 4)	0																		
PD to Death (State 3 to 4)	0																		
SD w/o AE to Death (State 1 to 4)	0																		
SD w/ AE to Death (State 2 to 4)	0																		

Everolimus

Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
AE Risk (State 1 to 2)	0																		
SD w/o AE to PD (State 1 to 3)	0																		
SD w/AE to PD (State 1 to 4)	0																		
PD to Death (State 3 to 4)	0																		
SD w/o AE to Death (State 1 to 4)	0																		
SD w/ AE to Death (State 2 to 4)	0																		

10.6 Appendix 6: Adverse event treatment schedules

This appendix contains the sheets from the economic model relating to the drug and resource use assumptions for adverse events where specific treatment schedules have been defined.

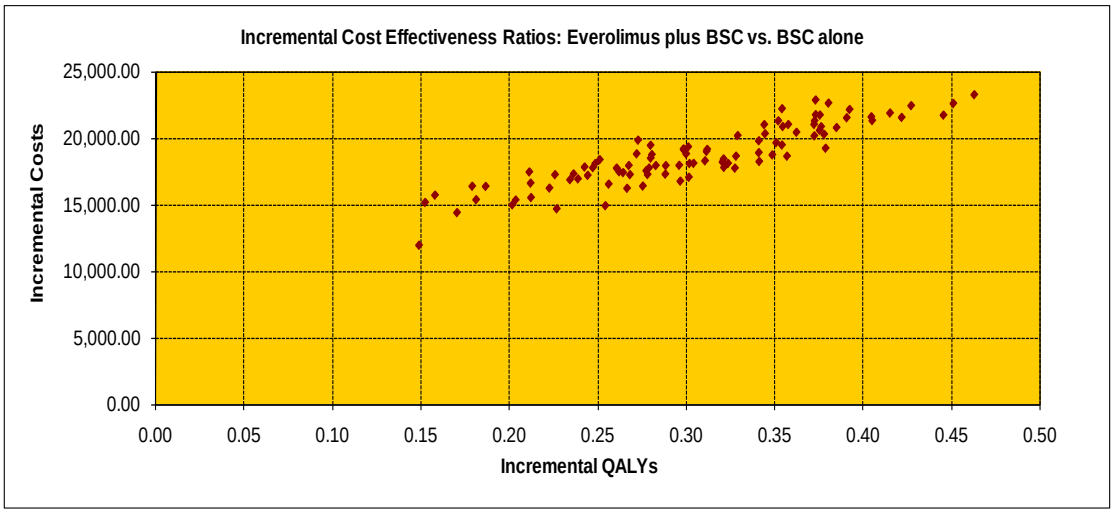
Anorexia/Cachexia													
Drug Care												282.43	
Treatment	Formulation	Req. Dose	Unit/day	Tx. Duration	Unit	Unit Dose	Unit	Unit Cost	Quantity/Packaging	Unit	Incidence	Total Cost	Currency
Nutrition Supplementation											100%	140.40	GBP
Artificial Nutrition Supplementation											100%	140.40	GBP
Enrich Plus	200-ml Can		1 carton	60	days	1	carton	2.34	1	can	100%	140.40	GBP
Apetite Stimulation											100%	142.03	GBP
Other Apetite Stimulant											90%	36.95	GBP
Metoclopramide											10%	4.11	GBP
	Tablets		75 mg	60	days	10	mg/tablet	0.014	1	tablet	33.30%	2.10	GBP
	Oral Soln		75 mg	60	days	5	5mg/5ml	3.83	200	ml pack	33.30%		GBP
	Injection		75 mg	60	days	5	mg/ml	0.26	2	ml-amp	33.30%	38.96	GBP
Wt. Avg Cost of Metoclopramide												41.06	GBP
Corticosteroids											20%	14.39	GBP
Dexamethasone											50%	35.96	GBP
	Tablets		12 mg	60	days	2	mg/tablet	0.1	1	tablet	33.30%	11.99	GBP
	Oral Soln		12 mg	60	days						33.30%		GBP
	Injection (available in		12 mg	60	days	4	mg/ml	1	1	ml-amp	33.30%	59.94	GBP
Wt. Avg. Cost of Dexamethasone												71.93	GBP
Prednisolone											20%	0.00	GBP
											100%		GBP
Wt. Avg. Cost of Prednisolone												0.00	GBP
Synthetic Progestogens											70%	90.69	GBP
Megastrol Acetate											50%	90.69	GBP
	Tablets		700 mg	60	days	160	mg	0.691	1	tablet	100%	181.39	GBP
Wt. Avg. Cost of Megastrol Acetate												181.39	GBP
Medroxyprogesteron Acetate			700 mg	60	days						50%	0.00	GBP
											50%		GBP
											50%		GBP
Wt. Avg Cost of Medroxypregesteron Acetate												0.00	GBP
Cannabinoid												0.00	GBP
Dronabinol											10%	0.00	GBP
													GBP
Wt. Avg. Cost of Dronabinol												0.00	GBP
Medical Care												160.70	GBP
Treatment	Formulation	Req. Dose	Unit/day	Tx. Duration	Unit	Unit Dose	Unit	Unit Cost	Quantity/Packaging	Unit	Incidence	Total Cost	Currency
Nutrition Consultation	Consultation												GBP
Hospitalizations	Hospital day (regular		1 day	5.94	days	1	day	270.54	1	day	10%	160.70	GBP
Oncologist Consultation	Consultation												GBP
Total Cost of Medical Care												160.70	GBP

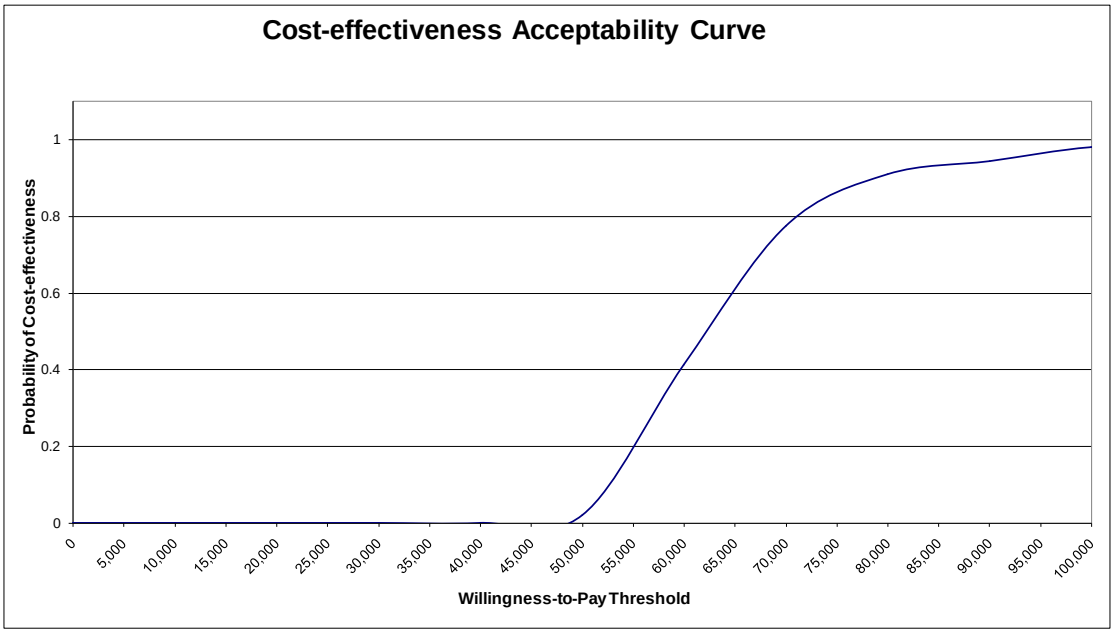
Pneumonitis													
Drug Care												13.73	GBP
Treatment	Formulation	Req. Dose	Unit/day	Tx. Duration	Unit	Unit Dose	Unit	Unit Cost	Quantity/Packaging	Unit	Incidence	Total Cost	Currency
Corticosteroids											20%	13.73	GBP
Dexamethasone											90%	18.88	GBP
	Tablets	10	mg	21	days	2	mg/tablet	0.1	1	tablet	33.30%	3.50	GBP
	Oral Soln	10	mg	14	days						33.30%		GBP
	Injection (available in	10	mg	21	days	4	mg/ml	1	1	ml-amp	33.30%	17.48	GBP
Wt. Avg. Cost of Dexamethasone												20.98	GBP
Prednisolone											10%	49.78	GBP
Treatment Initiation	Tablets	70	mg	14	days	2.5	mg	0.613	1	tablet	100%	240.30	GBP
Treatment Tapering	Tablets	35	mg	30	days	2.5	mg	0.613	1	tablet	100%	257.46	GBP
Wt. Avg. Cost of Prednisolone												497.76	GBP
Solu-Medrol (methylprednisolone)											90%	0.00	GBP
													GBP
Wt. Avg. Cost of Solu-Medrol												0.00	GBP
Medical Care												187.30	GBP
Treatment	Formulation	Req. Dose	Unit/day	Tx. Duration	Unit	Unit Dose	Unit	Unit Cost	Quantity/Packaging	Unit	Incidence	Total Cost	Currency
Hospitalizations	Hospital day (regular	1	day	4.87	days	1	day	288.5	1	day	10%	140.50	GBP
Temporary Ventilary Suppc	Oxygen	12	hours	5	days	1	hour	0.78	1	hour	100%	46.80	GBP
Total Medical Care Cost												187.30	GBP

Dyspnea													
Drug Care												2.87	GBP
Treatment	Formulation	Req. Dose	Unit/day	Tx. Duration	Unit	Unit Dose	Unit	Unit Cost	Quantity/Packaging	Unit	Incidence	Total Cost	Currency
Opioids for Cough											100%	0.84	GBP
Morphine											90%	0.84	GBP
	Morphine soln (Oram	40	mg	5	days	2	mg/ml	0.00935	100	ml pack	100%	0.94	GBP
Wt. Avg. Cost of Morphine												0.94	GBP
Benzodiazapines (adjunctive to morphine treatment)											100%	2.03	GBP
Lorazepam											70%	2.03	GBP
	Tablets	4	mg	2	days	1	mg	0.391786	1	tablet	90%	2.82	GBP
	Injection	4	mg	2	days	4	mg/ml	0.37	1	ml-amp	10%	0.07	GBP
Wt. Avg. Cost of Lorazepam												2.89	GBP
Medical Care												2,899.00	GBP
Treatment	Formulation	Req. Dose	Unit/day	Tx. Duration	Unit	Unit Dose	Unit	Unit Cost	Quantity/Packaging	Unit	Incidence	Total Cost	Currency
Hospitalizations	Hospital day (regular	1	day	2	days	1	day	288.5	1	day	10%	57.70	GBP
Temporary Ventilary Suppc	Oxygen	12	hours	5	days	1	hour	0.78	1	hour	100%	46.80	GBP
O2 Therapy	Oxygen tanks	15	hours	270	hours	1	hour	0.69	1	hour	100%	2,794.50	GBP
Total Medical Care Costs												2,899.00	GBP

Infection/Infestation												
Bacterial Infection												
Drug Care											299.86	GBP
Antibiotics										90%	299.86	GBP
Treatment	Formulation	Req. Dose	Unit/day	Tx. Duration	Unit	Unit Dose	Unit	Unit Cost	Quantity/Packaging	Unit	Incidence	Total Cost	Currency
Ceftazidime	Itravenous injection	6	g/day	5	days	1	gram vial	8.5	1	Vial	33%	84.92	GBP
Meropenem	1 gram IV every 8hs	3	g/day	5	days	1	gram vial	28.65	1	Vial	33%	143.11	GBP
Piperacillin/Tazobactam (T	4.5 grams IV every 6	18	g/day	5	days	4.5	gram vial	15.79	1	Vial	33%	105.16	GBP
Medical Care											0		GBP
Treatment	Formulation	Req. Dose	Unit/day	Tx. Duration	Unit	Unit Dose	Unit	Unit Cost	Quantity/Packaging	Unit	Incidence	Total Cost	Currency
Hospitalizations													GBP
Physician Visits													GBP
Total Medical Care Costs												0.00	GBP
Fungal Infections													
Drug Care												292.80	GBP
Treatment	Formulation	Req. Dose	Unit/day	Tx. Duration	Unit	Unit Dose	Unit	Unit Cost	Quantity/Packaging	Unit	Incidence	Total Cost	Currency
Anti-fungals											100%	292.80	GBP
fluconazale	400 mg daily intraver	400	mg/day	5	days	200	mg/bottle	29.28	1	bottle	100%	292.80	GBP
Medical Care											0		GBP
Treatment	Formulation	Req. Dose	Unit/day	Tx. Duration	Unit	Unit Dose	Unit	Unit Cost	Quantity/Packaging	Unit	Incidence	Total Cost	Currency
Hospitalizations													GBP
Physician Visits													GBP
Total Medical Care Costs												0.00	GBP
Viral Infections													
Drug Care												203.79	GBP
Treatment	Formulation	Req. Dose	Unit/day	Tx. Duration	Unit	Unit Dose	Unit	Unit Cost	Quantity/Packaging	Unit	Incidence	Total Cost	Currency
Anti-virals											100%	203.79	GBP
Acyclovir											20%	0.00	GBP
	5mg/kg	1050	mg/day	8	days	250	mg/vial	10.91	1	vial	100%		GBP
	10-12 mg/kg	2310	mg/day	8	days	250	mg/vial	10.91	1	vial	100%		GBP
Wt. Avg. Cost of Acyclovir												0.00	GBP
Valacyclovir											20%	13.12	GBP
	1 gm PO TID	3000	mg/day	5	days	500	mg/tablet	2.186	1	tablet	100%	65.58	GBP
Wt. Avg. Cost of Valacyclovir												65.58	GBP
Famciclovir											20%	66.80	GBP
	250 mg PO TID	750	mg/day	5	days	250	mg/tablet	7.42	1	tablet	100%	111.30	GBP
	500 mg PO TID	1500	mg/day	5	days	500	mg/tablet	14.847	1	tablet	100%	222.71	GBP
Wt. Avg. Cost of Famciclovir												334.01	GBP
Ganciclovir											20%	123.87	GBP
Initial Dose	5 mg/kg every 12 hs	700	mg/day	14	days	500	mg/vial	31.6	1	vial	100%	619.36	GBP
Tapering dose	Net price 500-mg via	350	mg/day	14	days						100%		GBP
Wt. Avg. Cost of Ganciclovir												619.36	GBP
Valganciclovir											20%	0.00	GBP
											100%		GBP
Foscarnet											20%	0.00	GBP
	Solution - Acyclovir-r	8400	mg/day	8	days	6000	mg/ 250-ml bo	34.49	1	bottle	100%		GBP
Initial dose	Solution - CMV disea	12600	mg/day	14	days	6000	mg/ 250-ml bo	34.49	1	bottle	100%		GBP
Following doses		8400	mg/day	14	days	6000	mg/ 250-ml bo	34.49					GBP
Wt. Avg. Cost of Foscarnet												0.00	GBP
Medical Care												0.00	GBP
Treatment	Formulation	Req. Dose	Unit/day	Tx. Duration	Unit	Unit Dose	Unit	Unit Cost	Quantity/Packaging	Unit	Incidence	Total Cost	Currency
Hospitalizations													GBP
Physician Visits													GBP
Total Medical Care Costs												0.00	GBP

10.7 Appendix 7: Scatter plot and Cost-effectiveness acceptability curve (without patient access scheme)





10.8 Appendix 8: Draft PAS Registration Form – See separate file

Technology appraisal of everolimus for the treatment of aRCC - response from Novartis on points of clarification

Thank you for the opportunity to respond to the queries raised by the ERG and the NICE technical team. Some of the queries sent by NICE to Novartis were modified upon further discussion with NICE. Responses to the final queries agreed with NICE are presented below.

Section A: Clarification of the effectiveness data

A1 The RECORD-1 trial

a. Please clarify whether there were any differences in progression free survival in terms of age and/or ethnic group? Also please clarify whether there were any differences in overall survival in terms of age and / or ethnic group?

The influence of age on the benefit of everolimus as measured by progression free survival (PFS) was examined in a post-hoc analysis using a stratified Cox proportional hazard model with age included as a covariate. Age was grouped into two classes; ≥ 65 years and < 65 years. The analysis carried out at the February 2008 cut off showed that everolimus offers a benefit in terms of PFS regardless of age (<65 HR: 0.34 [95% CI: 0.25, 0.47] p <0.001 and for ≥65 HR: 0.33 [95% CI: 0.21, 0.51] p<0.001, unstratified one-sided logrank test).

It was not possible to determine the influence of ethnic group on PFS, as this analysis was not performed. It should be noted that the study sample was predominantly Caucasian (88.8% of the total study sample), and therefore the number of patients in the sample from other ethnic groups was small, making firm conclusions from any such analyses difficult.

Analyses of the impact of age and ethnic group on overall survival (OS) were not carried out as this was not the primary end point of the study. In addition, it was recognised that the OS results would be confounded if a large number of patients crossed over from the placebo plus BSC arm to the everolimus plus BSC arm of the trial upon progressing. At the February 2008 analysis, 76% of patients had crossed over from the placebo plus BSC arm to the everolimus plus BSC arm of the trial.

b. How transferable is the trial population to UK clinical practice, particularly with regards to performance status?

The majority of patients recruited into the RECORD-1 study had a Karnofsky performance status of greater than 90/100 and patients were not allowed to enter the trial unless they had performance status equal to or greater than 70/100 (see Table 1 below for breakdown of patients according to performance status). A Karnofsky performance status of equal to or greater than 70/100 is equivalent to an ECOG performance status of 0-1.

Table 1: Karnofsky performance status of RECORD-1 trial participants

Karnofsky PS	Everolimus n (%)	Placebo n (%)	All patients n (%)
100	78 (28.2)	41 (29.5)	119 (28.6)
90	98 (35.4)	53 (38.1)	151 (36.3)
80	72 (26.0)	30 (21.6)	102 (24.5)
≥70	28 (10.1)	15 (10.8)	43 (10.3)
Missing	1 (0.4)	0 (0.0)	1 (0.2)

The performance status of patients recruited into the RECORD -1 study is likely to be representative of the performance status of patients eligible for everolimus in the UK. Recommendations set out in TA169, stipulate that patients receiving sunitinib as a first-line therapy for aRCC should have an ECOG performance status of 0-1. This means that all patients receiving sunitinib will initiate treatment with a KPS equal to or greater than 70/100. It is not anticipated that these patients will experience a dramatic decline in performance status on initial progression in the majority of cases. These are the patients that will be eligible for everolimus treatment in the UK. In general, patients who are managed on systemic therapy do not experience a rapid deterioration in performance status.

In summary, the patients evaluated in the RECORD-1 trial are likely to be representative of those who are eligible for everolimus treatment in the UK.

Performance status alone is not considered to be informative in terms of prognosis. In addition, ethnicity is not a clinical feature and has not been demonstrated to have any implications on prognosis for aRCC (see MSKCC prognostic criteria, [1]).

c. Please clarify the definition of BSC used in the clinical trial

Best supportive care such as drug and non-drug therapies, nutritional support, and/or physical therapy was allowed during the study. All medications including non-drug therapies (physical therapy, blood transfusions etc.) taken prior to and after the start of the study drug were recorded on the appropriate case report forms (CRFs).

Patients were instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator asked the patient about any new medications he/she was taking or had taken after the start of the study drug.

Best supportive treatments that were permitted during the study included:

- Bisphosphonate therapy for treatment of bone metastases which had to be started prior to the first dose of the study medication.
- Pain medications to allow the patient to be as comfortable as possible.
- Localized radiotherapy for the treatment of pre-existing, painful bone metastases was allowed only in the absence of radiological progression. Radiotherapy for brain metastases was not permitted during the study as radiation to the brain was indicative of disease progression.
- Nutritional support as recommended by the investigator.
- Megestrol acetate could be prescribed during the course of the study as an appetite stimulant (not applicable to Japan).
- Oxygen therapy and blood transfusions.
- Leukocyte growth factors (e.g. CSF and GM-CSF) could be prescribed by the investigator for severe neutropenia if this was thought to be appropriate.

d. Page 37 of the submission specifies "An earlier version of the full clinical study report for the second interim analysis results is also available, although for this analysis cut-off the Lancet publication represents the primary evidence source". Please provide a copy of this report.

Please see the pdf file accompanying this response (CSR_RECORD-1, 2nd interim analysis.pdf). This is the Clinical Study Report relating to the second interim analysis. **Please note that this document is to be considered as commercially confidential.**

e. Regarding the blinding of outcome assessment, please clarify whether the CT and MRI scans were read blind and whether more than one person assessed the scans.

CT and MRI scans collected during the study were read by two sets of assessors; a local assessor and independent central radiologists from ICON Medical Imaging. Both sets of assessors used the RECIST criteria to determine tumour response and progression. If required by the central assessor, ICON also had a single central adjudicator to define if progression had occurred. Both sets of assessors were blinded to patient allocation during the blinded treatment phase (ie up to the point of disease progression). After disease progression was confirmed or a serious AE occurred and the patient was consequently unblinded, the local assessor was no longer blinded to treatment, but the independent central radiologists remained blinded. It is the results from the central radiologists that were used as the basis for the primary analysis of PFS.

f. Page 205 of the submission states that the IPCW approach was assessed by an independent statistician, of which details are available upon request. Please could you provide a copy of this assessment?

A copy of the report from the independent statistician can be found as a separate document accompanying this response:

See file: Novartis use_of_IPCW_in_survival_studies[1]010709.doc

The author of this report was:

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Section B. Clarification on cost-effectiveness analysis

B1 Efficacy estimates in the model

a. In the report, the use of the Inverse Probability of Censoring Weights (IPCW) method was used to correct for cross-over and this has been compared with the Rank Preserving Structural Failure Time (RPSFT) model. There are, however, several other approaches to this issue. [2, 3] Please clarify whether any of these alternative approaches were considered, and if so, why they were rejected in favour of the IPCW method?

A number of statistical methods to correct for confounding due to cross over are discussed in the publications cited in your letter. The Branson and Whitehead (2002) and White (2005) articles suggest utilising randomised-based efficacy estimates (RBEEs) and an accelerated failure time model to model a survival outcome in RCT trials with non-compliance to randomisation. White (2005) states that this methodology allows estimation based on "finding a value of the treatment effect parameter that achieves baseline balance in potential untreated outcome". IPCW analysis is similar to the accelerated life models since it allows for an appropriate estimation of a treatment effect in RCT trials where patients do not always comply with their randomised treatments.

However, although there are some similarities between the accelerated failure time models suggested by Branson and Whitehead (2002) and White (2005), and the IPCW approach utilised in this analysis, there are also some important differences. Accelerated failure time models provide estimates of the effect on survival time between treated and untreated patients, whilst the IPCW-adjusted Cox models produce a hazard ratio. Moreover, the accelerated failure time models are parametric and require an assumed distribution (e.g. Weibull, log-normal), while the IPCW-

adjusted Cox models do not assume any distribution. We investigated applying various parametric distributions to the RECORD-1 trial data, and did not find any distribution that provided a good fit to the data for all transitions (PFS to progression, PFS to death, progression to death). Therefore, it was deemed more appropriate to utilise a methodology which provided a hazard ratio which could be used directly to adjust the relevant transition probabilities in the model.

Another notable difference between accelerated failure time models and IPCW models is that with accelerated failure time models, the significance level of the original ITT analysis is maintained whereas for IPCW, a new significance level is generated, based on the strength of the hazard ratio estimated by the new approach. Due to the bias from cross-over for estimating the overall survival treatment effect of everolimus with ITT analysis, our objective was to utilise methodology which could provide a potentially more powerful estimate of treatment effect on survival and its significance. This is better provided by the IPCW-adjusted Cox modelling than the accelerated failure time models.

In summary, although there are a number of approaches which could have been utilised to correct for confounding due to crossover, the IPCW approach represents a robust and valid method which provides data that can be used simply and easily within the health economic model.

b. **Please provide an additional cost-effectiveness analysis using the raw intention-to-treat (ITT) data from the RECORD-1 trial (i.e. without the use of the IPCW - or any other - statistical method to correct for the bias associated with cross-over).**

As requested, please find below results from the cost-effectiveness analysis based on the RECORD-1 ITT data (see Table 2).

The value of the results from the cost-effectiveness analysis based on ITT data is highly questionable as 106/139 (76%) patients randomised to placebo plus BSC crossed over to the everolimus plus BSC arm of the study (February 2008 analysis). In addition, over half of these patients crossed over from placebo to everolimus within 8 weeks of randomisation. In practice this means that the ITT results largely represent a group of patients who start on everolimus straight away compared to a group of patients that start on everolimus after a relatively short time lag.

Consequently, the ITT analysis does not represent the true magnitude of the survival benefit associated with everolimus plus BSC when compared to placebo plus BSC.

Table 2: the results from cost-effectiveness analysis using the ITT analysis using data from the February 2008 cut-off.

	everolimus plus BSC QALY	**BSC alone QALY**	**Inc QALY**	**everolimus plus BSC cost (£)**	**BSC alone cost (£)**	**Inc cost (£)**	**ICER for everolimus plus BSC versus BSC alone (£/QALY)**
With PAS: ITT (Feb 2008 cut-off)	0.607	0.492	0.115	25,222	14,758	10,463	91,256
Without PAS: ITT (Feb 2008 cut-off)	0.607	0.492	0.115	27,328	14,758	12,570	109,627

In summary, as 76% of patients randomised to the placebo plus BSC arm of the trial crossed over to the everolimus plus BSC arm and over half of these crossed over within 8 weeks of randomisation, the ITT analysis does not represent a reliable estimate of the survival benefit and therefore cost-effectiveness of everolimus when compared to BSC. The estimate of cost-effectiveness based on the IPCW approach utilises data from the RECORD-1 trial to generate all of the transition probabilities for everolimus as well as the transition probabilities from stable disease to progression for the BSC arm of the study. The transition probabilities for the placebo plus BSC treatment arm were derived using the IPCW data. This results in a prediction of LYG of 0.426 (5.1 months) for the placebo plus BSC arm of the study. The face validity of this estimate appears to be reasonable based on the fact that evidence from the literature suggests that untreated patients survive for around 6-12 months [4,5]. Patients in the RECORD-1 trial were heavily pre-treated, end-stage patients and therefore it is plausible that the estimated survival of the BSC patients would be at the lower end of this range or less. In addition, recent meta-analysis research has demonstrated that OS is greater than PFS ie 1 month PFS is associated with a >1 month OS in aRCC [6]. This meta-analysis showed in a sub-group of 24 aRCC controlled trials where cross-over was not an issue; a 1 month treatment effect on time to disease progression was associated with a 1.61 month improvement in overall survival. Based on this correlation, for the 3 month improvement in PFS found for everolimus in the RECORD-1 trial this would translate to an approximate 4.8 month gain in overall survival which is similar to the 4.97 month benefit predicted by the Markov model using the IPCW adjusted HR. A RPSFT analysis of the RECORD-

1 trial was recently presented by Korhonen at the Joint 15th Congress of the European CanCer Organisation (ECCO) and 34th Congress of the European Society for Medical Oncology (ESMO), 20–24 September 2009 [7]. The results from this analysis show an estimated survival benefit associated with everolimus plus BSC treatment of 1.9 times that conferred by placebo plus BSC which results in a median OS of 14.8 months for everolimus plus BSC versus 10 months for placebo plus BSC with a difference of around 4.8 months. These results are broadly similar to the mean estimates of difference in survival estimated by the Markov model of 4.97 months using the IPCW analysis (mean of 10.1 months for everolimus plus BSC versus 5.1 months for placebo plus BSC).

In conclusion, the IPCW approach is a robust and valid approach which provides estimates of survival that are broadly consistent with other sources of available information. The large proportion of patients who crossed over from the placebo plus BSC to the everolimus plus BSC and the speed with which over half of the patients crossed over means that the ITT analysis cannot be relied upon to produce any meaningful results.

c. The method used to calculate transition probabilities in the Excel spreadsheet. The model provided by Novartis uses the reciprocal of the 0.55 hazard ratio (1.818) to directly multiply the mortality transition probabilities in the treatment arm to establish the mortality transition probabilities for the BSC comparator arm (range C57:U59 in the 'Transition Probabilities' worksheet of the Excel model). Please clarify why this approach was used in favour of converting the transition probabilities to rates before applying a multiplier, that is:

- **The transition probabilities are converted to rates [using the formula - (LN (1-prob))]**
- **The calculated new rate can then be converted back to the revised transition probability [using the formula 1-EXP(-rate)).**

As the transition probabilities in the model were based on the rate of deaths calculated explicitly for each cycle from the RECORD-1 trial, (i.e. the duration of time for calculating the rates was exactly the same as the cycle length—8 weeks) the

transition probability and transition rate for each cycle will be the same. For example if we had only one cycle and 50 percent of the patients had died, the calculated rate would be 0.5 and the transition probability would be the same in order for the model prediction to be valid. We have therefore assumed that applying the HR to the transition probability directly is equivalent to applying it to the rate. Moreover, for low transition probabilities (eg less than 20%) applying the suggested formulas for conversion to rates, the difference in the resulting transition probabilities is very small. However, we acknowledge that another approach would be to apply the HR to the rate using the suggested formulas. In order to evaluate the impact of applying the HR to the rate we have recalculated the transition probabilities and re-run them in the model. The revised cost/QALY is £53,479 ie less than £2k more than the base case cost/QALY of £51,613. The disaggregated results from the two approaches are presented in the table below for comparison (see Table 3). Tables comparing the transition probabilities derived from the two approaches are also provided below for your information (see Table 4 and Table 5).

Table 3: the results from cost-effectiveness analysis examining the effect of converting transition probabilities to rates before applying the multiplier (February 2008 data cut-off, IPCW with PAS).

	everolimus plus BSC QALY	**BSC alone QALY**	**Inc QALY**	**everolimus plus BSC cost (£)**	**BSC alone cost (£)**	**Inc cost (£)**	**ICER for everolimus plus BSC versus BSC alone (£/QALY)**
IPCW, no prior conversion to rate	0.607	0.302	0.304	£25,222	£9,517	£15,704	£51,613/QALY (£37,893/LYG)
IPCW prior conversion to rate	0.607	0.325	0.282	£25,222	£10,146	£15,075	£53,479/QALY (£39,499/LYG)

Table 4 Transition probabilities with the HR applied directly to the probabilities

		Point Estimate	Lower 95% CI	Upper 95% CI
Rate of OS	Afinitor	0.55	0.314	0.97
	BSC	1.818	3.185	1.031

Per Patient Model (BSC)

Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
AE Risk	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Progression Risk SD w/o AE	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Prog. Risk from SD w/AE	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Death from PD	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Stable N-Death	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Stable w/ AE N-Death	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX

Per Patient Model (Afinitor)

Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
AE Risk	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Progression Risk SD w/o AE	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Prog. Risk from SD w/AE	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Death from PD	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Stable N-Death	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Stable w/ AE N-Death	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX

Table 5: Transition probabilities when the HR is applied to the rates and converted back to probabilities

Per Patient Model (BSC)																			
Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
AE Risk	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Progression Risk SD w/o AE	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Prog. Risk from SD w/AE	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Death from PD	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Stable N-Death	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Stable w/ AE N-Death	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX

Per Patient Model (Afinitor)																			
Cycle	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
AE Risk	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Progression Risk SD w/o AE	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Prog. Risk from SD w/AE	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Death from PD	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Stable N-Death	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX
Stable w/ AE N-Death	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX	XXX

References

1. Motzer RJ, Bacik J, Schwartz LH, Reuter V, Russo P, Marion S, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol 2004 Feb 1;22(3):454-63.

2. Branson M and Whitehead J (2002) Estimating a treatment effect in survival studies in which patients switch treatment. Statist. Med. 21:2449-2463

3. White IR (2005) Uses and limitations of randomization-based efficacy estimators. Stats in Med. Res. 14:327-347

4. Tian GG, Dawson NA. New agents for the treatment of renal cell carcinoma. Expert Rev Anticancer Ther 2001 Dec;1(4):546-54.

5. National Institute for Health and Clinical Excellence (NICE). Everolimus for the second-line treatment of advanced and/or metastatic renal cell carcinoma: Final scope.

6. Delea TE, Khuu A, Kay A, Zheng J, Baladi JF. Association between time to disease progression (TDP) endpoints and overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC). Poster 7124. Joint ECCO 15 and 34th ESMO Multidisciplinary Congress, Berlin 20th-24th September 2009.

7. Korhonen P, Haas T, Zuber E., Kay A,, Lebwohl D,, Motzer R. Overall survival among metastatic renal cell carcinoma (MRCC) patients corrected for crossover using a rank preserving structural failure time (RPSFT) model: analyses from the everolimus phase III trial (abstract P-7155 and poster #7155) European Journal of Cancer Supplements, Vol 7 No 2, September 2009, Page 440

Date 1st October 2009

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Dear Carole

Patient Access Scheme - Afinitor

I am writing to confirm the Department of Health's position on the Patient Access Scheme (PAS) arrangements that have been proposed by Novartis for Afinitor in the treatment of Advance Renal Cell Carcinoma.

The Department is content for NICE to consider the PAS proposed by Novartis.

Yours sincerely

Simon Reeve
Head of Clinical and Cost Effectiveness,
Medicines, Pharmacy and Industry Group

16th October 2009

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Dear [redacted],

Single Technology Appraisal – Everolimus for Advanced Renal Cell Carcinoma

The Evidence Review Group, Peninsula Technology Assessment Group (PenTAG) and the technical team at NICE have now had an opportunity to take a look at the submission by Novartis. In general terms they felt that it was well presented and clear. However the ERG and the NICE technical team would like some further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these points in their reports. As you will only receive the evidence review group report for information 5 days prior to the Appraisal Committee meeting, you may want to address the points below and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by **30th October 2009**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed. **Please also note that due to a member of the ERG being off sick, some minor additional clarification requests may be sent to you on 27th October**. Please accept my apologies for any inconvenience caused.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in red and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

If you have any further queries on the technical issues in this letter then please contact Helen Tucker – Technical Analyst (Helen.Tucker@nice.org.uk). Procedural questions should be addressed to Laura Malone – Project Manager (Laura.Malone@nice.org.uk) in the first instance.

Yours sincerely

pp Frances Sutcliffe
Associate Director – Appraisals
Centre for Health Technology Evaluation

Section A: Clarifications of the effectiveness data

A1 The RECORD-1 trial

a. Please clarify whether there were any differences in progression free survival, or overall survival, before and after the point of crossover in terms of age and / or ethnic group?

b. How transferable is the trial population to UK clinical practice, particularly with regards to performance status?

c. Please clarify the definition of best supportive care (BSC) used in the trial.

d. Please provide an analysis for progression free survival before the point of crossover from BSC to everolimus + BSC.

e. Regarding the blinding of outcome assessment, please clarify whether the CT and MRI scans were read blind and whether more than one person assessed the scans.

Section B. Clarification on cost-effectiveness analysis

B1 Efficacy estimates in the model

a. In the report, the use of the Inverse Probability of Censoring Weights (IPCW) method was used to correct for cross-over and this has been compared with the Rank Preserving Structural Failure Time (RPSFT) model. There are, however, several other approaches to this issue. [1, 2] Please clarify whether any of these alternative approaches were considered, and if so, why they were rejected in favour of the IPCW method?

b. Please provide an additional cost-effectiveness analysis using the raw intention-to-treat (ITT) data from the RECORD-1 trial (i.e. without the use of the IPCW - or any other - statistical method to correct for the bias associated with cross-over).

References

1. Branson M and Whitehead J (2002) Estimating a treatment effect in survival studies in which patients switch treatment. Statist. Med. 21:2449-2463
2. White IR (2005) Uses and limitations of randomization-based efficacy estimators. Stats in Med. Res. 14:327-347

KIDNEY CANCER UK

(KCUK)

SUBMISSION TO NICE

HEALTH TECHNOLOGY APPRAISAL

Everolimus for the second-line treatment

of metastatic renal cell carcinoma

September 2009

KCUK is delighted that there is now a further proven treatment option available to people living in the United Kingdom with advanced kidney cancer. It is pleased that it will provide great help to those where disease has progressed following treatment with a targeted therapy, like the drug sunitinib. The availability of everolimus is an important step in enabling this population of poor-prognosis patients to have their disease further controlled.

KCUK strongly supports approval of everolimus for NHS funding (1) on the ground of clinical need (2) as an end-of-life medicine and (3) because it breaks new ground with an innovative mode of action in the treatment of the disease.

We now consider these three points in turn.

Clinical need

Some most encouraging results from clinical trials show that everolimus has much to offer patients. First of all it doubles the median time without tumour growth and reduces the risk of the disease worsening (or the patient dying) by 67 per cent compared with placebo. [Escudier, B. et alia. 'Phase III randomised trial of everlimus vs. placebo in metastic renal cell carcinoma'. Presented at the European Society for Medical Oncology 33rd Congress, Stockholm, 16 September 2008.) These results are most welcome and encouraging, especially since patients with advanced kidney cancer have very limited options once tumours progress following standard first-line therapy. (Motzer, R.J. et alia. 'Efficacy of everolimus in advanced renal cell carcinoma: a double-blind randomised, placebo-controlled phase III trial'. *The Lancet*, August 2008: 372; 9637: 449-56.) Reviewing these results, a recently published paper on expert consensus opinion recommended

everolimus as a treatment option for advanced kidney cancer based on class 1 evidence. (Nathan, P. et alia. 'UK guidelines for the systemic treatment of renal cell carcinoma'. *British Journal of Hospital Medicines.* Vol 70, Issue 5, 13 May 2009.)

A further advantage with everolimus is that it is relatively well tolerated by patients. Its side effects are less troublesome than is the case with many other anti-cancer drugs. This is a very important consideration for patients, many of whom, especially the older ones, often present with other medical conditions as well as cancer.

The drug has recently been licensed for treatment of advanced kidney cancer after failure of treatments which prevent the growth of the tumour's blood vessels. The European Commission approved everolimus on 3 August 2009.

End-of-life Medicine

The Richards Review on *Improving access to medicines for NHS patients* made certain recommendations about end-of-life medicines, recommendations which were taken up by the Government, appraised by NICE and implemented in the multiple technology assessment of four kidney cancer drugs published earlier this year. The recommendation of most crucial significance in the present context is the proposal for NICE to recommend drugs used as end-of-life medicines for rarer cancers, to recommend them even when their incremental cost-effectiveness ratios are about the £30,000 per QALY benchmark.

The criteria to be used in selecting drugs to which this may apply are put as follows. First the drug must be licensed for the treatment of a patient population not exceeding 7,000 patients each year. Then the drug must be indicated for the treatment of

patients with a diagnosis of a terminal illness and who are not, on average, expected to live more than 24 months. Finally there must be sufficient evidence to indicate that the drug offers a substantial average extension to life compared to the current alternative treatment.

Everolimus meets these criteria very closely indeed.

Everolimus easily meets the patient population criterion. Annually there are just less than 7,000 new registrations of renal cell carcinoma, of which only about 40 per cent present (or go on to present) with metastatic disease. Even amongst those with metastatic disease, only a certain proportion survive long enough to require second-line treatment. Thus everolimus is to serve the needs of a small number of patients with a rarer cancer. As mentioned above, the review of expert opinion published in the *British Journal of Hospital Medicine* clearly indicates everolimus as the recommended second-line treatment. As we are all only too painfully aware, the average life expectancy of patients prescibed everolimus is way below the 24 months figure. Finally, the 67 per cent reduction in risk referred to above equates to a median progression free survival of 4.90 months for everolimus plus best supportive care versus 1.87 months for placebo plus best supportive care. So even considering just progression free survival, let alone overall survival, there is a substantial extension to life that everolimus can bestow.

Innovation

There is currently no drug recommended for NHS funding for second-line treatment of renal cell carcinoma. Everolimus fulfils that need; and it also represents a major step forward in the field of kidney cancer. It is a highly innovative drug, being

a selective kinase inhibitor that blocks the action of the mTor [mammalian target of rapamvcin] protein. It can be distinguished by being the only drug of its kind that can be administered orally.

It is clear that there are very likely to be a further set of drugs to deal with advanced kidney cancer. Currently there are around 25 to 30 of these drugs at various stages in their development. Innovation is proceeding apace; and a very important secondary benefit to come from the prescription of everolimus is what can be learnt from applying the drug in practice.

It is unfortunate but the UK has not been exactly the best country in the world in which to combat metastatic renal cell carcinoma. Patients have had more chances of gaining free access to new drugs if they were resident in North America or in many countries in Western Europe. The UK has often compared unfavourably against other countries in this respect. Even in countries such as Romania, Slovakia and the Czech Republic, as well as in Argentina and South Korea, patients often have greater chances of access to newly developed drugs. So in this respect the UK compares unfavourably, not just against counties at similar stages in development, but also against some less advanced countries. It is possible that these unfavourable comparisons are also reflected in international cancer survival rates. Some statistics recently released appear to indicate that, whilst survival rates are improving everywhere, other countries are tending to improve at a faster speed than is being achieved here in the UK. Of course there could be a whole host of reasons explaining why survival rates vary over time and from country to country. But it has more than just crossed our minds that variation in the speed at which new innovative anti-cancer drugs are taken up has got something to do with variation in survival rates. This is a general point affecting all forms of cancer, but it seems

especially germane to kidney cancer where the improvement in survival rates has been so disappointingly slow.

Everything should be done to encourage innovation here.

* * * * *