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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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

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Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
The James Whale Fund for Kidney Cancer	***Whether we consider that all the relevant evidence has been taken into account.*** It is our assertion that meaningful patient input is missing from the ACD. The James Whale Fund feel the evidence should be revisited and the patient perspective must be included and given due weight if N I C E wish to present a balanced and rounded appraisal.	The patient perspective was acknowledged by the Committee. See FAD sections 4.1, 4.2 and 4.3
The James Whale Fund for Kidney Cancer	The spend on cancer drugs is higher in other EU Countries. A recent report from Policy Exchange states that spending on cancer medicines in England is only 60% of that spent by other advanced EU countries and our cancer death rate is 6% higher than the EU average, it would be naïve not to see the connection between those two figures. Cancer patients in England are hugely disadvantaged by this process of rationing by cost.	Comment noted. The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturer's submission and the ERG report.
The James Whale Fund for Kidney Cancer	The last 10 years has seen much research into innovative anti-cancer drugs come to fruition. In the case of Kidney Cancer , NICE has reviewed 5 such new drugs and has only approved one 1st line new drug (Sunitinib) and refused all 2nd line sequential treatments. The drugs refused by N I C E are widely available in all western countries and NICE's justification for denying access to innovative new cancer drugs to NHS patients are based on esoteric cost calculations and statistics which are incomprehensible to patients and the general public. Denying treatment to terminally ill cancer patients has been hugely controversial and the Department of Health, through N I C E, has been forced to react to public criticism by introducing an "End of Life" criteria to ensure that modern and comparably costly drugs, are not automatically refused when they fail the notorious and arbitrary N I C E QALY. There is no evidence that the EOL criteria have been applied to this application for Everolimus even though Everolimus fits the criteria perfectly. The consequence of this unfair approach is that mRCC patients have only 1 drug for 1st line treatment (accepting there maybe some limited use for 20 year old immunotherapy treatments such as interferon alfa), none at all for sequential 2nd	Comments noted. The Appraisal Committee considered the supplementary advice and it agreed that everolimus does fulfil the criteria as a life extending, end-of-life treatment. However, the Committee concluded that everolimus for the second-line treatment of advanced RCC would not be a cost-effective use of NHS resources. See FAD sections 4.14 and 4.15.

Consultee	Comment	Response
	line treatment leaving only, as a last resort, best supportive care. Once again kidney cancer patients in the UK are disadvantaged by the N I C E model of cost analysis.	
The James Whale Fund for Kidney Cancer	The figure of the £30,000 Q A L Y has not been updated since its inception – one can imagine the furore if other cost areas in the NHS i.e. salaries and expenses had remained unchanged for 9 years. A simple calculation shows if the QALY had been adjusted in line with other NHS costs, a £50/55,000 Q A L Y would be the norm and taking the figure of 1.4 quoted recently by Professor Stevens as the multiplier, the EOL Q A L Y should now be £70/75,000. N I C E appears to exist in a time warp for this one area of their work. Today's treatments for today's patients should not be judged against a set of "rules" which are nearly 10 years old.	Comment noted
The James Whale Fund for Kidney Cancer	(patient quote) "Cancer survival rates are much higher in other EU countries especially when sequential treatment is available."	Comment noted. The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturer's submission and the ERG report.
The James Whale Fund for Kidney Cancer	***Whether we consider that the summaries of the clinical effectiveness and cost effectiveness are reasonable interpretations of the evidence and the preliminary views on the resource impact and implications for the NHS are appropriate*** It is apparent to us from talking and listening to patients and the general public that the majority of people do not understand the pseudo-science of mathematical models, ICER's and QALY's. Patients do not understand how an actual invoice cost of £31,000 pa can, following an appraisal by N I C E, be transformed into a cost to the NHS of £75,000 pa. If N I C E cannot find a way to explain their processes to patients denied access to	Comment noted The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the Methods of Technology Appraisal section 5.2.11 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.p

Consultee	Comment	Response
	clinically effective treatments that Clinicians wish to prescribe, then we suggest it is out of touch with the NHS patients it is meant to be serving.	df)
The James Whale Fund for Kidney Cancer	patient quote) "It's so difficult to understand what they are saying, with all that gobblygook, when Sutent stops working for me, can I really expect to live another 11 or 12 months without any proper cancer treatment at all. That's not what I read on the patients forums. Do other stage 4 patients and the Oncologists agree with that I wonder?"	Comment noted. The Committee noted that there is an unmet clinical need and that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5).
The James Whale Fund for Kidney Cancer	NICE should take into account the wider societal benefits of access to end of life drugs for cancer patients when assessing cost effectiveness. If patients on active treatment can continue to work and support their families, is that worth nothing?	Comment noted The reference case stipulates that that, the perspective on outcomes should be all direct health effects, whether for patients or, when relevant, other people (principally carers). The perspective adopted on costs should be that of the NHS and PSS. See Guide to the Methods of Technology Appraisal sections 5.2.7 and 5.5.10 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
The James Whale Fund for Kidney Cancer	(patient quote) " The NHS has a forecast underspend against budget this year of £1.4 billion – is it a cost effective use of NHS resources to keep that money sitting in NHS bank accounts rather than spend it on front line services like cancer treatments for patients who desperately need them."	Comment noted.

Consultee	Comment	Response
The James Whale Fund for Kidney Cancer	If this decision is not changed , NICE will have recently rejected all five 2nd line kidney cancer treatments despite promised greater flexibility from NICE for EOL drugs	Comment noted. The Committee noted that there is an unmet clinical need and that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5).
The James Whale Fund for Kidney Cancer	Is there a figure being used as the benchmark for "end of life" drugs? How do patients or the public know whether that figure is "reasonable"? How can we comment when the information is not made available? What is a cost effective use of resources when keeping any patient alive? Is it the cost of kidney dialysis per year; is it the cost of an organ transplant operation and ongoing drugs for life?	The supplementary advice does not suggest for Committee to apply a particular weight for the cost effectiveness estimate to fall within the acceptable threshold range. The Committee is asked to come to a value judgment on whether the magnitude of additional weight, that would need to be assigned to the original QALY benefits in the patient group for the cost effectiveness of the drug to fall within the current threshold range, would be acceptable in light of the evidence presented.
The James Whale Fund for Kidney Cancer	(Patient quote)"Our drugs will always be more expensive as there are far fewer of us and pharmaceutical companies have to recoup R & D costs. Drugs must cost the same to get a license whether they are prescribed to 1000 rarer cancer patients or 40,000 patients."	Comment noted. The Committee's judgements on cost effectiveness are not influenced by the prevalence of a condition. See Guide to the Methods of Technology Appraisal section 6.2.18 (Available from URL

Consultee	Comment	Response
		http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
The James Whale Fund for Kidney Cancer	(patient quote) "Everolimus is cost effective – it works, it does what it says on the tin. I know what it is worth because I'm taking the drug."	Comment noted. The Committee noted that there is an unmet clinical need and that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5).
The James Whale Fund for Kidney Cancer	(patient quote) "N I C E is just rationing treatments based on money, but rarer cancer patients obviously are still coming off worse".	Comment noted. See response above, in addition, the Committee's judgements on cost effectiveness are not influenced by the prevalence of a condition. See Guide to the Methods of Technology Appraisal section 6.2.18 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
The James Whale Fund for Kidney Cancer	***Whether we consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS.*** The general feeling from the kidney cancer community is that they are passionate defenders of the NHS and the principle of universal care, but do not understand why a committee set up to appraise cancer drugs would do so without a leading Oncologist on	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submission and the ERG report. The Committee noted that everolimus was likely to be

Consultee	Comment	Response
	the panel and without the added value and experience of a cancer patient. To exclude both viewpoints from membership of the Appraisal committee in favor of multiple commissioning and health economics input seems perverse.	clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of everolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that everolimus would not be a cost-effective uses of NHS resources.
The James Whale Fund for Kidney Cancer	(patient quote) "Rarer cancer patients are discriminated against & feel disenfranchised by the N I C E process"	Comment noted. The Committee's judgements on cost effectiveness are not influenced by the prevalence of a condition. See Guide to the Methods of Technology Appraisal section 6.2.18 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
The James Whale Fund for Kidney Cancer	patient quote) "Kidney cancer patients have paid into the NHS ; I've paid a lifetime of taxes - we have paid into the system now all we want is to have treatment options like other cancer patients"	Comment noted. In developing clinical guidance for the NHS, no priority should be given based on individuals' income, social class or position in life and individuals' social roles, at different ages, when considering cost effectiveness (SVJ principle 8).
The James Whale Fund for Kidney Cancer	(patient quote) "This QALY figure is arbitrary, it is out of date and based on goodness knows what? Was it guesswork?"	Comment noted The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-

Consultee	Comment	Response
		adjusted life year. See Guide to the Methods of Technology Appraisal section 5.2.11 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
The James Whale Fund for Kidney Cancer	The James Whale Fund for Kidney Cancer ask the Appraisal Committee to take account of the following general points from the perspective of the hundreds of kidney cancer patients who will be affected by their ultimate decision. We feel the principle of cost effectiveness is applied randomly – N I C E asserts it is the guardian of NHS resources by applying clinical effective evidence in a rigorous manner. It tells us that NHS funded treatments must be evidence –based. Despite this assertion cancer patients know there is striking evidence this principle is not consistant across the NHS. It is difficult for kidney cancer patients to reconcile the control N I C E exerts over clinically effective and proven cancer drugs and yet fails to apply to other NHS funded treatments – 1. Homeopathy, which is available on the NHS at huge cost and yet is unproven and felt by many to be no better than placebo. 2. Acupuncture, which is available on the NHS with very little peer reviewed evidence. 3. Alternative medicines available on the NHS and not subject to NICE scrutiny. 4. The swine flu panic now agreed to have led to the waste of huge NHS resources 5. The winter flu jab for the over 65's, now seen as failing to deliver measurable benefit. These examples are proof to patients the NHS is not consistent and N I C E is a questionable guardian of precious NHS resources and yet N I C E persist in denying treatments to fulfil an unmet clinical need for a 2nd line treatment for terminally ill kidney cancer patients.	Comments noted. The Committee does not consider the affordability that is costs alone, of new technologies but rather their cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, paragraphs 6.2.6.1 – 6.2.6.3).

Consultee	Comment	Response
The James Whale Fund for Kidney Cancer	Patients tell us they are actively encouraged to enter clinical trials for new cancer drugs. They do so for a number of reasons; it may be the only route to active treatment, they feel they are "doing a good thing" helping to further medical knowledge and they feel their involvement may help future generations of cancer patients. Each time that N I C E deny access to effective drugs, the effect on those patients who took part on the clinical trials is immediate and diminishes their contribution; they feel let down and some feel hoodwinked. Their hopes of enabling effective treatment to be used to help other cancer patients are dashed. The knock on effect for further research and trials in the UK must be recognized as must the effect on patients whose hopes are raised when they hear first hand in their Clinics, about good results and evidence, but then discover N I C E will not allow these new compounds to be funded by the NHS.	Comment noted
The James Whale Fund for Kidney Cancer	We urge the committee on the 9th March to acknowledge the value of the patient experience, we have asked that our expert patient [redacted] should be available for your committee to talk to about the points we have raised in our submission and we would like your agreement to that request. In conclusion we will share with your committee the words of a stage 4 kidney cancer patient who, until disease progression 3 months ago, was taking a kidney cancer drug refused by N I C E, a cancer drug that has given him 3 years of extra life - not a few weeks as we hear quoted in the media, but 3 years during which time he has continued to work and play a full role in his family ***"Being told you have terminal kidney cancer is not the worst thing in the world to happen to you – far worse is knowing there are proven drugs that can help you, but you can't have them."*** Patients in this situation now need sequential 2nd line treatment: who is going to sit this patient down and say to him…… ***"It has become too expensive for us to keep you alive."***	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submission and the ERG report. The Committee noted that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of everolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that everolimus would not be a cost-effective uses of NHS resources.

Consultee	Comment	Response
The James Whale Fund for Kidney Cancer	**Are there any equality related issues that need special consideration that are not covered in the ACD?** Do kidney cancer patients just have the "wrong type of cancer" Patients are dying prematurely because they simply have the bad luck to have been diagnosed with a rare cancer, through no fault of their own. Nothing will change until the NHS accepts that rarer cancer patients need a separate process of appraisal. A one size HTA does not fit all.	Comment noted. The Committee's judgements on cost effectiveness are not influenced by the prevalence of a condition. See Guide to the Methods of Technology Appraisal section 6.2.18 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
The James Whale Fund for Kidney Cancer	patient quote) "Everolimus is available in other EU countries as 2nd line treatment for mRCC, why not in Great Britain?"	Comment noted. The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturer's submission and the ERG report.
The James Whale Fund for Kidney Cancer	(patient quote) "KC patients have limited treatment options unlike more common cancers (chemotherapy & radiotherapy do not work for kidney cancer) Why can't similar amounts of money that other cancer patients have access to for their treatments be given to us to help pay for drugs we need. If patients with rarer cancers can't get treatment because they are in a minority surely this is a form of discrimination."	Comment noted. The Committee's judgements on cost effectiveness are not influenced by the prevalence of a condition. See Guide to the Methods of Technology Appraisal section 6.2.18 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
The James Whale Fund for Kidney	(patient quote) "The majority of KC patients are aged 60+; not everyone has access to computers and NICE website is awful, it is not user friendly, it puts you off before you start; how we are expected to appeal properly. We only have 20 days to appeal against	Comment noted

Consultee	Comment	Response
Cancer	refusal for our drugs and yet this was referred to NICE in November 2008. The NHS and the N I C E Quango take as much time & money as they want to get their arguments marshalled, but again we get no help, no resources at all to put our case forward."	
The James Whale Fund for Kidney Cancer	(patient quote) "The Human Rights Act, article two, gives every human being THE RIGHT TO LIFE, denial of a proven clinically effective treatment which gives an individual that right cannot therefore be legal under the convention."	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. The Committee concluded that everolimus fulfilled the end-of-life criteria and considered it as such.
Kidney Cancer UK	**Do you consider that all of the relevant evidence has been taken into account?** Not in our view. Evidence on patient benefits has scarcely been considered in the ACD, compared with the enormous amount of space devoted to discussion of the evidence on costs. In our view the central measure of a QALY is a woefully inadequate measure of patient benefit, calibrated as it is on the basis of a number of truly heroic assumptions. Patient benefit encompasses far more than a QALY.	The patient perspective was acknowledged by the Committee. See FAD sections 4.1, 4.2 and 4.3. The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the Methods of Technology Appraisal section 5.2.11

Consultee	Comment	Response
		(Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
Kidney Cancer UK	A more academically respectable approach to the evaluation would have involved calculation of net present values [NPVs] in a full-blown cost-benefit analysis. Admittedly, NPV calculations would be much more difficult to make, given that they would require direct valuation of patient benefits. But in this-as in everything else-there is more to be said for *rough* estimates of the *precise* concept than for *precise* estimates of some *rough* concept. An incremental cost effectiveness ratio [ICER] per QALY is a pretty rough concept; and sometimes it is, solemnly, and most precisely, given down to the last £1**.**	Comment noted. The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the Methods of Technology Appraisal section 5.2.11 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf
Kidney Cancer UK	**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?** Not in our view The summaries rest very heavily on certain assumptions regarding how long patients can survive solely on best supportive care after treatment with Sunitinib has failed. PenTAG's ICER per QALY of £75,000 is associated with a mean survival of 11 months in the best-supportive- care arm. But there are reasons to believe that 11 months is an unrealistic estimate of survival on best supportive care. For instance, in a paper by Di Lorenzo et alia published in *The Journal of Clinical Oncology* [10.1200/JCO, 2009, August] it is shown that patients failing on Sunitinib and then going on to receive Sorafenib as second-line treatment lived for a median period of just 32 weeks [or a little less than 7.4 months]. It seems inconceivable that patients on best supportive care would survive longer than patients receiving an active drug.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submission, revised cost-effectiveness estimates submitted in response to the appraisal consultation document and corresponding ERG reports. It also carefully considered the comments received from consultees and commentators in response to the Appraisal Consultation Document. The Committee noted that the overall survival associated with best supportive care in the ERG analysis

Consultee	Comment	Response
		(10.8 months) was likely to be higher than in clinical practice. The Committee noted the difference in overall survival between treatment arms was 8.2 months in the manufacturer's revised RPSFT analysis and 5.9 months in the ERG's revised RPSFT analysis. It noted evidence from the manufacturer and the clinical specialists that an increase in overall survival of 1.4 months per month of increased progression-free survival would be considered plausible. Therefore, the Committee agreed that the incremental overall survival derived using the manufacturer's revised RPSFT analyses was almost twice as much as would be expected, given that the trial had observed an increase of 3 months in progression-free survival. The Committee accepted that the ERG's estimate of the incremental difference in overall survival for everolimus versus best supportive care (5.9 months) was more plausible than that derived by the manufacturer and was based on all the available data. See FAD section 4.10

Consultee	Comment	Response
Kidney Cancer UK	A further piece of evidence is found in a study by Z. Liu et alia presented at the Joint 15th Congress of the European CanCer Organisation [ECCO] and 34th Congress of the European Society for Medical Oncology [ESMO] Berlin, 20-24 September 2009. In this study, the median overall survival for patients who received no active treatment after Sunitinib is found to be only 5.2 months.	See above response.
Kidney Cancer UK	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** Not in our view We feel that, on more realistic assumptions regarding relative survival, the ICER per QALY for Everolimus would come down to around the same level as that at which Sunitinib was approved for NHS funding, namely £54,000. We note that it is accepted that, like Sunitinib, Everolimus is deemed eligible to be designated as an end-of-life medicine. Accordingly, we suggest that the final decision on Everolimus be aligned with that on Sunitinib.	The supplementary advice does not suggest for Committee to apply a particular weight for the cost effectiveness estimate to fall within the acceptable threshold range. The Committee is asked to come to a value judgment on whether the magnitude of additional weight, that would need to be assigned to the original QALY benefits in the patient group for the cost effectiveness of the drug to fall within the current threshold range, would be acceptable in light of the evidence presented.
Royal College of Nursing	**Do you consider that all of the relevant evidence has been taken into account?** We are unaware of any evidence that has not been included in this technology appraisal	Comment noted. No action required.
Royal College of Nursing	**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?** We agree with the interpretations of the clinical evidence. We do not have enough expertise to comment on cost- effectiveness and the methodology used.	Comment noted. No action required.

Consultee	Comment	Response
Royal College of Nursing	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** It is regretful that the preliminary recommendations contained in the document, mean that a second line treatment would not be available to patients but note that these recommendations are in line with the previous technology appraisal of Sorafenib.	Comment noted. No action required.
Royal College of Nursing	**Are there any equality related issues that need special consideration that are not covered in the ACD?** We are not aware of any equality related issues that need special consideration which have not been covered in the ACD.	Comment noted. No action required.
Royal College of Physicians	I write on behalf of the NCRI/RCP/RCR/ACP/JCCO with relation to this ACD consultation. We are grateful for the opportunity to respond and would like to make the following comments. Our thanks go to our clinical expert nominee, [redacted] for coordinating the response. We are disappointed with the ACD decision not to fund everolimus for second line treatment of patients with metastatic renal cancer, after failure of sunitinib therapy. The evidence review group agreed that everolimus has been shown to be clinically effective, increasing survival by 3 months, and meets the end-of-life criteria for drug funding. However, they have declined funding for this small group of patients purely on the basis of cost. Health economic analyses are sensitive to small changes in inputted data and there is often disagreement, even amongst the experts, about interpretation of the results.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submission and the ERG report. The Committee noted that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of everolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that everolimus would not be a cost-effective uses of NHS resources.

Consultee	Comment	Response
Royal College of Physicians	We are concerned that the committee have misunderstood the prognosis for this group of patients. Section 4.15 quotes 'life expectancy for people with advanced RCC receiving best supportive care alone was unlikely to be greater than 24 months and was potentially as low as 6 months'; this range is actually for patients receiving first line sunitinib. For patients who fail sunitinib, the likely survival without further active treatment is only in the region of 4 or 5 months (expert opinion). It is important that the committee reconsider their decision in the light of this misunderstanding.	Comment noted. This has been amended in the FAD. See section 4.15.
Royal College of Physicians	It is also important to note that the results of the RECORD-1 clinical trial. Patients in both arms of the study received further lines of therapy after everolimus, resulting in a median overall survival of 13 months. This would not of course be the case for the British public with advanced renal cancer. They will be able to receive sunitinib (now NICE approved) but no further treatment if this ACD is ratified in the Final Appraisal Determination.	Comment noted. The Committee understood that there had been crossover after disease progression and that statistical techniques to control for this crossover were necessary. See FAD section 4.6. The Committee noted that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of everolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that everolimus would not be a cost-effective uses of NHS resources.
Expert 1	The rejection of Everolimus in the context of NICE's rejection of avastin, nexavar and torisel means that oncologists have only 1 drug –sutent –to treat advanced RCC in the first line and no second line treatments with the exception of old discredited drugs such as interleukin or interferon. This situation means that patients are denied modern drugs	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments

Consultee	Comment	Response
	which prolong life simply on cost grounds. This is neither moral nor just.	which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. The Committee concluded that everolimus fulfilled the end-of-life criteria and considered it as such.
Expert 1	Everolimus fits the EOL criteria –short like expectancy, 3 months plus life extension, ICER over £30k per annum, no available alternatives-. I can see no evidence that NICE have taken these criteria into account . They were designed specifically to cope with the problems encountered by very expensive life prolonging drugs and yet they have been ignored.	Comments noted. The Committee took in to account the end of life criteria in reaching its decision. See FAD sections 4.14 and 4.15
Expert 1	RCC patients are being discriminated against by the nature of the QALY which turns a cost of £ 30000 into a fantastic figure of over £ 70000 per annum. The application of the current rule set and methodology means that it is almost certain that all modern new drugs for RCC will be rejected leaving England in a situation where these life extending drugs are denied whereas they are widely available across Europe and the USA	Comment noted. The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the Methods of Technology Appraisal section 5.2.11 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
Expert 1	There is no doubt that Everolimus is clinically effective in extending life. RCC is a lethal disease with very poor outcomes. NICE has placed patients in a situation where life extending drugs have been denied on the grounds of cost and cost alone but a cost	Comment noted. The Committee agreed that everolimus was likely to be clinically effective. However, for

Consultee	Comment	Response
	based on the strange world of the QALY which no patient or carer can understand and is unrecognisable in the real world. Patients deserve transparency and not to be at the mercy of cold blooded health economics.	both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of everolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that everolimus would not be a cost-effective uses of NHS resources.
Novartis	Everolimus is licensed for the treatment of patients with advanced renal cell carcinoma (aRCC), whose disease has progressed on or after treatment with VEGF-targeted therapy. The only current NICE approved therapy for 1st-line treatment of aRCC is the VEGF-targeted therapy sunitinib. Therefore in the absence of everolimus there are no other effective treatment options available for UK patients via the NHS.	Comment noted. The Committee heard from clinical specialists and patient experts that there are limited treatment options for people with advanced RCC. See FAD section 4.2
Novartis	The preliminary decision to not recommend everolimus is based on the estimates of cost-effectiveness presented by PenTAG. It was felt that Novartis had under-estimated overall survival (OS) in the best supportive care (BSC) arm using both modelling approaches presented. In order to correct for this perceived underestimation of OS in the BSC arm in the Novartis models, PenTAG made various adjustments which resulted in incremental cost-effectiveness ratios (ICERs) of £65,200 and £75,700 (IPCW and RPSFT methods respectively). However, as the difference in OS between everolimus and BSC is one of the biggest influences on the resulting incremental cost-effectiveness ratio (ICER) it is important that the estimates of OS in the BSC arm are realistic and justified based on the available evidence.	Comment noted. The Committee noted that the overall survival associated with best supportive care in the ERG analysis (10.8 months) was likely to be higher than in clinical practice. The Committee noted that the difference in overall survival between treatment arms was 8.2 months in the manufacturer's revised RPSFT analysis and 5.9 months in the ERG's revised RPSFT analysis. It noted evidence from the manufacturer and the clinical specialists that an increase in overall survival of 1.4 months per month of increased progression-free survival would be

Consultee	Comment	Response
		considered plausible. Therefore, the Committee agreed that the incremental overall survival derived using the manufacturer's revised RPSFT analyses was almost twice as much as would be expected, given that the trial had observed an increase of 3 months in progression-free survival. The Committee accepted that the ERG's estimate of the incremental difference in overall survival for everolimus versus best supportive care (5.9 months) was more plausible than that derived by the manufacturer and was based on all the available data. See FAD section 4.10
Novartis	Critically, it is noted that the ICER of £75,700 presented by PenTAG is based on an OS in the BSC arm of 10.9 months (discounted). Novartis strongly believe a mean OS of 10.9 months is not reflective of clinical outcomes in patients who fail 1st-line sunitinib therapy and then receive only BSC in the 2nd-line setting. As with any modelling if the results are not reflective of clinical reality then the resulting ICERs need to be challenged.	Comment noted. See above response.
Novartis	In the original submission Novartis presented an economic analysis based on the Inverse Probability Censoring Weights (IPCW) statistical approach using the February 2008 data cut of the pivotal, phase III, everolimus, RECORD-1 trial. In response to comments in the ERG Report that a rank preserving structural failure time (RPSFT) statistical approach might be preferable, Novartis undertook to conduct the RPSFT analysis, based on the November 2008 data cut, and presented the results within a two week timeframe. This was conducted in the hope of providing a more comprehensive evidence base to inform the Appraisal Committee and thus facilitate a faster decision. Both the IPCW and RPSFT economic analyses presented by Novartis were subsequently adjusted by PenTAG to	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submission, revised cost-effectiveness estimates submitted in response to the appraisal consultation document and corresponding ERG reports. It also

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	allow for a perceived underestimation of survival in the BSC arm of the economic model. However, based on an additional body of evidence described below, including the views of national and international clinical experts experienced in treating aRCC, the PenTAG adjustment to the RPSFT analysis giving a cost/QALY of £75,700 is not clinically plausible as it relies on an estimate of mean survival in the BSC arm of 10.9 months (11.2 months undiscounted). Moreover we have been able to show by statistical means that the PenTAG suggested correction to the IPCW model results in an overall, effective hazard ratio of 0.6 rather than the intended HR of 0.55. This means that survival in the BSC arm is over-estimated thus inflating the ICER. In order to provide the Appraisal Committee with the most plausible and robust estimates of cost-effectiveness we have updated both of our analyses (IPCW and RPSFT) to take into account PenTAG's criticisms and incorporate the longest term clinical data from the RECORD-1 trial ie data from the November 2008 analysis. This has resulted in revised estimates of cost-effectiveness of £49,537/QALY (RPSFT) and £52,648/QALY (IPCW). The underlying estimates of mean overall survival in the BSC arm are 7.9 months and 9.6 months respectively (discounted values).	carefully considered the comments received from consultees and commentators in response to the Appraisal Consultation Document.
Novartis	Based on the evidence that we have compiled since the ACD was issued, the latter estimates of survival are more plausible, than the estimates presented by PenTAG. These updated incremental cost-effectiveness ratios are lower than those previously presented due to the greater survival demonstrated in the longer term November 2008 analysis and the addition of further cycles in the model to capture the additional benefit. The original model was developed for the February 2008 data cut and therefore only required 18 cycles to capture the available data. However, as stated in our submission of the RPSFT analysis, due to the fact that the November 2008 data-cut suggests greater survival than the February 2008 data-cut, there are more everolimus patients still alive in the final cycle (cycle 18) of the original economic model. Unfortunately, there was insufficient time to add further cycles to the model to account for this when we submitted the RPSFT analysis (due to the 2 week turnaround required) but we have now been able to update the model in order that all of the benefits of everolimus can be reflected in the economic analysis [39 cycles are required to fully account for the additional survival]. The overall impact of allowing this greater survival to be taken into account in the model has	The Committee discussed the manufacturer's revised cost-effectiveness estimates submitted in response to the appraisal consultation document. The Committee noted that the updated cost-effectiveness estimates incorporated more recent data from the RECORD-1 trial. Therefore it accepted the extension of the time horizon of the model from 144 weeks (18 cycles) to 312 weeks (39 cycles). See FAD sections 3.24 and 4.12

Consultee	Comment	Response
	been to reduce the ICER. This is because there is greater survival and therefore QALY's in the everolimus arm but no further everolimus treatment costs as these are only applicable for the stable disease states. Full details of these updated analyses follow in the remainder of the document. The results from the PenTAG, RPSFT adjusted analysis and updated Novartis analyses are provided in the following table for ease of comparison. Table – not included here.	
Novartis	All of the results presented in the above table take into account the patient access scheme (PAS) which was put in place by agreement between Novartis and the DoH, prior to our submission in order to facilitate a positive decision as soon as possible. As this scheme has been approved by the DoH, and is already being implemented by the NHS, the results which incorporate the PAS are the appropriate ones to be considered.	The Committee understood that the cost effectiveness estimates included a patient access scheme which had been agreed with the Department of Health. See FAD Section 4.11
Novartis	The following section summarises an additional body of clinical evidence in order to help the Appraisal Committee decide what constitutes the most plausible estimate of survival in patients receiving BSC following sunitinib failure. The evidence supplied includes the most recent, relevant publications and a survey reflecting UK clinical expert opinion. It should be noted that the reason for conducting the survey was not revealed to the respondents. Finally, because of the lack of directly applicable publications in this area Novartis also requested, and was provided with, primary patient data from clinicians with experience of 1st line sunitinib use to demonstrate what happens to patient's with no 2nd line treatment. Although retrospective in nature, this crucially provides actual UK clinical data from two large London teaching hospitals, The Queen Elizabeth hospital in Birmingham and from two hospital's in the Royal Wolverhampton NHS trust to demonstrate OS in routine clinical practice for patients that received sunitinib therapy and no active 2nd-line therapy following sunitinib failure. A table comparing OS in patients failing on 2nd-line sunitinib is presented below. Table – not included here.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submission, revised cost-effectiveness estimates submitted in response to the appraisal consultation document and corresponding ERG reports. It also carefully considered the comments received from consultees and commentators in response to the Appraisal Consultation Document. The Committee noted that the overall survival associated with best supportive care in the ERG analysis (10.8 months) was likely to be higher

Consultee	Comment	Response
		than in clinical practice. The Committee noted that the difference in overall survival between treatment arms was 8.2 months in the manufacturer's revised RPSFT analysis and 5.9 months in the ERG's revised RPSFT analysis. It noted evidence from the manufacturer and the clinical specialists that an increase in overall survival of 1.4 months per month of increased progression-free survival would be considered plausible. Therefore, the Committee agreed that the incremental overall survival derived using the manufacturer's revised RPSFT analyses was almost twice as much as would be expected, given that the trial had observed an increase of 3 months in progression-free survival. The Committee accepted that the ERG's estimate of the incremental difference in overall survival for everolimus versus best supportive care (5.9 months) was more plausible than that derived by the manufacturer and it was based on all the available data. See FAD section 4.10
Novartis	Because of the lack of prospective clinical data Novartis approached 4 institutions to ask if they were able to provide data to us for the purpose of verifying in UK clinical practice what the OS was for patients who received 1st line sunitinib and then no further anti-	Comments noted. See detailed response above.

Consultee	Comment	Response
	cancer therapy. St Bartholemew's hospital in central London has had gained a lot of experience with sunitinib because of its involvement with the Pfizer expanded access programme and other sunitinib clinical trials. Data from clinical practice which included patients from 2006 to present showed that the median time from CT defined progression to death is 5 months (95% CI 3-7 months). No patient received targeted therapy in the 2nd-line, however some did receive chemotherapy. Patients were excluded from the analyses if they stopped treatment before assessment of disease progression occurred, if they stopped due to toxicity or died on sunitinib or were not assessable for disease progression. It was also noted by the clinician that "most patients continued on sunitinib" even though disease progressed according to RECIST criteria. Novartis feel this is likely to be because of the maintenance of clinical benefit even when disease is progressing according to RECIST criteria.	
Novartis	Novartis would also like to highlight to the Appraisal Committee that patients may have continued to receive sunitinib post-progression due to the lack of alternative active treatment options, especially where the patient maintained performance status, and there was the perception of clinical benefit for the patient and/or clinician beyond RECIST criteria measures.	Comment noted. See detailed response above.
Novartis	The Royal Marsden hospital in South West London also provided retrospective data to Novartis as a result of their long term access to sunitinib through clinical trials and the Pfizer expanded access programs. The data included a total of 87 patients with advanced RCC starting sunitinib at the Royal Marsden Hospital between 2005 and December 2008 that had progressed after an adequate period of treatment and died (not including patients who died on sunitinib treatment or stopped due to toxicity). For the 62 patients who received no 2nd-line therapy the median time to death from stopping sunitinib treatment was 64.5 days (2.12 months). Again considerably shorter than the average 10.9 months OS suggested by the PenTAG model (discounted).	Comment noted. See detailed response above.
Novartis	In addition to this The Queen Elizabeth hospital, Birmingham, provided us with audit data for aRCC patients treated with sunitinib and no further treatment. Due to the centres involvement with sunitinib clinical trials and the expanded access program experience	Comment noted. See detailed response above.

Consultee	Comment	Response
	dated back to 2006 and included patients right up to the present time there was data for 94 patients. For these patient's the median OS was found to be 3.8 months. This data does include patients not yet dead although as there are 23 patients, if these patients are excluded the median overall survival would be much lower.	
Novartis	A clinician with experience of sunitinib use from two hospitals that are part of the Royal Wolverhampton NHS Trust provided data for 8 patients started between 03/2007 and 05/2009. Here the median OS from stopping treatment to death is 2.6 months (2 patients have stopped treatment but remain alive so are not part of this calculation). Patients were not part of the audit if they were taken off treatment due to toxicity or death.	Comment noted. See detailed response above.
Novartis	Finally, Novartis undertook a quantitative on-line survey of clinicians experienced in treating advanced RCC in the UK. No information was provided to respondents about the reason for the survey or who was sponsoring it. Thirty seven clinicians responded to the questionnaire, of these, 26 were consultant grade and 11 were specialist registrars (year 5+) and 34 of the 37 responders were from either teaching hospitals or tertial centres. On average the clinicians treated 33 aRCC patients a year. As Novartis have previously submitted to NICE an estimated eligible patient pool of 982 we believe this covers most of the aRCC population. Novartis feels the sample represents clinicians sufficiently experienced in the treatment of the disease and likely to be involved in prescribing these drugs. The survey results showed clinicians expected the mean OS after failure on sunitinib with no further active treatment to be 6.1 months (6 months median). 57% of clinicians anticipated the range would be between 6-9 months and only 8% of those surveyed believed OS would be 10-12 months.	Comment noted. See detailed response above.
Novartis	There is no published evidence directly in line with the decision problem ie patients who receive BSC only following failure on sunitinib therapy. However, the publication by Di Lorenzo *et al*. 2009, is informative with regards to OS for 2nd- line patients following sunitinib. The study evaluated the efficacy of sorafenib following failure on sunitinib. The median OS for these patients was 7.4 months.[i] In many respects the patients in this study were reflective of those in the everolimus study (RECORD-1) but patients on the Di Lorenzo study could be considered as having a slightly better prognosis based on the	Comment noted. See detailed response above.

Consultee	Comment	Response
	fact patients in this study generally had better MSKCC profiles which included better performance status and lower rates of metastatic disease in organs such as the liver, lungs and lymph nodes.[i,vi] Considering the fact that these patients were on active anti-tumour therapy and the patients generally had superior prognostic scores, the median OS of 7.4 months might be expected to be a best case scenario or even superior compared to patients who get BSC only following sunitinib.[i]	
Novartis	Finally, Liu *et al*. presented a poster at European CanCer Organisation/European Society for Medical Oncology (ECCO/ESMO) in September 2009 which retrospectively evaluated patients survival following discontinuation of sunitinib or sorefenib in aRCC patients from routine clinical practice. The median OS results in this study for patients who only received sunitinib was 5.2 months.[ii]	Comment noted. See above response
Novartis	In summary, the preliminary recommendations are based on estimates of cost-effectiveness resulting from PenTAG's adjustments to the Novartis analyses i.e £75,700 and £65,200. However, these estimates are misleading and are unlikely to represent the true value of everolimus. This is because the estimate of £75,700 relies on an estimate of survival in the BSC arm which is unrealistic based on the evidence which has been collated since the Appraisal Committee meeting on the 13th January. In addition, the £65,200 is based on an earlier data cut from the RECORD-1 trial and does not reflect the intended overall, effective mortality HR of 0.55. It is important that the final decision regarding the use of everolimus for aRCC patients should rely on estimates of cost-effectiveness that are based on assumptions of OS in BSC patients that are realistic and consistent with the best available clinical evidence.	Comment noted.
Novartis	We therefore respectfully request that due consideration is given to the additional evidence and revised estimates of cost-effectiveness which take into account all of PenTAG's criticisms, as well as the longer term data available from the RECORD-1 trial. These results demonstrate that everolimus is clinically-effective and based on the end of life criteria, a cost-effective treatment for patients with aRCC who fail on 1st-line sunitinib therapy.	The Committee discussed the manufacturer's revised cost-effectiveness estimates submitted in response to the appraisal consultation document. The Committee noted that the updated cost-effectiveness estimates incorporated more recent data from the RECORD-1 trial.

Consultee	Comment	Response
		Therefore it accepted the extension of the time horizon of the model from 144 weeks (18 cycles) to 312 weeks (39 cycles). See FAD sections 3.24 and 4.12
Novartis	**Detailed Response to Matters Arising from the Appraisal Consultation Document** The preliminary decision not to recommend everolimus is based on the estimates of cost-effectiveness presented by PenTAG. This is because it was felt that Novartis had underestimated OS in the BSC arm using both modelling approaches presented. Based on the information that we have compiled from the published literature, data from routine clinical practice and clinical expert opinion, Novartis strongly believe that the preliminary recommendation is not justified. Therefore based on the above, we do not believe that the provisional recommendations of the Appraisal Committee are sound nor do they constitute a suitable basis for the preparation of guidance to the NHS.	Comment noted.
Novartis Novartis	Section A – Main concern **A1. the preliminary recommendations are based on estimates of cost-effectiveness resulting from PenTAG's adjustments to Novartis' analyses i.e £75,700 and £65,200. However, these estimates are misleading and are unlikely to represent the true value of everolimus. The reasons for this are as follows:** **- the estimate of £75,700 from PenTAG's "exploratory analysis" using RPSFT is underpinned by a clinically unrealistic estimate of OS in the BSC arm of 10.9 months (11.2 months undiscounted). This estimate is therefore unlikely to either represent the most plausible estimate of cost-effectiveness, or reflect the true magnitude of survival benefit conferred by everolimus**	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submission, revised cost-effectiveness estimates submitted in response to the appraisal consultation document and corresponding ERG reports. It also carefully considered the comments received from consultees and commentators in response to the Appraisal Consultation Document.

Consultee	Comment	Response
		The Committee noted that the overall survival associated with best supportive care in the ERG analysis (10.8 months) was likely to be higher than in clinical practice. The Committee noted that the difference in overall survival between treatment arms was 8.2 months in the manufacturer's revised RPSFT analysis and 5.9 months in the ERG's revised RPSFT analysis. It noted evidence from the manufacturer and the clinical specialists that an increase in overall survival of 1.4 months per month of increased progression-free survival would be considered plausible. Therefore, the Committee agreed that the incremental overall survival derived using the manufacturer's revised RPSFT analyses was almost twice as much as would be expected, given that the trial had observed an increase of 3 months in progression-free survival. The Committee accepted that the ERG's estimate of the incremental difference in overall survival for everolimus versus best supportive care (5.9 months) was more plausible than that derived by the manufacturer and it was based on all available data.

Consultee	Comment	Response
		See FAD section 4.10
Novartis	**- we have been able to show by statistical means that PenTAG's adjustment to the IPCW analysis results in an overall effective HR of 0.6 rather than 0.55. Therefore the estimate of cost-effectiveness of £65,200 is artificially inflated and should not be used as the basis for decision-making. In addition, this estimate is based on the less mature, February 2008 data cut, from the RECORD-1 trial.**	Comment noted.
Novartis	**B. The current recommendations do not take into account all of the available evidence. In addition, the provisional recommendations as detailed in the ACD are not justified, nor do they constitute a reliable basis for the provision of sound guidance to the NHS.**	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submission, revised cost-effectiveness estimates submitted in response to the appraisal consultation document and corresponding ERG reports. It also carefully considered the comments received from consultees and commentators in response to the Appraisal Consultation Document.
Novartis	**B1. The preliminary decision is based on the conclusion that PenTAG's estimates of cost-effectiveness are more plausible than those presented by Novartis. However, the survival estimate for BSC of 11.2 months (undiscounted) which underpins PenTAG's cost/QALY of around £75,700 is not deemed to be clinically plausible based on the available evidence.**	The Committee noted that the overall survival associated with best supportive care in the ERG analysis (10.8 months) was likely to be higher than in clinical practice. The Committee noted that the difference in overall survival between treatment arms was 8.2 months in the manufacturer's revised RPSFT analysis and 5.9 months in the ERG's

Consultee	Comment	Response
		revised RPSFT analysis. It noted evidence from the manufacturer and the clinical specialists that an increase in overall survival of 1.4 months per month of increased progression-free survival would be considered plausible. Therefore, the Committee agreed that the incremental overall survival derived using the manufacturer's revised RPSFT analyses was almost twice as much as would be expected, given that the trial had observed an increase of 3 months in progression-free survival. The Committee accepted that the ERG's estimate of the incremental difference in overall survival for everolimus versus best supportive care (5.9 months) was more plausible than that derived by the manufacturer and was based on all available data. See FAD section 4.10
Novartis	B1. i) A paper by Di Lorenzo *et al.* 2009 reports on a study which evaluated the efficacy of sorafenib, in patients who failed sunitinib therapy.[i] These patients were receiving active treatment for their disease as well as being well matched to the RECORD-1 patients with respect to baseline characteristics and, where there were differences, these favoured the sorafenib patients ie the prognostic risk factors such as MSKCC profile, performance status and rates of metastases in liver, lungs and lymph nodes were such that one might expect the patients in the sorafenib study to live longer than those in the RECORD-1 study. This means that survival in the sorafenib patients might be a reasonable and conservative proxy for the BSC patients in the RECORD-1 study.[i,iv] The results from the	Comment noted. See above response

Consultee	Comment	Response
	Di Lorenzo study demonstrated that the median survival in the sorafenib patients was 7.4 months. This is broadly consistent with the estimate of survival from the Novartis RPSFT analysis which estimates a mean survival in BSC patients of 7.9 months, (8.1 months undiscounted).[i]	
Novartis	B1. ii) A poster by Liu *et al.* presented at the European CanCer Organisation/European Society for Medical Oncology (ECCO/ESMO) in September 2009, evaluated survival rates following discontinuation of sunitinib and sorafenib in aRCC patients in routine clinical practice.[ii] This study involved a retrospective review of data from a US claims database on patients with aRCC. Patients were included in the study if they received sunitinib only, sorafenib only or both treatments and then discontinued treatment with no further active therapy. Survival was estimated as time from discontinuation of sunitinib or sorafenib to death. Of the 451 patients identified, 264 patients discontinued treatment and did not restart therapy. Of these 131/264 patients had received sunitinib, 70/264 patients had received sorafenib and 63/264 had received both sunitinib and sorafenib. The median survival in patients who received sunitinib only was 5.2 months.[ii]	Comment noted.
Novartis	B1. iii) As presented in our submission evidence from the literature suggests that, if left untreated, patients with advanced renal cell carcinoma (aRCC) have a limited life expectancy, with a median survival without treatment of 6 to 12 in the first-line setting.[iii,iv,v,] Data from the years prior to VEGF targeted therapy clearly demonstrate that patient's given hormone treatment (medroxyprogesterone) aimed at symptom relief only have a median OS of 6 months.[vii]	Comment noted. See responses above.
Novartis	There is no direct data published to inform the Appraisal Committee on a patient's OS after TKI therapy if they receive no further active therapy i.e. BSC only 2nd-line. This is mostly because cross over from placebo to active treatment upon progression remained high in trials with targeted agents or because information on PFS is not provided.	Comment noted. See response above.
Novartis	However, patients who are eligible for everolimus will be more advanced with respect to time from diagnosis of aRCC compared to those who have not already failed on at least one previous therapy.[vi] This is important because there is an increasing amount of pre-clinical evidence to suggest that disease may progress more rapidly after resistance	Comment noted. See response above.

Consultee	Comment	Response
	develops with sunitinib use,[viii] raising the possibility that once patients progress on sunitinib they will have a shorter median OS compared to patients untreated in the 1st line. There is also some limited clinical evidence to support this hypothesis in aRCC clinical practice. In a small, UK clinical study, patients were given chemotherapy after progression on sunitinib. The results of this study for patients with aRCC who had previously been progressed on cytokine therapy and then sunitinib the OS was a median of 4.2 months. [ix]	
Novartis	B1. iv) St Bartholemew's hospital in central London has gained a lot of experience with sunitinib because of its involvement with the Pfizer expanded access programme and other sunitinib clinical trials. Data from clinical practice which included patients from 2006 to current use showed that the median time from CT defined progression to death is 5 months (95% CI 3-7 months). No patient received targeted therapy in the 2nd-line however some did receive chemotherapy. Patients were excluded from the analyses if they stopped treatment due to toxicity or died on sunitinib. It was also noted by the clinician that "most patients continued on sunitinib" even though disease progressed according to RECIST criteria. Novartis feel this is likely to be because of the maintenance of clinical benefit.	Comment noted. See response above.
Novartis	Novartis would also like to highlight a point made in our initial submission that patient's may have continued on sunitinib post-progression due to the lack of alternative active treatment options where the patient remained fit and there was the perception of clinical benefit for the patient and/or clinician.	Comment noted. See response above.
Novartis	The Royal Marsden Hospital in South West London also provided retrospective data to Novartis as a result of their long term access to sunitinib through clinical trials and the Pfizer expanded access programs. The data included a total of 87 patients with advanced RCC starting sunitinib at the Royal Marsden Hospital between 2005 and December 2008 that had progressed after an adequate peroid of treatment and died (not including patients who died on sunitinib treatment or stopped due to toxicity). For the 62 patients who received no 2nd line therapy the median time to death from stopping sunitinib treatment was 64.5 days (2.12 months). Again considerably shorter than the average 10.9 months OS suggested by the PenTAG model (discounted). In addition to this The Queen Elizabeth hospital, Birmingham, provided us with audit data	Comment noted. See response above.

Consultee	Comment	Response
Novartis	for aRCC patients treated with sunitinib and no further treatment. Due to the centres involvement with sunitinib clinical trials and the expanded access program experience dated back to 2006 and included patients right up to the present time there was data for 94 patients. For these patient's the median OS was found to be 3.8 months. This data does include patients not yet dead although as there are 23 patients, if these patients are excluded the median OS would be lower.	
Novartis	A clinician with experience of sunitinib use from 2 hospitals that are part of the Royal Wolverhampton NHS Trust provided data for 8 patients started between 03/2007 and 05/2009. Here the median OS from stopping treatment to death is 2.6 months (2 patients have stopped treatment but remain alive so are not part of this calculation). Patients were not part of the audit if they were taken off treatment due to toxicity or death.	Comment noted. See response above.
Novartis	B1. v) The results from a market research survey demonstrate that 57% of the oncologists surveyed believe, that based on experience, patients live for an average of 6-9 months from discontinuation of sunitinib, if left untreated. Compared to only 8% of responders believing that OS would be 10-12.	Comment noted. See response above.
Novartis	B1 vi) Section 3.19, page 13 of the ACD referring to the Novartis RPSFT model states, "The ERG stated that the mortality risk in the best supportive care arm had been overestimated." and "The ERG conducted an exploratory analysis using revised transition probabilities for the best supportive care arm of the model." The exploratory analysis conducted by PenTAG involved ignoring the last transition probability (cycle 6), calculating a mean of the two previous cycles (cycles 4 and 5) and then applying this value from cycle 6 to cycle 18 in the model. The impact of this revision was to increase the estimated mean survival in the BSC arm from 7.7 months (undiscounted) to 11.2 months (undiscounted). As described above, the latter estimate of mean survival for BSC patients post-sunitinib is likely to be unrealistic whereas the estimate of 7.7 months presented in our original RPSFT model is more consistent with the available evidence base whilst remaining conservative.	Comment noted. The Committee accepted that the use of a Weibull distribution, which used all available data, was a more appropriate method for estimating overall survival and produced a better fit to the empirical data points. See FAD section 4.9

Consultee	Comment	Response
Novartis	In order to address PenTAG's concerns that our estimate of survival is based on a single data point we have presented an updated analysis which uses an average of the last two cycles ie the same approach as that adopted by PenTAG in their exploratory analysis. The results from this analysis give a cost/QALY for everolimus of £49,537. Full details of this updated analysis are provided in Section C1, i) below.	Comment noted. See response above.
Novartis	B1 vii) Section 3.15, page 11 of the ACD referring to the Novartis IPCW model states, "Secondly, the ERG stated that in applying the mortality hazard ratio, the manufacturer overestimated the mortality in the best supportive care arm." In order to correct for this overestimation, PenTAG applied a hazard rate multiplier to each cycle in the model, under the assumption that if each cycle HR equates to 0.55 then the overall effective HR across all cycles would also be 0.55. To evaluate whether the PenTAG adjustment actually results in the intended effect, we analysed the survival curve outputs from the economic model following application of PenTAG's adjustments using regression analysis. A virtual cohort of 20,000 patients (10,000 per arm) were run through the PenTAG adjusted economic model and the resulting survival distributions were analysed using Cox proportional hazards regression with the dependent variable being death and the independent variable being treatment assignment. Patients alive at the end of the model were censored at that point. The results from this analysis demonstrate that the impact of PenTAG's adjustment results in an effective mortality HR of around 0.60 ie mortality in the BSC is underestimated. This was confirmed by an independent health economics statistician from ScHARR, Dr Patrick FitzGerald. Consequently this means that the associated ICER of £65,200 produced by PenTAG is artificially inflated. In order to provide a more robust estimate of cost-effectiveness from the IPCW model, we have updated the analysis to include data from the November 2008 analysis. In addition, we have taken into account PenTAG's criticisms relating to overestimation of mortality in the BSC arm, applying the hazard ratio to rates rather than	Comment noted. This error was correct by the ERG in their analysis derived from the revised RPFST analysis (See FAD Section 3.24)

Consultee	Comment	Response
	the transition probabilities and applying the discounting from cycle 2 rather than year 2. In order to check that our approach to applying the 0.55 HR resulted in the desired effect we used the same statistical approach described above and calibrated the results to yield an overall effective HR of 0.55. This confirmed that the implementation of the IPCW method in the model resulted in the intended HR of 0.55. The results from this analysis give a cost/QALY of £52,648. Full details of this updated analysis are provided in Section C1, ii) below.	
Novartis	In summary, as detailed above, the conclusion that PenTAG's estimates of survival in the BSC arm and associated estimates of cost-effectiveness are the most plausible is not supported by the available evidence base nor is it consistent with the views of clinical experts who have experience of treating aRCC. In addition, we have demonstrated through statistical means that the PenTAG adjustment to the IPCW approach did not result in the intended effective mortality hazard ratio of 0.55 but resulted instead in a hazard ratio of 0.60. This means that the PenTAG adjustment underestimated mortality in the BSC arm thus providing an inflated estimate of cost-effectiveness for everolimus. For these reasons, Novartis believe the preliminary decision published in the ACD cannot be considered as sound in the light of the evidence and the draft recommendation does not represent a fair, balanced or evidence based foundation for the provision of guidance to the NHS.	Comment noted
Novartis	**C1. Updated Estimates of Cost-effectiveness** In order to provide the Appraisal Committee with the most robust and plausible estimates of cost-effectiveness we have updated both of our analyses (RPSFT and IPCW) to take into account PenTAG's criticisms and incorporate the longest term clinical data from RECORD-1 ie data from the November 2008 analysis.	Comment noted. See response below.
Novartis	C1. i) Updated RPSFT Analysis The RPSFT analysis was conducted in response to comments in the Evidence Review Group (ERG) Report that an RPSFT analysis would be preferable to the IPCW approach. Novartis therefore sought and received permission to undertake an RPSFT analysis within a two week timeframe. This initial analysis showed that results from the RPSFT approach were similar to those presented for the IPCW approach. As stated in our submission of the RPSFT results, the limited timeframe did not allow us to add further	The Committee discussed the manufacturer's and ERG's cost-effectiveness estimates derived using the RPSFT method. The Committee considered that the time horizon and discounting in the analyses were appropriate. See FAD sections 4.11

Consultee	Comment	Response
	cycles to the model to fully capture the additional survival in the RECORD-1 trial demonstrated by the November 2008 data cut as compared to the survival indicated from the earlier February 2008 analysis. In the aforementioned submission we highlighted that the impact of adding further cycles to the RPSFT model would be to decrease the incremental cost-effectiveness ratio due to the additional life years gained (LYG), and therefore QALY's, in the everolimus arm but no further everolimus treatment costs as these are only applicable for the stable disease states. In order to take into account PenTAG's criticisms of our RPSFT analysis and fully incorporate the additional survival benefits demonstrated by the November 2008 data cut the following revisions have been made: - the number of cycles in the model have been increased from 18 to 39 in order to capture the greater survival demonstrated by the November 2008 data cut; - as suggested by PenTAG, discounting at a rate of 3.5% has been applied from cycle 2; - in the BSC arm, for states leading to death, rather than carry the last transition probability forward for the remaining cycles (as in our previous model), we have calculated an average of the transition probabilities from cycles 5 (0.21) and 6 (0.5) and applied this average value (0.35) to all remaining cycles ie cycles 7 to 39. All other aspects of the model remain unchanged. The associated transition probabilities are provided in Appendix 1. The results from these revisions are presented in the table below. [not reproduced here]	and 4.12
Novartis	The deterministic results from this analysis give an incremental cost-effectiveness ratio of £49,537 (with PAS). This is underpinned by a mean estimated survival of 7.9 months in the BSC arm and 16.1 months in the everolimus arm. In order to achieve a target threshold of £30,000 per QALY gained, a QALY weight of 1.66 would be required. This QALY weight is within previously accepted limits based on products meeting the end of life criteria.	The Committee discussed the manufacturer's cost-effectiveness estimate of £49,500 per QALY gained which incorporated estimates of clinical effectiveness using the RPSFT method. See FAD Sections 4.10 and 4.11

Consultee	Comment	Response
Novartis	C1. ii) Updated IPCW Analysis The IPCW analysis presented in our original submission was based on data from the February 2008 data cut. The later November 2008 data cut demonstrated greater survival in everolimus patients than that indicated by the February 2008 analysis. In order to take account of the updated results and take into account PenTAG's criticisms the following revisions have been made to the IPCW analysis: - data from the November 2008 data cut has been used to populate the model; -the number of cycles in the model have been increased from 18 to 39 in order to capture the greater survival demonstrated by the November 2008 data cut; - as suggested by PenTAG, discounting at a rate of 3.5% has been applied from cycle 2; - as suggested by PenTAG, the HR multiplier has been applied to rates rather than the transition probabilities: - as suggested by PenTAG, in the BSC arm, for states leading to death, rather than carry the last transition probability forward for the remaining cycles (as in our previous model), we have calculated an average of the transition probabilities from cycles 10 (0.24) and 11 (0.23) and applied this average value (0.23) to all remaining cycles ie cycles 12 to 39. - overestimation of mortality in BSC arm is corrected by applying the same rate to all transitions leading to death ie from stable disease with adverse events, stable disease without adverse events and progressed disease to death. - transition probabilities were calibrated to ensure an effective HR of 0.55. The effective HR was checked by running a virtual cohort of patients through the model and analysing the survival output using a Cox proportional hazards model. All other aspects of the model remain unchanged. The associated transition probabilities are provided in Appendix 1. The results from the updated analysis are presented in the table below. [not reproduced here]	The Committee noted that the key factor in determining the cost effectiveness was the estimate of overall survival and discussed the IPCW and the RPSFT methods used to estimate this from the RECORD-1 trial data. It heard from the ERG that it considered the RPSFT method to be more methodologically robust than the IPCW method because it does not assume that there are no unmeasured confounders. In addition, the Committee understood that the manufacturer's revised IPCW analysis contained a number of unexplained differences between the original and revised models, and so the ERG could not conduct a full critique of the revised IPCW analysis. The Committee also noted that the RPSFT method had been used previously in 'Sunitinib for the treatment of gastrointestinal stromal tumours' (NICE technology appraisal guidance 179). The Committee therefore concluded that, in this instance, it was more appropriate to evaluate the cost effectiveness of everolimus based on the estimates generated using the RPSFT method. See FAD section 4.8

Consultee	Comment	Response
Novartis	The deterministic results from this analysis give an incremental cost-effectiveness ratio of £52,648 (with PAS). This is underpinned by a mean estimated survival of 9.7 months in the BSC arm and 16.2 months in the everolimus arm. In order to achieve a target threshold of £30,000 per QALY gained, a QALY weight of 1.75 would be required. This QALY weight is within previously accepted limits based on products meeting the end of life criteria. In addition, this is likely to be a conservative estimate of cost-effectiveness as it is underpinned by an assumption of survival in the BSC arm which is optimistic based on the available evidence.	The Committee concluded that, in this instance, it was more appropriate to evaluate the cost effectiveness of everolimus based on the manufacturer's revised estimates generated using the RPSFT method. See FAD section 4.8
Novartis	**D. We do not believe that the provisional recommendations as detailed in the ACD are justified nor do they constitute a reliable basis for the provision of sound guidance to the NHS.** **D1. The decision not to recommend everolimus for the treatment of patients with advanced renal cell carcinoma (aRCC), whose disease has progressed on or after treatment with VEGF-targeted therapy is inappropriate as it relies on the view that the estimates of cost-effectiveness presented by PenTAG are more plausible than those presented by Novartis. This is contrary to the available evidence base.**	Comment noted. See responses above and below.
Novartis	As detailed in Section A1 of this document, Novartis strongly believes the rejection of everolimus for aRCC is perverse in the light of the evidence for the following reasons: - the estimate of survival for BSC patients (11.2 months undiscounted) which underpins PenTAG's estimate of cost-effectiveness is not clinically plausible. This means that the resulting estimate of £75,700/QALY is highly conservative and does not reflect the true value of everolimus; **-** the estimate of cost-effectiveness of around £65,200/QALY has been shown using statistical means to overestimate survival in the BSC arm thus artificially inflating the cost/QALY.	The Committee noted that the overall survival associated with best supportive care in the ERG analysis (10.8 months) was likely to be higher than in clinical practice. The Committee noted that the difference in overall survival between treatment arms was 8.2 months in the manufacturer's revised RPSFT analysis and 5.9 months in the ERG's revised RPSFT analysis. It noted evidence from the manufacturer and the clinical specialists that an increase

Consultee	Comment	Response
		in overall survival of 1.4 months per month of increased progression-free survival would be considered plausible. Therefore, the Committee agreed that the incremental overall survival derived using the manufacturer's revised RPSFT analyses was almost twice as much as would be expected, given that the trial had observed an increase of 3 months in progression-free survival. The Committee accepted that the ERG's estimate of the incremental difference in overall survival for everolimus versus best supportive care (5.9 months) was more plausible than that derived by the manufacturer and it was based on all the available data. See FAD section 4.10 The Committee then discussed the manufacturer's and ERG's cost-effectiveness estimates derived using the RPSFT method: £49,500 and £58,300 per QALY gained respectively. The Committee noted its earlier conclusions that the ERG's analysis (which extrapolated the overall survival with best supportive care using all of the available trial data) resulted in the most plausible

Consultee	Comment	Response
		incremental overall survival for everolimus versus best supportive care. The Committee therefore concluded that the ICER of £58,300 per QALY gained (derived by the ERG) was the most plausible. See FAD section 4.11
Novartis	In summary, the preliminary recommendations are perverse in the light of the evidence and accordingly, do not constitute a reasonable or sound basis on which to base guidance to the NHS. In particular, the belief that the estimates of survival for BSC, and therefore cost-effectiveness, are more plausible based on PenTAG's adjustments and exploratory analysis are not supported by the available evidence base or the views of clinical experts. We therefore respectfully request that due consideration is given to the additional evidence and revised estimates of cost-effectiveness which take into account all of PenTAG's criticisms, as well as the longer term data available from the RECORD-1 trial. The revised estimates of cost-effectiveness £49,537/QALY (RPSFT analysis) and £52,648/QALY (IPCW) analysis. These results demonstrate that everolimus is a clinically-effective treatment for aRCC patients with estimates of cost-effectiveness which are within acceptable limits based on previous appraisals for products meeting the end of life criteria.	Comment noted. The Committee agreed that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of everolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that everolimus would not be a cost-effective uses of NHS resources.
Novartis	**E. Other comments** **Section 3.7, page 7** This section states, "There were more adverse events and serious adverse events (grades 3 to 4) in the everolimus plus best supportive care arm (40.1%) than the placebo plus best supportive care arm (22.6%)." This is confusing as the section refers to both adverse events and serious adverse	Comment noted. The FAD has been amended accordingly. See FAD section 3.8.

Consultee	Comment	Response
	events. We therefore propose the following amendment, "There were more serious adverse events in the everolimus plus best supportive care arm (40.1%) than the placebo plus best supportive care arm (22.6%)."	
Novartis	**Section 3.18, page 13** This section states, "This equated to a mean overall survival of 15.18 months with everolimus plus best supportive care and 7.67 months with best supportive care alone (a non-statistically significant gain of 7.51 months)." This statement is misleading as the estimates of survival quoted are generated by the economic model which are not the subject of statistical testing. We therefore propose that the statement is amended as follows, "Estimates of mean overall survival of 15.18 months with everolimus plus best supportive care and 7.67 months with best supportive care alone were generated by the economic model."	Comment noted. The FAD has been amended accordingly. See FAD section 3.19.
Novartis	**Section 4.8, page 17** This section states, "Firstly it did not agree with the assumption that people starting everolimus therapy would all have stable disease without adverse events." It is not clear what is meant by this statement. All patients enter the economic model in the stable disease state without adverse events. Once on treatment, some patients will develop adverse events. The rate at which patients move from the stable disease without adverse events health state to the stable disease with adverse events health state is calculated based on patient data from the RECORD-1 study.	Comment noted. The Committee agreed that the cost estimates used for adverse events in the model were acceptable. See FAD section 4.12

Consultee	Comment	Response
Novartis	**Section 4.13, page 19** This section states, " The Committee heard concerns from the ERG that the RPSFT method had been applied incorrectly by the manufacturer. The application of the transition probabilities led to overestimation of the mortality risk." It is not clear why the ERG considered the application of the transition probabilities to be an overestimation of the mortality risk. The RPSFT analysis presented by Novartis resulted in an estimate of mean survival in the BSC arm of around 8 months. Based on the available evidence this estimate of survival is likely to be more plausible than the estimate of mean survival in PenTAG's analysis of around 11 months.	Comment noted. The Committee discussed the validity of the estimates of overall survival from the manufacturer's and ERG's RPSFT analyses. The Committee noted the ERG's criticism that the manufacturer's extrapolation of long-term survival in the best supportive care arm was still not based on all of the available data (it was based on the mean of cycles 5 and 6 derived from the RPSFT analysis) and that these data may not be representative of the whole trial population. The Committee accepted that the use of a Weibull distribution, which used all available data, was a more appropriate method for estimating overall survival and produced a better fit to the empirical data points. See FAD section 4.9
Novartis	**Section 4.15, page 20** This section states, " The Committee heard that the life expectancy for people with advanced RCC receiving best supportive care alone was unlikely to be greater than 24 months and was potentially as low as 6 months." This statement is misleading. Patients who are eligible for everolimus are those who have failed treatment with sunitinib ie everolimus is indicated for a 2nd line setting. The available evidence suggests that the life expectancy of patients on BSC following	Comment noted. See above response.

Consultee	Comment	Response
	sunitinib failure is likely to be considerably less than 11 months.	

Comments received from members of the public

Member of the public 1	Appraisal Committee's preliminary recommendations	I strongly disagree with the Appraisal Committees (AC) preliminary recommendations to not recommend Everolimus for the second-line treatment of advanced renal cell carcinoma. . Kidney Cancer patients have a rare form of cancer and proper consideration has not been given to this important fact. Â This small patient population have access to only one of the ?newer class? of drugs on the market. They are hugely disadvantaged due to the patient numbers being so small. Â Chemotherapy and radiotherapy are not suitable for Kidney Cancer Patients, this leaves access to Sutent as the only possible hope for Kidney cancer patients.	Comment noted. The Committee's judgements on cost effectiveness are not influenced by the prevalence of a condition. See Guide to the Methods of Technology Appraisal section 6.2.18 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)

Member of the public 1	Manufacturer's submission	The actual cost of Everolimus is on a par with Sutent, roughly Â£100 per day. Â Sutent has already been approved by NICE. It is a widely accepted practice in other countries to implement a package of ?Sequential Treatment? for Kidney Cancer patients. If Sutent should stop working a different treatment is used for a period of time and at some point the patient will revert to Sutent. Sequential Treatment is successfully managed in other countries as Â a proven and acknowledged method of treating Kidney Cancer. Â If NICE have accepted the cost of treatment with Sutent, this method of ?Sequential Treatment?, which will incur no significant increase in cost, should be an accepted course without further question of cost.	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. The Committee concluded that everolimus fulfilled the end-of-life criteria and considered it as such.
Member of the public 1		The manufacturers submission and the trials that have taken place demonstrates without doubt that Everolimus is a clinically effective treatment for Kidney Cancer. Â The Evidence Review Group (ERG) have at no point taken into account when commenting on the QALY figures, the fact that the QALY figure was originally introduced nearly 10 years ago and at no point has consideration been made of inflation and increased production costs. At no point is reference made to the ?small? patient numbers involved who will benefit from this treatment, as Kidney Cancer is a rare cancer.	Comment noted. The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the Methods of Technology Appraisal section 5.2.11 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf

Member of the public 1	Consideration of the evidence	?The Committee therefore concluded that although there was sufficient evidence that everolimus increased progression-free and overall survival compared with best supportive care, the magnitude of the overall survival gain was uncertain?. It is despicable that because of the small number of patients involved, large clinical trials are impossible in such a short period of time Â (whereas in other much larger Â patient groups the data available at this stage in a drugs life is somewhat more detailed and far more extensive), this very fact is being used against this group as a reason to refuse. Â Large clinical trials are impossible when considering such a small patient group. This is a factor that has clearly not been taken into account, as although Â the committee felt that Everolimus is a treatment that is effective, they are refusing on the basis that there is no mass of data available to support this.	Comment noted. The Committee noted that the difference in overall survival between patients receiving everolimus and those receiving best supportive care was 8.2 months in the manufacturer's revised RPSFT analysis and 5.9 months in the ERG's revised RPSFT analysis. It noted the earlier conclusion that an increase in overall survival of 1.4 months per month of increased progression-free survival was plausible. Therefore, the Committee agreed that the incremental overall survival derived using the manufacturer's revised RPSFT analysis (8.2 months) was greater than expected, based on the increase in progression-free survival of 3 months observed in the RECORD-1 trial. The Committee accepted that the ERG's estimate of overall survival for patients receiving best supportive care using the RPSFT analysis was higher than observed in clinical practice, but the incremental difference in overall survival for everolimus versus best supportive care (5.9 months) was more plausible than that derived by the manufacturer and was based on all the available data. See FAD section 4.10.

Member of the public 1	Implementation	It is accepted that the cost of Everolimus is similar to Sunitinib, it is widely accepted throughout other countries to offer ?Sequential Treatment?, therefore ?additional? costings using this method of Sequential Treatment are not applicable as the cost to the NHS is roughly the same, it is simply a case of switching treatments for a short period.	Comment noted. The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturer's submission and the ERG report.
Member of the public 1	Related NICE guidance	"For over a decade Kidney Cancer patients have had to cope with no new treatments available to beat this aggressive disease. Â After a lengthy battle, Sunitinib was approved by NICE for use by this small patient group. Â But to date no other treatment is available, there is no alternative for patients who cannot tolerate Sunitinib or for patients for whom Sunitinib will not work. Â As Health Secretary Alan Johnson promised this whole area would be addressed and that Â NICE would offer greater flexibility for End Of Life Treatments, but NICE have reviewed 5 new drugs and approved only 1 for first line treatment. Additionally there is no evidence that NICE have applied the EOL criteria to this treatment. This small patient group is severely disadvantaged just by having a cancer that is Rare."	Comments noted. The Committee's judgements on cost effectiveness are not influenced by the prevalence of a condition. See Guide to the Methods of Technology Appraisal section 6.2.18 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf) The Committee took in to account the end of life criteria in reaching its decision. See FAD sections 4.14 and 4.15

Member of the public 1	Proposed date of review of guidance	To consider reviewing the technology in 3 years time when we live in a period of huge dynamic and technological growth in Â cancer fighting treatments is archaic, out dated and totally of no use Â to this small patient group. The only way to provide the 'magnitude' of results that NICE are requiring is to allow the patients to have access to this treatment. But this is a vicious circle that will never end. Everolimus is to treat a rare cancer, the masses of lengthy trial data will never be gathered due to small patient numbers, and no further data will be allowed to be gathered unless patients are allowed access to this treatment.	Comments noted. The Committee's judgements on cost effectiveness are not influenced by the prevalence of a condition. See Guide to the Methods of Technology Appraisal section 6.2.18 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
Other 1	Appraisal Committee's preliminary recommendations	It is disgraceful, shameful and unethical that NHS cancer patients are denied the opportunity to access treatments recommended by their oncologists and recognised throughout the world and by the UKs medical profession, for reasons of cost, when the NHS spends millions of pounds on treating entirely self-inflicted lifestyle conditions, from obesity and alcoholism to drug addiction and removing tattoos. NHS priorities must change immediately, to allow oncologists to prescribe drugs such as Evarolimus to those patients they consider may benefit in terms of extended lifetime. NICE should immediately approve the use of Evarolimus for patients deemed suitable by their oncologists. Cancer patients should not be condemned to a more premature death than current therapies can prevent, in order merely to allow NHS funds to be diverted to less life-threatening or self-inflicted conditions.	Comment noted. The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturer's submission and the ERG report.

Patient 1	Consideration of the evidence	If Sutent, the only ?End of Life? drug considered acceptable by NICE, either does not work OR cannot be tolerated OR stops working, there is NO alternative treatment. NICE themselves have agreed that chemotherapy OR radiotherapy do not work for kidney cancer. Everolimus is readily available and routinely used in other EU countries as a second line treatment for mRCC Everolimus is clinically cost effective and is proving to work as we already have patients in the UK successfully taking the drug. Additionally, consider the significant number of patients worldwide who have had access to this treatment for long periods of time and are successfully responding to the treatment. The cost of Everolimus works out about the same as Sutent 4 weeks active treatment Â Â£100 per day When considering the cost of Everolimus, the small patient numbers who will need it, should be taken into account more than the actual cost. Our kidney cancer Clinicians want to use Everolimus when Sutent fails. This is referred to as ?sequential treatment? and is a practice successfully used to treat Kidney Cancer patients in other countries. We need the same treatment option here in the UK. Rarer cancer patients are DISCRIMINATED against as their treatments will always be more expensive, due to patient groups being much smaller. This is particularly the case by NICE. Please provide equality, a basic human requirement. I find it absolutely disgusting that NICE with all their significant and costly resources have been considering Everolimus for the past 14 MONTHS. Yet they have only provided Kidney cancer patients just 3 WEEKS to appeal.	Comments noted. The Committee agreed that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of everolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that everolimus would not be a cost-effective uses of NHS resources. The Committee's judgements on cost effectiveness are not influenced by the prevalence of a condition. See Guide to the Methods of Technology Appraisal section 6.2.18 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)

Patient 2	Appraisal Committee's preliminary recommendations	Complete shock as everolimus works & widely available in EU USA Canada as second line treatment for mRCC. Â Chemo & radiotherapy ineffective for mRCC. Â No other effective alternative treatment for patients after sunitinib or for those unable to tolerate re side effects, high blood pressure etc or when it has ceased to work or doesnt work. Â Referred to NICE in November 2008 taken too long to assess grossly unfair to give patients only 3 weeks to respond many will be unaware of your decision. Â Typical mRCC patients in their 60s/70s many with no access to computers or not used to Internet. Â Patients totally DISENFRANCHISED from the process regarding life & death decisions made in their name! Â Jargon is that of statisticians engaged at huge cost to taxpayers/stakeholders & to the layman is incomprehensible. Â No level playing field for us to make meaningful comments in appeal. Â System flawed as QALY set at Â£30,000 max in 1999 no adjustment for inflation since. Â Lack of transparency re your methodology process model & means of calculation of placing value on human life. Up against NHS lobby group CSAS now unfairly influencing appraisal process despite obvious conflict of interest.	Comment noted. The Institute recognises that guidance from other organisations may differ from its own guidance, because of different criteria for making decisions. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturer's submission and the ERG report. Comment noted The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the Methods of Technology Appraisal section 5.2.11 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)

Patient 2	The technology	It is not clear that the cost models take into consideration generous discounts & free benefits offered by manufacturer. Cost effective analysis model cannot be used for rarer cancer drugs as there is no tested real time comparator available due to the few people with mRCC. Â The overall cost will be lower than sunitinib as there are fewer patients compared with other cancers. Maximum cost approx Â£4 million pa when NHS wasted Â£40 million on lawyers fees for abandoned IT project & huge amount wasted on unused drugs.	The Committee's judgements on cost effectiveness are not influenced by the prevalence of a condition. See Guide to the Methods of Technology Appraisal section 6.2.18 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
Patient 2	manufacturer's submission	Everolimus is the only oral mTOR inhibitor thus saving NHS support costs compared to intravenous dosage. Â At 3.3 It is clear that everolimus performs well for those unable to tolerate sunitinib or where it does not work with a 66% reduction in risk of disease progression with everolimus plus best supportive care compared with placebo. Â This in itself justifies NICE recommendation to give ALL patients longer survival prospects. Â At 3.5/3.10 found to DOUBLE overall survival a more significant & valued measure than health related QOL for patients. Â No consideration has been given to Outliers (patients surviving for longer) on everolimus which could skew the Mean in a small patient group. Â The NICE calculation of ICER cannot apply to a small patient group for obvious statistical reasons. Â Calculation of QALY also not consistent as will always be high as there is no netting-off of existing drug as there is none to consider making the process cruel and unfair.	Comment noted. The Committee agreed that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of everolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that everolimus would not be a cost-effective uses of NHS resources.

Patient 2	consideration of the evidence	The flexible approach promised by last Health Secretary, Alan Johnson, not properly considered. Â We as a small patient group qualify for inclusion in this and we are aware that a cost-effectiveness of up to Â£70,000 was agreed to be considered in these circumstances. Â However, NICE have increased their estimate from Â£65,200 to Â£75,700 per QALY gained in a timely manner therefore lifting us out of this category and denying extra life to many again. Â I cannot believe that these decisions are made with no medical renal oncologist on the Appraisal Committee. Â We will never be able to lift the appalling five-year cancer survival rates in this country to match the EU standard unless patients have access to SEQUENTIAL TREATMENT as commonly seen in many other countries.	The supplementary advice does not suggest for Committee to apply a particular weight for the cost effectiveness estimate to fall within the acceptable threshold range. The Committee is asked to come to a value judgment on whether the magnitude of additional weight, that would need to be assigned to the original QALY benefits in the patient group for the cost effectiveness of the drug to fall within the current threshold range, would be acceptable in light of the evidence presented.
Patient 2	implementation	NICE guidance needs to be made mandatory as already PCTs are adopting differing approaches to sunitinib access	Comment noted.
Patient 2	related NICE guidance	Pazopanib referred to NICE November 2008. Â FAD not expected until December 2010 at earliest. Â As with sunitinib many patients will again die without treatment due to your delay tactics and we pay your salaries!	Comment noted.
Patient 2	proposed date of review of guidance	As with sunitinib many patients will again die without treatment due to your delay tactics and we pay your salaries. We dont seem to be getting through to you people - WE CANNOT WAIT!!	Comment noted.

Carer 1	Appraisal Committee's preliminary recommendations	There is no other effective treatment for patients who cannot tolerate, or who have become immune to Sunitinib effectiveness. There has to be something else for RCC patients to fall back on. Traditional chemotherapy does not work, so patients will be left with no other option other than give up and die. You have already rejected 3 other RCC drugs when Alan Johnson promised greater flexibility from NICE for EOL drugs. I do feel that this is a class decision, patients who can afford to buy privately (like yourselves) will do so, others will not be able to afford it. I feel that that is discrimination!	Comment noted. The Committee agreed that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of everolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that everolimus would not be a cost-effective uses of NHS resources.
Carer 1	The technology	side effects are much less than Sunitinib and is usually well tolerated.	Comment noted. The Committee was advised by the patient experts and clinical specialists that everolimus would be tolerated by most people with advanced RCC, and the adverse events would not be significantly worse than those experienced with first-line sunitinib therapy. See FAD section 4.3
Carer 1	manufacturer's submission	The evidence is clear that this does work, obviously, if given too late then its overall effect will be less than if given at the right time as decided by a clinician. It is available throughout Europe and other countries and this appraisal goes to show why our survival rates are so low compared with other countries.	Comment noted. The Committee agreed that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of everolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that everolimus would not be a cost-effective uses of NHS resources.

Carer 1	(consideration of the evidence)	The qualy has not been changed for more than 10 years. To deny a drug that is clinically effective breaches the Human Rights act, it is in effect sentencing patients to an early death. I also note that the committe did not have an RCC specialist there and so specialist knowledge was missing. Surely this is wrong. The input of a specialised clinician is crucial.	Comment noted The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. See Guide to the Methods of Technology Appraisal section 5.2.11 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
Carer 1	Related NICE guidance	patients cannot wait for the decision about pazopanib, they need something now.	Comment noted.
Carer 1	(proposed date of review of guidance	what will be different in 2013, if you have the statistics now, why would you change your mind in 2013? Are you just deferring due to cost?	Comment noted. NICE guidance is considered for review typically 3 years after publication of guidance.
Patient 3	Appraisal Committee's preliminary recommendations	I disagree with this decision. Â If Sutent stops working or indeed doesnt work in the first place then Everolimus is the only viable option.	Comment noted. The Committee heard from clinical specialists and patient experts that there are limited treatment options for people with advanced RCC. See FAD sections 4,2 and 4.3.
NHS professional 1	Appraisal Committee's preliminary recommendations	Although the magnitude of the extension of life with this drug are difficult to estimate because of the cross over in the trial these patients are surviving on average 14.78 months. Â This is a significant extension of life which should not be denied to these patients. Â This agent is being used widely across Europe and it is breach of UK patients human rights to deny them access to this medicine.	Comment noted. The Committee discussed the clinical effectiveness of everolimus in people with advanced RCC whose disease had progressed within 6 months of stopping VEGF-targeted treatment. See FAD section 4.4

NHS professional 1	manufacturer's submission	It is important to remember that the median survival of patients treated with interferon as first line therapy for metastatic RCC is around 14 months (without any second line therapy). Â The median survival of patients randomized to second line everolimus was 14.78 months. Â This means that with the use of sunitinib (median survival 26.4 months)followed by everolimus the median survival will be in the order of 41 months i.e. almost three times longer than in the pre-targeted therapy days!	The Committee noted that the difference in overall survival between patients receiving everolimus and those receiving best supportive care was 8.2 months in the manufacturer's revised RPSFT analysis and 5.9 months in the ERG's revised RPSFT analysis. It noted the earlier conclusion that an increase in overall survival of 1.4 months per month of increased progression-free survival was plausible. Therefore, the Committee agreed that the incremental overall survival derived using the manufacturer's revised RPSFT analysis (8.2 months) was greater than expected, based on the increase in progression-free survival of 3 months observed in the RECORD-1 trial. The Committee accepted that the ERG's estimate of overall survival for patients receiving best supportive care using the RPSFT analysis was higher than observed in clinical practice, but the incremental difference in overall survival for everolimus versus best supportive care (5.9 months) was more plausible than that derived by the manufacturer and was based on all the available data. See FAD section 4.10

Carer 2	Notes	My husband has been on Sutent for over four years and is doing fine. He was told it would work for maybe six months on the RCC he has had since July 2004. Hopefully if he needs it everolimus will do the same but as it is now he will be unable to get it. What right has NICE got to deny anyone the chance to live. They pay for IVF, Cosmetic Surgery and many more expensive not life saving procedures so why deny a relatively small proportion of people this chance.	Comment noted. The Committee's judgements on cost effectiveness are not influenced by the prevalence of a condition. See Guide to the Methods of Technology Appraisal section 6.2.18 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
Carer 2	Appraisal Committee's preliminary recommendations	Why when it has been proven to work	Comment noted. The Committee agreed that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of everolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that everolimus would not be a cost-effective uses of NHS resources.
Carer 2	the technology	If this is not approved drug compays might as well give up on their R & D	Comment noted
Carer 2	(manufacturer's submission)	Statistics never stand up there is always some that do not get the side effects and do well for a greater time	Comment noted
Carer 2	related NICE guidance	Please just pass all these drugs and stop using money on all the unnecessary meetings and paper work which is going on at the moment	Comment noted

Carer 2	(proposed date of review of guidance	The burden that would be lifted off the the already drained patients relatives and carers of this relatively small group of people if this drug could be approved is unimaginable. Â Just to give them hope is all that is needed to lift their Â spirits and relieve them of the constant worry that is there every minuet of the day and night	Comment noted
Patient 4	Notes	Time to show some backbone and leadership.You are the NI of "Clinical Excellence" The drug works for some people.Now standard treatment in the US and most European Countries , are we always to be the poor mans health service.The decision to prescribe should be down to the Clinicians/Oncologists.It is up to the Government to fund.	Comment noted
Patient 4	Appraisal Committee's preliminary recommendations	Confirms there is no intention of making the NHS cancer services "First Class"	Comment noted
Patient 4	the technology	As it is in tablet form it is cheap to deliver the service to patients.	Comment noted
Patient 4	manufacturer's submission	This proves that it is an effective treatment	Comment noted. The Committee discussed the clinical effectiveness of everolimus in people with advanced RCC whose disease had progressed within 6 months of stopping VEGF-targeted treatment. See FAD section 4.4
Patient 4	consideration of the evidence	A significant number of patients are living with Advanced RCC well over 24 months eg.Myself 5 years	Comment noted.
Patient 4	related NICE guidance	12 months is desperately slow for people with a life threatening disease. 3 months should be the maximum	Comment noted

Patient 4	proposed date of review of guidance	Far too long. Reviews should be every 6 months	Comment noted. NICE guidance is typically considered for review 3 years after guidance is published.
Patient 5	Appraisal Committee's preliminary recommendations	Confirms there is no intention of making the NHS cancer services "First Class"	Comment noted
Patient 5	The technology	As it is in tablet form it is cheap to deliver the service to patients.	Comment noted.
Patient 5	Manufacturer's submission	This proves that it is an effective treatment	Comment noted. The Committee discussed the clinical effectiveness of everolimus in people with advanced RCC whose disease had progressed within 6 months of stopping VEGF-targeted treatment. See FAD section 4.4
Patient 5	Consideration of the evidence	A significant number of patients are living with Advanced RCC well over 24 months eg.Myself 5 years	Comment noted
Patient 5	related NICE guidance	12 months is desperately slow for people with a life threatening disease. 3 months should be the maximum	Comment noted
Patient 5	proposed date of review of guidance	Far too long. Reviews should be every 6 months	Comment noted

Patient 6	Notes	I have rcc stage iv Ive been on sutent now for almost a year, N.I.C.E refused initially to fund sutent but my PCT finally had to agree that my case was justified and allowed funding, shortly before N.I.C.E Â passed it as available to all patients. IT IS WORKING FOR ME, SOME TUMOURS HAVE DIED COMPLETELY AND ALL OTHERS ARE SHRINKING AND BECOMING LESS SOLID SHOWING CYSTIC CHANGES. These drugs work but if sutent should stop working for me I DESERVE THE RIGHT TO BE GIVEN THE NEXT DRUG TO CONTINUE TO BENEFIT FROM THE EXPENSIVE RESEARCH THESE DRUGS HAVE UNDERGONE TO ALLOW US PATIENTS TO LIVE. WE HAVE A RIGHT TO LIFE.	Comment noted. The Committee agreed that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of everolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that everolimus would not be a cost-effective uses of NHS resources.
Patient 6	Appraisal Committee's preliminary recommendations	IT SHOULD BE ALLOWED, WE CAN ONLY RECEIVE ONE DRUG AT A TIME SO COST IS NOT AN ISSUE.WHAT IS THE POINT OF MILLIONS BEING SPENT ON RESEARCH IF WE ARE NOT PERMITTED TO HAVE THESE DRUGS.	Comment noted
Patient 6	the technology)	COST IS NOT AN ISSUE, OTHER DRUGS COST AS MUCH AND ARE BEING PRESCRIBED.IT WILL ONLY BE GIVEN IF OF BENEFIT SO WE DESERVE THE RIGHT TO BENEFIT FROM THESE NEW DRUGS.	Comment noted
Patient 6	manufacturer's submission	EACH INDIVIDUAL PATIENT WITH GUIDANCE FROM THEIR ONCOLOGIST SHOULD DECIDE ON WHAT IS QUALITY OF LIFE. NO ONE HAS THE RIGHT TO DECIDE ON THE COST OF A LIFE. WE SHOULD ALL DO WHATEVER IT TAKES TO GIVE LIFE WHERE THERE ARE TREATMENTS THAT CAN HELP.	Comment noted
Patient 6	consideration of the evidence	EVIDENCE SHOWS THAT IT CAN EXTEND LIFE, IT SHOULD BE A PATIENTS CHOICE TO HAVE THIS DRUG WITHOUT COST BEING AN ISSUE!	Comment noted

Patient 6	implementation)	IT SHOULD BE PATIENTS WHO GIVE IMPLEMENTATION ADVICE ON DRUGS NOT PEOPLE WHO HAVE VIRTUALLY NO EXPERIENCE OF WHAT WE ARE GOING THROUGH!	Comment noted
Patient 6	related NICE guidance	N.I.C.E GUIDANCE IS OUTDATED AND UNFAIR, WE ARE NOT NUMBERS WE ARE HUMAN BEINGS.THIS GUIDANCE IS BEING PUT INTO ACTION BY DOCTORS AND PROFESSIONALS BUT NOT ONE IS A SPECIALIST IN CANCER, RENAL CELL CANCER OR ONCOLOGY! WOULD YOU LET A BRICK LAYER COOK YOU A 3 COURSE MEAL AND EXPECT A LA CARTE? I THINK NOT!	Comment noted
Patient 6	proposed date of review of guidance	THE PROPOSED DATE FOR REVIEW OF GUIDANCE IS TOO FAR IN THE FUTURE TO BENEFIT PATIENTS NEEDING TREATMENT NOW.	Comment noted
Carer 2	Appraisal Committee's preliminary recommendations	I think once again NICE have let down RCC Patients and left them with no alternative tratments. Â Clearly a life in England is worth nothing. Â If there were alaternative treatments available that were approved by NICE this decision would not be so devastating for patients and their family. Â I cannot understsnd why NICE put finances before approvingany treatment 1st or 2nd line for Kidney cancer patients.	Comment noted
Carer 2	the technology	Actually i do not understand why the medications cost so much and I believe hoe the Drug companies reaches a price needs to be reviewed. Â It is partly this that stop the drug being accessed by patients who need it. Â How is this good business. Â Certainly not for the patients in the UK.	Comment noted
Patient 7	the technology	Why are we putting Â£Â£Â£Â£Â£Â£ Â before people. Â Does this drug need to be so expensive ?????	Comment noted

Other 2	Notes	Ok, so NICE admits that Evirolimus/Afinitor does work, but it's too expensive for the NHS to administer, so some people will die early if they can't cough up the dosh. It's the end of the argument for most people who have kidney cancer (maybe?). ////// Q. That's personally fine by me as I'm rich enough to go out and buy these pills if and when I need to, but what about the people who are not as lucky as me? A. They will die earlier than I will, most probably. ////// Q. The NHS was founded on the fundamental principle of free health care for all UK citizens and it strikes me that the top level management of our national health care rationing system cannot broker a better deal with the private industries who do the research, development and marketing of 21st century health care. Are the Government doing a good job given how much taxpayer's money is spent on NICE? A. I don't know, as there is little public evidence either way as far as I can work out, but my MP here in Witney has so far confirmed a casual interest in the Justice for Kidney Cancer Patients campaign. ////// Q. At the moment is NICE promoting a divided society based on wealth? A. As the Churchill nodding dog would say, "Oh Yes". ///// Q. Given that NICE is a public authority and therefore open to scrutiny do they comply promptly to requests under the Freedom of Information Act? A. Absolutely not, and the Information Commissioner will back me up on this issue.	Comment noted. The Committee agreed that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of everolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that everolimus would not be a cost-effective uses of NHS resources.

Other 2	Appraisal Committee's preliminary recommendations	Ok, so NICE admits that Evirolimus/Afinitor does work, but it?s too expensive for the NHS to administer, so some people will die early if they can?t cough up the dosh. It?s the end of the argument for most people who have kidney cancer (maybe?). Q. That?s personally fine by me as I?m rich enough to go out and buy these pills if and when I need to, but what about the people who are not as lucky as me? A. They will die earlier than I will, most probably. Q. The NHS was founded on the fundamental principle of free health care for all UK citizens and it strikes me that the top level management of our national health care rationing system cannot broker a better deal with the private industries who do the research, development and marketing of 21st century health care. Are the Government doing a good job given how much taxpayer?s money is spent on NICE? A. I don?t know, as there is little public evidence either way as far as I can work out, but my MP here in Witney has so far confirmed a casual interest in the Justice for Kidney Cancer Patients campaign. Q. At the moment is NICE promoting a divided society based on wealth? A. As the Churchill nodding dog would say, ?Oh Yes?.	Comment noted. The Committee agreed that everolimus was likely to be clinically effective. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of everolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that everolimus would not be a cost-effective uses of NHS resources.
Other 3	implementation	How can you put a price on someones life?????????? What it if it was a member of your family??? Would be different then.	Comment noted

Carer 3	Appraisal Committee's preliminary recommendations	There is no second-line treatment option for kidney patients who fail to respond to sunitab and this drug has proven results. Â It should be provided as general treatment and not on the basis of location.	Comment noted. The Committee heard from clinical specialists and patient experts that there are limited treatment options for people with advanced RCC. See FAD sections 4,2 and 4.3.
Member of the Public 2	Appraisal Committee's preliminary recommendations	As only a small number of patients suffer this condition, the drugs are bound to be expensive as the volume is small. By making the recommendation that it is not made available to patients, surely drugs companies are less likely to continue to research cures for this area, as the wont be selling many of these drugs. These drugs may give someone more time with their family and some precious extra life before succumbing to their condition. Please reconsider.	Comment noted.The Committee's judgements on cost effectiveness are not influenced by the prevalence of a condition. See Guide to the Methods of Technology Appraisal section 6.2.18 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
Patient 8	Appraisal Committee's preliminary recommendations	Everolimus has been proven to extend patients lives as a second line treatment and is widely available in other places around the world. As a rarer cancer this treatment will only be appropriate for and used in a relatively few cases and for a relatively short amount of time. Nevertheless this time is invaluable to the patients and their families as, for instance, additional time can be spent with children to prepare them for your death and to make arrangements which will make life easier for everyone. By stating that it is not available it causes untold stress which in itself has a cost attached not just for the patient but also on family and friends. This stress is incurred not just by those who actually need the treatment but also those who may need it some time in the future.	Comment noted. The Committee's judgements on cost effectiveness are not influenced by the prevalence of a condition. See Guide to the Methods of Technology Appraisal section 6.2.18 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)

Patient 8	the technology	If/when sutent fails this has been proven to extend life even if only for a few months (see comments above. The cost is not "until further notice" as it will only work for a limited period of time but that time is invaluable. It is easy to administer and side effects can be controlled.	Comment noted
Patient 8	manufacturer's submission	QALY - the time spent with friends and family preparing one for ones death will help them cope. Please read and listen to the manufacturers submission. There are no other second line treatments for kidney cancer - this is ageist (many kidney cancer patients are over 60 but many are much younger)and sexist (many patients are men although increasing numbers of women are diagnosed now). This would not be condoned for breast cancer. Kidney cancer is seen as an easy target as relatively few people are diagnosed but because of this the sums make sense (rarer cancer). End of life drugs should be available to all.	Comment noted.The Committee's judgements on cost effectiveness are not influenced by the prevalence of a condition. See Guide to the Methods of Technology Appraisal section 6.2.18 (Available from URL http://www.nice.org.uk/media/B52/A7/TAMethodsGuideUpdatedJune2008.pdf)
Patient 8	consideration of the evidence	Equality issues - breast cancer and other more "attractive" cancers seem to have huge funding poured in whereas if you are a woman suffering with kidney cancer there is relatively little.	Comment noted
Patient 8	implementation	People are dying while this is being debated	Comment noted

Carer 4	Appraisal Committee's preliminary recommendations	3-4 months is the average amount of time, there will and have been patients who it has helped for considerably longer. what are these "limited resources" that NICE refer to every time theres a contentios decision? Â£1.4 Billion forecast NHS surplus this year enough to fund this? where does it sit with the Â£40 Million we have spent on legal consultation fees for the non existent IT system? These patients need another option if initial treatment is not tolerated, and pharma companies need to be incentivised to continue to research more efficient drugs that will provide better results in the future. Are we really committed to beating Cancer, especially those rarer cancers? Money and time need to be stripped out of the multi tiered quango structure that comprises PCTs and various advisory boards, and remove the duplication so we can have a faster and more equitable way of ensuring the right drugs are available at the right costs to the Patients that need them.	Comment noted
Carer 4	the technology	I wouls question procurement practises here, and look for some risk sharing initiatives based on other more succesful drugs	Comment noted
Carer 4	manufacturer's submission	The QALY has not been reviewed for over 10 years, how can this still be a relevant benchmark?	Comment noted

Carer 4	implementation	3-4 months is the average amount of time, there will and have been patients who it has helped for considerably longer. what are these "limited resources" that NICE refer to every time theres a contentios decision? Â£1.4 Billion forecast NHS surplus this year enough to fund this? where does it sit with the Â£40 Million we have spent on legal consultation fees for the non existent IT system? These patients need another option if initial treatment is not tolerated, and pharma companies need to be incentivised to continue to research more efficient drugs that will provide better results in the future. Are we really committed to beating Cancer, especially those rarer cancers? Money and time need to be stripped out of the multi tiered quango structure that comprises PCTs and various advisory boards, and remove the duplication so we can have a faster and more equitable way of ensuring the right drugs are available at the right costs to the Patients that need them. 3-4 months is the average amount of time, there will and have been patients who it has helped for considerably longer. what are these "limited resources" that NICE refer to every time theres a contentios decision? Â£1.4 Billion forecast NHS surplus this year enough to fund this? where does it sit with the Â£40 Million we have spent on legal consultation fees for the non existent IT system? These patients need another option if initial treatment is not tolerated, and pharma companies need to be incentivised to continue to research more efficient drugs that will provide better results in the future. Are we really committed to beating Cancer, especially those rarer cancers? Money and time need to be stripped out of the multi tiered quango structure that comprises PCTs and various advisory boards, and remove the duplication so we can have a faster and more equitable way of ensuring the right drugs are available at the right costs to the Patients that need them.	Comment noted

Carer 4	related NICE guidance	Why is this scheduled to take so long? This goes against the 3 month turnaround time for consultation and guidance - please explain - You have had this for over a year already	Comment noted
Carer 4	proposed date of review of guidance	3 week is not long enough to digest the data and return a coherent argument, the initial decision should be made quicker, and patients/carers should have 6 weeks to make a considered response.	Comment noted
Patient 8	Notes	The devastating effect that cancer has on patients and families is boundless. After successful nephrectomies, surely patients are entitled to drugs to benefit them in the future. Kidney cancer is not self-inflicted as other health issues can be, yet they get treated, why cant we? Its disgraceful that drugs are marketed and not available on the NHS to which we have all subscribed over our working years.	Comment noted
Patient 8	Appraisal Committee's preliminary recommendations	Why not? Because of cost, obviously. So why are patients with other health issues being treated and not kidney cancer patients?	Comment noted
Patient 8	the technology	There are side effects to most drugs - live with it if the medication works	Comment noted
Patient 8	manufacturer's submission	Drug companies are making too much money from this - you cannot put a price on ones health and everyone who is eligible, should be given the chance of survival even for only a few more months if that is the case	Comment noted
Patient 8	consideration of the evidence	Any chance for someone to extend their life however long or short, should be offered.	Comment noted
Patient 8	proposed date of review of guidance	2013????? How many will die before then?	Comment noted

PENTAG RESPONSE TO THE NOVARTIS UPDATED SUBMISSION (RECEIVED ON 24 MARCH 2010)

Everolimus for the Treatment of Advanced Renal Cell Carcinoma – Update Analysis (received 24/3/10)

BACKGROUND

In their original STA submission Novartis reported the following base case ICER outputs for Everolimus versus Best Supportive Care (BSC) as a result of their cost-effectiveness analysis: £51,613 per QALY with Patient Access Scheme (PAS) and £61,330 per QALY without PAS. This analysis depended critically on the statistical approach of Inverse Probability of Censoring Weights (IPCW) to correct for patients switching between treatment arms in the RECORD-1 trial which formed the primary data source for the economic model.

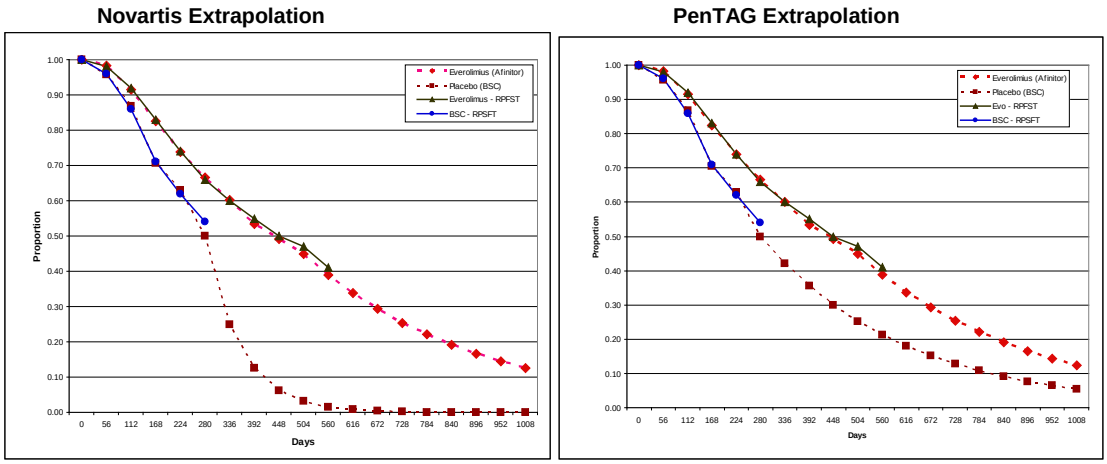
On examination of the original Novartis model the Evidence Review Group (ERG) based at the Peninsula Technology Assessment Group (PenTAG) revealed a number of structural errors in the Novartis model. The ERG corrections to the Novartis model resulted in the following base case ICER outputs: £65,231 with PAS (£76,070 without PAS).

In response to the ERG critique of their original analysis, Novartis requested the submission of a further cost-effectiveness analysis in advance of NICE appraisal committee meeting held on 13 January 2010. This submission (dated 18 Dec 2009) made use of an analysis based on Rank Preserving Structural Failure Time (RPSFT) which had been commissioned by Novartis and dated 1st April 2009 (no citation to this RPSFT analysis was given in Novartis' original STA submission). The RPSFT analysis provides an alternative statistical approach to IPCW for the adjustment of trial bias due to patient switching and has been previously advocated to use to correct for patient switching arms in trails.

The subsequent analysis supplied by Novartis based on the RPSFT approach claimed a base case ICER of £53,128 (with PAS). This was presented alongside the ICER of £51,613 (with PAS) reported in the original STA using the IPCW analysis (based on a structurally flawed model) to argue for a consistent ICER value.

PenTAG examined the revised outputs submitted by Novartis based on the RPSFT analysis. From this it appeared that the reported ICER of £53,128 relied on a questionable extrapolation of the RPSFT survival curves (see Figure 1 below). In order to model a more realistic extrapolation of the survival curves PenTAG re-analysed the cost-effectiveness based on an alternative extrapolation of the overall survival curves (see Figure 1 below). This resulted in the following estimates for the base case ICER derived from the RPSFT adjustment for trial switching bias: £75,725 with PAS (84,079 without PAS).

Figure 1 : Modelled Overall Survival Curves implied by the revised Novartis Analysis based on RPSFT and implied by PenTAGs adjusted extrapolation of curves



Subsequently, at the second appraisal committee meeting held on 9 March 2010, Novartis again requested to submit further analyses based on more a more recent data cut from the trial data and refinements to their cost effectiveness analysis. An assessment of this recent submission is given below.

EXAMIMATION OF THE RECENT NOVARTIS SUBMISSION

In the most recent Novartis cost-effectiveness submission (received by the ERG on 24 March 2010) the following base case outputs shown in Table 1 are provided from updated analyses based, firstly on the RPFST approach and, secondly on the IPCW approach. No sensitivity analyses (deterministic or probabilistic) were provided to accompany these results. The two revised analyses are examined separately below.

Table 1 : Summary outputs from Novartis updated submission (24 Mar 10)

	Everolimus plus BSC QALY	BSC alone QALY	Everolimus plus BSC LYG (months)	BSC alone LYG (months)	Inc LYG (months)	Inc QALY	Everolimus plus BSC cost (£)	BSC alone cost (£)	Inc cost (£)	ICER everolimus vs. BSC (£/QALY)
RPSFT, extended model	0.96	0.46	1.34 (16 months)	0.66 (7.9 months)	0.68 (8.2 months)	0.50	£38,353	£13,500	£24,853	£49,537
IPCW, extended model	0.96	0.56	1.35 (16.2 months)	0.807 (9.7 months)	0.54 (6.48 months)	0.398	£37,173	£16,224	£20,949	£52,648

EXAMINATION OF UPDATED RFSPT ANALYSIS

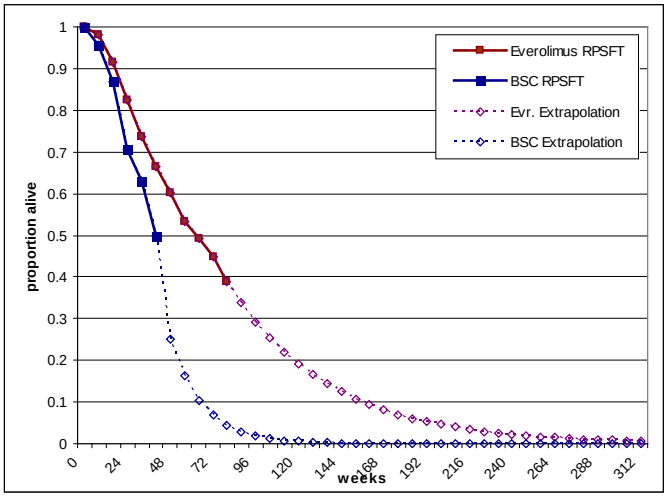
Importantly, it should be noted that the recent updated changes to the RPSFT analysis (provided on 24 March 10) do not involve the integration of any new data from the November 2008 data cut (since the previous RPSFT analysis submitted on 18 Dec 2009 was already based on the November 2008 data cut). It is rather a re-configuration of the cost-effectiveness analysis as submitted on 18 Dec 2009 based on the following two main changes to the model:

1. The time horizon of the economic model has been extended from 18 to 39 cycles (i.e from 144 to 312 weeks). This is justified given the length of the survival curves in the two arms of the model and results in a slight lowering of the base case ICER due to the inclusion of extra life years in the everolimus treatment arm.
2. The extrapolation used for overall survival curve in the BSC only arm of the model has been adjusted such that the average of the two final transition probabilities used have been to derive a constant value to extend the curve. Importantly however the updated Novartis' analysis still incorporates the questionable trial value of 0.5 in cycle 6 of the model and again uses this value for the curve extrapolation (i.e. as one of the two values averaged to provided transition values for cycles 7-39)

The resultant survival curves from the updated analysis as output by the model in the updated model are shown in Figure 2 below. This shows the curves derived from the RPSFT analysis as solid lines and the extrapolations used by Novartis as dashed lines.

Once again this graph illustrates the questionable assumption of using the single trial value (0.5) from the BSC arm of the RECORD-1 trial based on very few patients (who arguably are not typical or representative of the general population) for extrapolating the BSC curve in the model. It can be seen from Figure 2 that the use of this trial data point induces a sudden increase in the mortality hazard in the BSC arm at 48 weeks which seems difficult to justify.

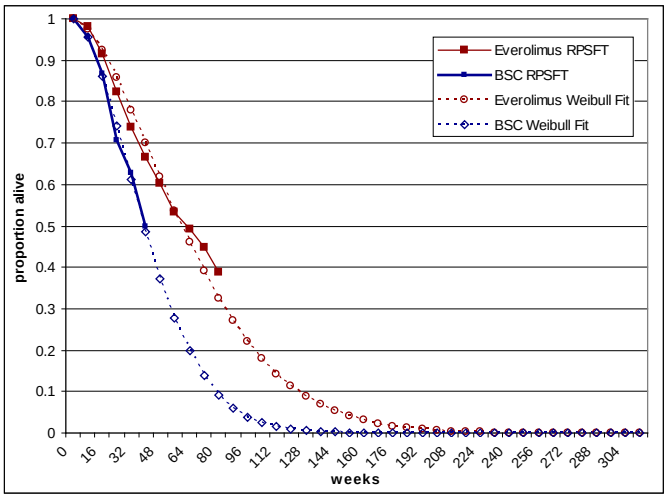
Figure 2: Overall survival curves based on Novartis updated RPSFT analysis (March 2010)



We believe, the incorporation of the cycle 6 trial data point in Novatis' model causes an over estimate of the mortality hazard for BSC arm of the model from this time point and therefore under-estimates the base case ICER for Everolimus versus BSC.

In order to investigate further the outcome of a systematic approach to extrapolation to the survival curves based on the RSFPT analysis, we fitted Weibull distribution curves to the points given in the original RPSFT analysis. The resultant fitted survival curves are shown in Figure 3 below.

Figure 3: Weibull surivival curves fitted to the original RPSFT survival curves foroverall survival of Everolimus versus BSC.



We then calibrated the model to reproduce these survival outputs by scaling the transition probabilities to death in both arms of the model such that overall survival followed the Weibull fitted curves for both Everolimus and BSC patient populations. The resultant base case outputs from the model are presented in Table 2 below.

Table 2 : Summary outputs from Model calibrated to Weibull Survival curve fits

	Everolimus QALY	BSC alone QALY	Everolimus plus BSC LYG (months)	BSC alone LYG (months)	Inc LYG (months)	Inc QALY	Everolimus plus BSC cost (£)	BSC alone cost (£)	Inc cost (£)	ICER everolimus vs. BSC (£/QALY)
RPSFT, calibrated to Weibull Fit	0.84	0.52	1.17	0.84	0.43	0.33	£33,854	£14,868	£18,986	**£58,316**

All Cost and Benefits discounted at 3.5%

EXAMINATION OF UPDATED IPCW

The updated cost-effectiveness analysis (received 24 Mar 10) based on the IPCW statistical approach to trial switching correction was provided by Novartis as an adjustment to incorporate the November 2008 data cut from the RECORD-1 trial. No sensitivity analyses were provided with these revised outputs.

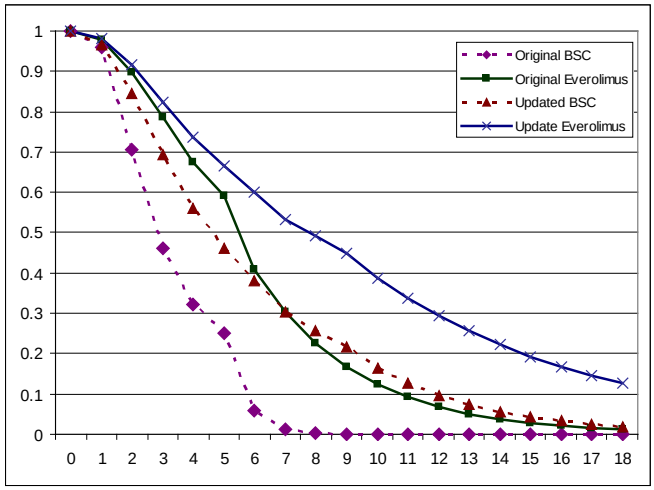
On examination of the revised IPCW analysis, we found the updated model differed considerably from the model provided in the original STA report. This is revealed clearly, for instance, through examination of the transition probabilities between the original and updated model. Table 3 below shows the transition probabilities for each arm of the original and the updated model for the first 10 cycles of the analysis. This shows clear differences, for instance, between not only the transitions to death but also for risk of adverse events and progression. Many of these changes are not fully explained in the updated Novartis submission (March 2010).

Table 3: Comparison of Transition Probabilities used in the Original Novartis model and the updated Model (submitted 24 March 2010)

BSC ARM Transition Probabilities : Original Model (STA Submission)											
cycle	0	1	2	3	4	5	6	7	8	9	10
AE Risk	[redacted]										
Progression 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]										
BSC ARM Transition Probabilities : Updated Model (March 2010)											
cycle	0	1	2	3	4	5	6	7	8	9	10
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]										
EVEROLIMUS ARM Transition Probabilities : Original Model (STA Submission)											
cycle	0	1	2	3	4	5	6	7	8	9	10
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]										
EVEROLIMUS ARM Transition Probabilities : Updated Model (March 2010)											
cycle	0	1	2	3	4	5	6	7	8	9	10
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]										

The major differences between the updated IPCW model and the original analysis is also revealed by the very different overall survival curves output by the models as shown in Figure 4 below.

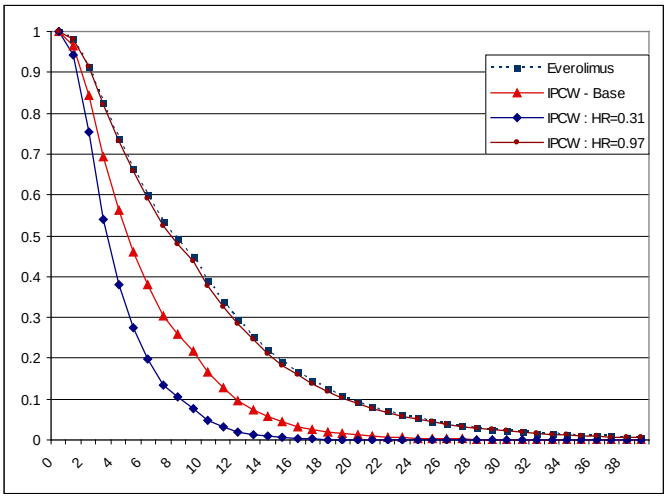
Figure 4 : Comparison of Overall Survival curves from orginal STA model and update model



Given that considerable changes have clearly been introduced to the updated IPCW model provided by Novartis and that only outline information has been provided, we were not able to provide a full critique of the updated base case analysis based on this approach. We also believe that there are good reasons to prefer the RPSFT approach over the IPCW approach for correcting for trial switching. In addition, it should be noted that there is very considerable uncertainty associated with the hazard ratio calculated using the IPCW method and that no sensitivity analyses are provided in Novartis' updated analysis.

Figure 5 below illustrates the very wide range of uncertainty associated with BSC survival curves from the IPCW analysis. This shows the survival curves at the 95% confidence limits (0.31-0.97) for the hazard ratio calculated using the IPCW method based on the RECORD-1 trial data.

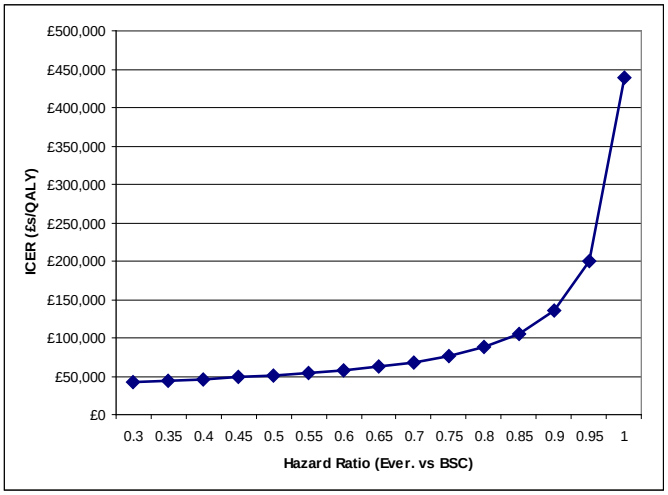
Figure 5 : BSC base case and overall survival curves at the 95% confidence limits and for the hazard ratio calculated using IPCW compared with the overall survival curve for Everolimus.



In order to analyse the effect of varying the hazard ratio for overall survival (Everolimus versus BSC) in the updated model, we varied this parameter within the model at intervals across the range 0.3 - 1. The resultant ICER values as a function of this key parameter are shown in Figure 6

below. This demonstrates that the model is highly sensitive to calculated hazard ratio for overall survival. This is especially important given the levels of uncertainty associated with its calculation (ie. 95% confidence limits = 0.31 to 0.97).

Figure 6 : Graph showing relationship between Hazard Ratio and ICER for Everolimus versus BSC using Novartis model supplied March 2010.



CONCLUSION

In conclusion, we would make the following summary points in relation to Novartis's recent submission (24 March 2010).

- The key driver for incremental QALY benefit in the model is the overall survival between modelled arms (represented by the area between the survival curves in each arm of the model).

- Incremental overall survival between arms relies on a statistical method made to correct for the large proportion of patient switching in the RECORD-1 trial. Both RPSFT and IPCW methods are presented as alternatives, although we believe there are good reasons to prefer RPSFT.

- The revised RPSFT analysis presented as part of the March submission does not use any more data than the previous RPSFT analysis submitted in December 2009 since this previous analysis also used the November 2008 data cut.

- In the revised RPSFT analysis, by extending the time horizon of the cost-effectiveness model, extra benefit incurred in the everolimus treatment arm due to patient survival beyond the original time horizon has been included. This leads to slightly increased incremental benefit and a small reduction in the ICER.

- We believe however that, in common with their previous RPSFT analysis, the revised base case ICER estimate of £49,537 in Novartis' latest submission relies on an unrealistic extrapolation of the RPSFT survival curves using a single trial data point derived from a small and unrepresentative trial population of the BSC arm.

- In order to re-evaluated the ICER based on a systematic approach to extrapolation, we fitted Weibull distribution curves to the RPSFT analysis and re-calibrated both arms of the model to output these overall survival curves. This suggests an ICER of £58,316 per QALY.

- The revised IPCW analysis provided by Novartis as part of their March 2010 submission differs considerably from that presented in the original STA submission. Insufficient information is provided in the re-submitted IPCW re-analysis to enable a full critique and only base case outputs are included.We believe that the very high levels of uncertainty associated with the overall survival hazard ratio calculated using the IPCW method entail that a sensitivity analysis based on this parameter is fundamental to its presentation.

Comments from Novartis Pharmaceuticals UK Limited on the Appraisal Consultation Document (ACD) for the Health Technology Appraisal of Everolimus for the second-line treatment of metastatic renal cell carcinoma

Thank you for your invitation to comment on the above referenced Appraisal Consultation Document (ACD) and accompanying documents, which were released on the 2nd February 2010.

Executive Summary

Everolimus is licensed for the treatment of patients with advanced renal cell carcinoma (aRCC), whose disease has progressed on or after treatment with VEGF-targeted therapy. The only current NICE approved therapy for 1st-line treatment of aRCC is the VEGF-targeted therapy sunitinib. Therefore in the absence of everolimus there are no other effective treatment options available for UK patients via the NHS.

The preliminary decision to not recommend everolimus is based on the estimates of cost-effectiveness presented by PenTAG. It was felt that Novartis had under-estimated overall survival (OS) in the best supportive care (BSC) arm using both modelling approaches presented. In order to correct for this perceived underestimation of OS in the BSC arm in the Novartis models, PenTAG made various adjustments which resulted in incremental cost-effectiveness ratios (ICERs) of £65,200 and £75,700 (IPCW and RPSFT methods respectively). However, as the difference in OS between everolimus and BSC is one of the biggest influences on the resulting incremental cost-effectiveness ratio (ICER) it is important that the estimates of OS in the BSC arm are realistic and justified based on the available evidence.

Critically, it is noted that the ICER of £75,700 presented by PenTAG is based on an OS in the BSC arm of 10.9 months (discounted). Novartis strongly believe a mean OS of 10.9 months is not reflective of clinical outcomes in patients who fail 1st-line sunitinib therapy and then receive only BSC in the 2nd-line setting. As with any modelling if the results are not reflective of clinical reality then the resulting ICERs need to be challenged.

In the original submission Novartis presented an economic analysis based on the Inverse Probability Censoring Weights (IPCW) statistical approach using the February 2008 data cut of the pivotal, phase III, everolimus, RECORD-1 trial. In response to comments in the ERG Report that a rank preserving structural failure time (RPSFT) statistical approach might be preferable, Novartis undertook to conduct the RPSFT analysis, based on the November 2008 data cut, and presented the results within a two week timeframe. This was conducted in the hope of providing a more comprehensive evidence base to inform the Appraisal Committee

and thus facilitate a faster decision. Both the IPCW and RPSFT economic analyses presented by Novartis were subsequently adjusted by PenTAG to allow for a perceived underestimation of survival in the BSC arm of the economic model. However, based on an additional body of evidence described below, including the views of national and international clinical experts experienced in treating aRCC, the PenTAG adjustment to the RPSFT analysis giving a cost/QALY of £75,700 is not clinically plausible as it relies on an estimate of mean survival in the BSC arm of 10.9 months (11.2 months undiscounted). Moreover we have been able to show by statistical means that the PenTAG suggested correction to the IPCW model results in an overall, effective hazard ratio of 0.6 rather than the intended HR of 0.55. This means that survival in the BSC arm is over-estimated thus inflating the ICER. In order to provide the Appraisal Committee with the most plausible and robust estimates of cost-effectiveness we have updated both of our analyses (IPCW and RPSFT) to take into account PenTAG's criticisms and incorporate the longest term clinical data from the RECORD-1 trial ie data from the November 2008 analysis. This has resulted in revised estimates of cost-effectiveness of £49,537/QALY (RPSFT) and £52,648/QALY (IPCW). The underlying estimates of mean overall survival in the BSC arm are 7.9 months and 9.6 months respectively (discounted values). Based on the evidence that we have compiled since the ACD was issued, the latter estimates of survival are more plausible, than the estimates presented by PenTAG. These updated incremental cost-effectiveness ratios are lower than those previously presented due to the greater survival demonstrated in the longer term November 2008 analysis and the addition of further cycles in the model to capture the additional benefit. The original model was developed for the February 2008 data cut and therefore only required 18 cycles to capture the available data. However, as stated in our submission of the RPSFT analysis, due to the fact that the November 2008 data-cut suggests greater survival than the February 2008 data-cut, there are more everolimus patients still alive in the final cycle (cycle 18) of the original economic model. Unfortunately, there was insufficient time to add further cycles to the model to account for this when we submitted the RPSFT analysis (due to the 2 week turnaround required) but we have now been able to update the model in order that all of the benefits of everolimus can be reflected in the economic analysis [39 cycles are required to fully account for the additional survival]. The overall impact of allowing this greater survival to be taken into account in the model has been to reduce the ICER. This is because there is greater survival and therefore QALY's in the everolimus arm but no further everolimus treatment costs as these are only applicable for the stable disease states. Full details of these updated analyses follow in the remainder of the document. The results from the PenTAG, RPSFT adjusted analysis and updated Novartis analyses are provided in the following table for ease of comparison.

Table 1 – Comparison of ICERs and Estimates of Survival in the BSC arm from the Economic Models

Analyses (Nov 2008 OS data)	Estimate of cost effectiveness - QALY (with PAS)	Mean OS on BSC arm*
PenTAG RPSFT	£75, 700	10.9 months
Novartis RPSFT	£49, 537	7.9 months
Novartis IPCW	£52, 648	9.6 months

* Discounted values of OS

NB: The PenTAG adjusted IPCW results have not been presented here as it is based on the February 2008 data cut which is not directly comparable with the results above.

All of the results presented in the above table take into account the patient access scheme (PAS) which was put in place by agreement between Novartis and the DoH, prior to our submission in order to facilitate a positive decision as soon as possible. As this scheme has been approved by the DoH, and is already being implemented by the NHS, the results which incorporate the PAS are the appropriate ones to be considered.

The following section summarises an additional body of clinical evidence in order to help the Appraisal Committee decide what constitutes the most plausible estimate of survival in patients receiving BSC following sunitinib failure. The evidence supplied includes the most recent, relevant publications and a survey reflecting UK clinical expert opinion. It should be noted that the reason for conducting the survey was not revealed to the respondents. Finally, because of the lack of directly applicable publications in this area Novartis also requested, and was provided with, primary patient data from clinicians with experience of 1st line sunitinib use to demonstrate what happens to patient's with no 2nd line treatment. Although retrospective in nature, this crucially provides actual UK clinical data from two large London teaching hospitals, The Queen Elizabeth hospital in Birmingham and from two hospital's in the Royal Wolverhampton NHS trust to demonstrate OS in routine clinical practice for patients that received sunitinib therapy and no active 2nd-line therapy following sunitinib failure. A table comparing OS in patients failing on 2nd-line sunitinib is presented below.

Table 2 – Comparison of Overall Survival in Patients Failing 1st-line Sunitinib

Source	Evidence type	First line-therapy	Second line therapy	Overall survival
Di Lorenzo 2009[i]	Published Journal of Clinical Oncology Aug. 2009	sunitinib	sorafenib	7.4 months*
Liu *et al 2009*[ii]	Abstract at ECCO/ESMO Sept. 2009	sunitinib	BSC	5.2 months*
St Bart's hospital, London (n= 49)	retrospective analyses of patient records from UK hospital	sunitinib	BSC	5.0 months from progression to death**
Royal Marsden hospital, London (n= 62)	retrospective analyses of patient records	sunitinib	BSC	2.12 months from stopping treatment to death**
Queen Elizabeth hospital, Birmingham (n=94)	retrospective analyses of patient records	sunitinib	BSC	3.8 months from disease progression to death* (includes data for all patients)
The Royal Wolverhampton NHS Trust (n= 8)	retrospective analyses of patient records	sunitinib	BSC	2.6 months from stopping treatment to death**
Clinician survey	on-line survey	sunitinib	BSC	6.1 months after failing

				first line treatment**

* median OS ** mean OS

Because of the lack of prospective clinical data Novartis approached 4 institutions to ask if they were able to provide data to us for the purpose of verifying in UK clinical practice what the OS was for patients who received 1st line sunitinib and then no further anti-cancer therapy.

St Bartholemew's hospital in central London has had gained a lot of experience with sunitinib because of its involvement with the Pfizer expanded access programme and other sunitinib clinical trials. Data from clinical practice which included patients from 2006 to present showed that the median time from CT defined progression to death is 5 months (95% CI 3-7 months). No patient received targeted therapy in the 2nd-line, however some did receive chemotherapy. Patients were excluded from the analyses if they stopped treatment before assessment of disease progression occurred, if they stopped due to toxicity or died on sunitinib or were not assessable for disease progression. It was also noted by the clinician that "most patients continued on sunitinib" even though disease progressed according to RECIST criteria. Novartis feel this is likely to be because of the maintenance of clinical benefit even when disease is progressing according to RECIST criteria.

Novartis would also like to highlight to the Appraisal Committee that patients may have continued to receive sunitinib post-progression due to the lack of alternative active treatment options, especially where the patient maintained performance status, and there was the perception of clinical benefit for the patient and/or clinician beyond RECIST criteria measures.

The Royal Marsden hospital in South West London also provided retrospective data to Novartis as a result of their long term access to sunitinib through clinical trials and the Pfizer expanded access programs. The data included a total of 87 patients with advanced RCC starting sunitinib at the Royal Marsden Hospital between 2005 and December 2008 that had progressed after an adequate period of treatment and died (not including patients who died on sunitinib treatment or stopped due to toxicity). For the 62 patients who received no 2nd-line therapy the median time to death from stopping sunitinib treatment was 64.5 days (2.12 months). Again considerably shorter than the average 10.9 months OS suggested by the PenTAG model (discounted).

In addition to this The Queen Elizabeth hospital, Birmingham, provided us with audit data for aRCC patients treated with sunitinib and no further treatment. Due to the centres involvement with sunitinib clinical trials and the expanded access program experience dated back to 2006 and included patients right up to the

present time there was data for 94 patients. For these patient's the median OS was found to be 3.8 months. This data does include patients not yet dead although as there are 23 patients, if these patients are excluded the median overall survival would be much lower.

A clinician with experience of sunitinib use from two hospitals that are part of the Royal Wolverhampton NHS Trust provided data for 8 patients started between 03/2007 and 05/2009. Here the median OS from stopping treatment to death is 2.6 months (2 patients have stopped treatment but remain alive so are not part of this calculation). Patients were not part of the audit if they were taken off treatment due to toxicity or death.

Finally, Novartis undertook a quantitative on-line survey of clinicians experienced in treating advanced RCC in the UK. No information was provided to respondents about the reason for the survey or who was sponsoring it. Thirty seven clinicians responded to the questionnaire, of these, 26 were consultant grade and 11 were specialist registrars (year 5+) and 34 of the 37 responders were from either teaching hospitals or tertial centres. On average the clinicians treated 33 aRCC patients a year. As Novartis have previously submitted to NICE an estimated eligible patient pool of 982 we believe this covers most of the aRCC population. Novartis feels the sample represents clinicians sufficiently experienced in the treatment of the disease and likely to be involved in prescribing these drugs.

The survey results showed clinicians expected the mean OS after failure on sunitinib with no further active treatment to be 6.1 months (6 months median). 57% of clinicians anticipated the range would be between 6-9 months and only 8% of those surveyed believed OS would be 10-12 months.

There is no published evidence directly in line with the decision problem ie patients who receive BSC only following failure on sunitinib therapy. However, the publication by Di Lorenzo *et al*. 2009, is informative with regards to OS for 2nd-line patients following sunitinib. The study evaluated the efficacy of sorafenib following failure on sunitinib. The median OS for these patients was 7.4 months.[i] In many respects the patients in this study were reflective of those in the everolimus study (RECORD-1) but patients on the Di Lorenzo study could be considered as having a slightly better prognosis based on the fact patients in this study generally had better MSKCC profiles which included better performance status and lower rates of metastatic disease in organs such as the liver, lungs and lymph nodes.[i,vi] Considering the fact that these patients were on active anti-tumour therapy and the patients generally had superior prognostic scores, the median OS of 7.4 months might be expected to be a best case scenario or even superior compared to patients who get BSC only following sunitinib.[i]

Finally, Liu *et al*. presented a poster at European CanCer Organisation/European Society for Medical Oncology (ECCO/ESMO) in September 2009 which retrospectively evaluated patients survival following discontinuation of sunitinib or sorefenib in aRCC patients from routine clinical practice. The median OS results in this study for patients who only received sunitinib was 5.2 months.[ii]

In summary, the preliminary recommendations are based on estimates of cost-effectiveness resulting from PenTAG's adjustments to the Novartis analyses i.e £75,700 and £65,200. However, these estimates are misleading and are unlikely to represent the true value of everolimus. This is because the estimate of £75,700 relies on an estimate of survival in the BSC arm which is unrealistic based on the evidence which has been collated since the Appraisal Committee meeting on the 13th January. In addition, the £65,200 is based on an earlier data cut from the RECORD-1 trial and does not reflect the intended overall, effective mortality HR of 0.55. It is important that the final decision regarding the use of everolimus for aRCC patients should rely on estimates of cost-effectiveness that are based on assumptions of OS in BSC patients that are realistic and consistent with the best available clinical evidence.

We therefore respectfully request that due consideration is given to the additional evidence and revised estimates of cost-effectiveness which take into account all of PenTAG's criticisms, as well as the longer term data available from the RECORD-1 trial. These results demonstrate that everolimus is clinically-effective and based on the end of life criteria, a cost-effective treatment for patients with aRCC who fail on 1st-line sunitinib therapy.

Detailed Response to Matters Arising from the Appraisal Consultation Document

The preliminary decision not to recommend everolimus is based on the estimates of cost-effectiveness presented by PenTAG. This is because it was felt that Novartis had underestimated OS in the BSC arm using both modelling approaches presented. Based on the information that we have compiled from the published literature, data from routine clinical practice and clinical expert opinion, Novartis strongly believe that the preliminary recommendation is not justified.

Therefore based on the above, we do not believe that the provisional recommendations of the Appraisal Committee are sound nor do they constitute a suitable basis for the preparation of guidance to the NHS.

The document is presented as follows:

Section A – Main concern

Section B – Reasons why the current recommendations do not take into account all of the available evidence.

Section C - Updated Estimates of Cost-effectiveness Incorporating PenTAG's Criticisms and November 2008 RECORD-1 data

Section D – Reasons why we do not believe that the provisional recommendations as detailed in the ACD are justified nor do they constitute a reliable basis for the provision of sound guidance to the NHS

Section A – Main Concern

Novartis' main concerns regarding the preliminary decision, are summarised below:-

A1. the preliminary recommendations are based on estimates of cost-effectiveness resulting from PenTAG's adjustments to Novartis' analyses i.e £75,700 and £65,200. However, these estimates are misleading and are unlikely to represent the true value of everolimus. The reasons for this are as follows:

- the estimate of £75,700 from PenTAG's "exploratory analysis" using RPSFT is underpinned by a clinically unrealistic estimate of OS in the BSC arm of 10.9 months (11.2 months undiscounted). This estimate is therefore unlikely to either represent the most plausible estimate of cost-effectiveness, or reflect the true magnitude of survival benefit conferred by everolimus;

- we have been able to show by statistical means that PenTAG's adjustment to the IPCW analysis results in an overall effective HR of 0.6 rather than 0.55. Therefore the estimate of cost-effectiveness of £65,200 is artificially inflated and should not be used as the basis for decision-making. In addition, this estimate is based on the less mature, February 2008 data cut, from the RECORD-1 trial.

These issues, as well as our other comments, are addressed in more detail below and are set out as per the requested headings.

B. The current recommendations do not take into account all of the available evidence. In addition, the provisional recommendations as detailed in the ACD are not justified, nor do they constitute a reliable basis for the provision of sound guidance to the NHS.

> **B1. The preliminary decision is based on the conclusion that PenTAG's estimates of cost-effectiveness are more plausible than those presented by Novartis. However, the survival estimate for BSC of 11.2 months (undiscounted) which underpins PenTAG's cost/QALY of around £75,700 is not deemed to be clinically plausible based on the available evidence.**
>
> B1. i) A paper by Di Lorenzo *et al.* 2009 reports on a study which evaluated the efficacy of sorafenib, in patients who failed sunitinib therapy.[i] These patients were receiving active treatment for their disease as well as being well matched to the RECORD-1 patients with respect to baseline characteristics and, where there were differences, these favoured the sorafenib patients ie the prognostic risk factors such as MSKCC profile, performance status and rates of metastases in liver, lungs and lymph nodes were such that one might expect the patients in the sorafenib study to live

longer than those in the RECORD-1 study. This means that survival in the sorafenib patients might be a reasonable and conservative proxy for the BSC patients in the RECORD-1 study.[i,iv] The results from the Di Lorenzo study demonstrated that the median survival in the sorafenib patients was 7.4 months. This is broadly consistent with the estimate of survival from the Novartis RPSFT analysis which estimates a mean survival in BSC patients of 7.9 months, (8.1 months undiscounted).[i]

B1. ii) A poster by Liu *et al.* presented at the European CanCer Organisation/European Society for Medical Oncology (ECCO/ESMO) in September 2009, evaluated survival rates following discontinuation of sunitinib and sorafenib in aRCC patients in routine clinical practice.[ii] This study involved a retrospective review of data from a US claims database on patients with aRCC. Patients were included in the study if they received sunitinib only, sorafenib only or both treatments and then discontinued treatment with no further active therapy. Survival was estimated as time from discontinuation of sunitinib or sorafenib to death. Of the 451 patients identified, 264 patients discontinued treatment and did not restart therapy. Of these 131/264 patients had received sunitinib, 70/264 patients had received sorafenib and 63/264 had received both sunitinib and sorafenib. The median survival in patients who received sunitinib only was 5.2 months.[ii]

B1. iii) As presented in our submission evidence from the literature suggests that, if left untreated, patients with advanced renal cell carcinoma (aRCC) have a limited life expectancy, with a median survival without treatment of 6 to 12 in the first-line setting.[iii,iv,v,] Data from the years prior to VEGF targeted therapy clearly demonstrate that patient's given hormone treatment (medroxyprogesterone) aimed at symptom relief only have a median OS of 6 months.[vii]

There is no direct data published to inform the Appraisal Committee on a patient's OS after TKI therapy if they receive no further active therapy i.e. BSC only 2nd-line. This is mostly because cross over from placebo to active treatment upon progression remained high in trials with targeted agents or because information on PFS is not provided.

However, patients who are eligible for everolimus will be more advanced with respect to time from diagnosis of aRCC compared to those who have not already failed on at least one previous therapy.[vi] This is important because there is an increasing amount of pre-clinical evidence to suggest that disease may progress more rapidly after resistance develops with sunitinib use,[viii] raising the possibility that once patients progress on sunitinib they will have a shorter median OS compared to patients

untreated in the 1st line. There is also some limited clinical evidence to support this hypothesis in aRCC clinical practice. In a small, UK clinical study, patients were given chemotherapy after progression on sunitinib. The results of this study for patients with aRCC who had previously been progressed on cytokine therapy and then sunitinib the OS was a median of 4.2 months. [ix]

B1. iv) St Bartholemew's hospital in central London has gained a lot of experience with sunitinib because of its involvement with the Pfizer expanded access programme and other sunitinib clinical trials. Data from clinical practice which included patients from 2006 to current use showed that the median time from CT defined progression to death is 5 months (95% CI 3-7 months). No patient received targeted therapy in the 2nd-line however some did receive chemotherapy. Patients were excluded from the analyses if they stopped treatment due to toxicity or died on sunitinib. It was also noted by the clinician that "most patients continued on sunitinib" even though disease progressed according to RECIST criteria. Novartis feel this is likely to be because of the maintenance of clinical benefit.

Novartis would also like to highlight a point made in our initial submission that patient's may have continued on sunitinib post-progression due to the lack of alternative active treatment options where the patient remained fit and there was the perception of clinical benefit for the patient and/or clinician.

The Royal Marsden Hospital in South West London also provided retrospective data to Novartis as a result of their long term access to sunitinib through clinical trials and the Pfizer expanded access programs. The data included a total of 87 patients with advanced RCC starting sunitinib at the Royal Marsden Hospital between 2005 and December 2008 that had progressed after an adequate peroid of treatment and died (not including patients who died on sunitinib treatment or stopped due to toxicity). For the 62 patients who received no 2nd line therapy the median time to death from stopping sunitinib treatment was 64.5 days (2.12 months). Again considerably shorter than the average 10.9 months OS suggested by the PenTAG model (discounted).

In addition to this The Queen Elizabeth hospital, Birmingham, provided us with audit data for aRCC patients treated with sunitinib and no further treatment. Due to the centres involvement with sunitinib clinical trials and the expanded access program experience dated back to 2006 and included patients right up to the present time there was data for 94 patients. For these patient's the median OS was found to be 3.8 months. This data does

include patients not yet dead although as there are 23 patients, if these patients are excluded the median OS would be lower.

A clinician with experience of sunitinib use from 2 hospitals that are part of the Royal Wolverhampton NHS Trust provided data for 8 patients started between 03/2007 and 05/2009. Here the median OS from stopping treatment to death is 2.6 months (2 patients have stopped treatment but remain alive so are not part of this calculation). Patients were not part of the audit if they were taken off treatment due to toxicity or death.

B1. v) The results from a market research survey demonstrate that 57% of the oncologists surveyed believe, that based on experience, patients live for an average of 6-9 months from discontinuation of sunitinib, if left untreated. Compared to only 8% of responders believing that OS would be 10-12.

B1 vi) Section 3.19, page 13 of the ACD referring to the Novartis RPSFT model states,

"The ERG stated that the mortality risk in the best supportive care arm had been overestimated." and

"The ERG conducted an exploratory analysis using revised transition probabilities for the best supportive care arm of the model."

The exploratory analysis conducted by PenTAG involved ignoring the last transition probability (cycle 6), calculating a mean of the two previous cycles (cycles 4 and 5) and then applying this value from cycle 6 to cycle 18 in the model. The impact of this revision was to increase the estimated mean survival in the BSC arm from 7.7 months (undiscounted) to 11.2 months (undiscounted). As described above, the latter estimate of mean survival for BSC patients post-sunitinib is likely to be unrealistic whereas the estimate of 7.7 months presented in our original RPSFT model is more consistent with the available evidence base whilst remaining conservative.

In order to address PenTAG's concerns that our estimate of survival is based on a single data point we have presented an updated analysis which uses an average of the last two cycles ie the same approach as that adopted by PenTAG in their exploratory analysis. The results from this analysis give a cost/QALY for everolimus of £49,537. Full details of this updated analysis are provided in Section C1, i) below.

B1 vii) Section 3.15, page 11 of the ACD referring to the Novartis IPCW model states,

"Secondly, the ERG stated that in applying the mortality hazard ratio, the manufacturer overestimated the mortality in the best supportive care arm."

In order to correct for this overestimation, PenTAG applied a hazard rate multiplier to each cycle in the model, under the assumption that if each cycle HR equates to 0.55 then the overall effective HR across all cycles would also be 0.55. To evaluate whether the PenTAG adjustment actually results in the intended effect, we analysed the survival curve outputs from the economic model following application of PenTAG's adjustments using regression analysis. A virtual cohort of 20,000 patients (10,000 per arm) were run through the PenTAG adjusted economic model and the resulting survival distributions were analysed using Cox proportional hazards regression with the dependent variable being death and the independent variable being treatment assignment. Patients alive at the end of the model were censored at that point. The results from this analysis demonstrate that the impact of PenTAG's adjustment results in an effective mortality HR of around 0.60 ie mortality in the BSC is underestimated. This was confirmed by an independent health economics statistician from ScHARR, Dr Patrick FitzGerald. Consequently this means that the associated ICER of £65,200 produced by PenTAG is artificially inflated. In order to provide a more robust estimate of cost-effectiveness from the IPCW model, we have updated the analysis to include data from the November 2008 analysis. In addition, we have taken into account PenTAG's criticisms relating to overestimation of mortality in the BSC arm, applying the hazard ratio to rates rather than the transition probabilities and applying the discounting from cycle 2 rather than year 2. In order to check that our approach to applying the 0.55 HR resulted in the desired effect we used the same statistical approach described above and calibrated the results to yield an overall effective HR of 0.55. This confirmed that the implementation of the IPCW method in the model resulted in the intended HR of 0.55. The results from this analysis give a cost/QALY of £52,648. Full details of this updated analysis are provided in Section C1, ii) below.

In summary, as detailed above, the conclusion that PenTAG's estimates of survival in the BSC arm and associated estimates of cost-effectiveness are the most plausible is not supported by the available evidence base nor is it consistent with the views of clinical experts who have experience of treating aRCC. In addition, we have demonstrated through statistical means that the PenTAG adjustment to the IPCW approach did not result in the intended effective mortality hazard ratio of 0.55 but resulted instead in a hazard ratio

of 0.60. This means that the PenTAG adjustment underestimated mortality in the BSC arm thus providing an inflated estimate of cost-effectiveness for everolimus. For these reasons, Novartis believe the preliminary decision published in the ACD cannot be considered as sound in the light of the evidence and the draft recommendation does not represent a fair, balanced or evidence based foundation for the provision of guidance to the NHS.

C1. Updated Estimates of Cost-effectiveness

In order to provide the Appraisal Committee with the most robust and plausible estimates of cost-effectiveness we have updated both of our analyses (RPSFT and IPCW) to take into account PenTAG's criticisms and incorporate the longest term clinical data from RECORD-1 ie data from the November 2008 analysis.

C1. i) Updated RPSFT Analysis

The RPSFT analysis was conducted in response to comments in the Evidence Review Group (ERG) Report that an RPSFT analysis would be preferable to the IPCW approach. Novartis therefore sought and received permission to undertake an RPSFT analysis within a two week timeframe. This initial analysis showed that results from the RPSFT approach were similar to those presented for the IPCW approach. As stated in our submission of the RPSFT results, the limited timeframe did not allow us to add further cycles to the model to fully capture the additional survival in the RECORD-1 trial demonstrated by the November 2008 data cut as compared to the survival indicated from the earlier February 2008 analysis. In the aforementioned submission we highlighted that the impact of adding further cycles to the RPSFT model would be to decrease the incremental cost-effectiveness ratio due to the additional life years gained (LYG), and therefore QALY's, in the everolimus arm but no further everolimus treatment costs as these are only applicable for the stable disease states. In order to take into account PenTAG's criticisms of our RPSFT analysis and fully incorporate the additional survival benefits demonstrated by the November 2008 data cut the following revisions have been made:

- the number of cycles in the model have been increased from 18 to 39 in order to capture the greater survival demonstrated by the November 2008 data cut;
- as suggested by PenTAG, discounting at a rate of 3.5% has been applied from cycle 2;
- in the BSC arm, for states leading to death, rather than carry the last transition probability forward for the remaining cycles (as in our previous model), we have calculated an average of the transition probabilities from cycles 5 (0.21) and 6 (0.5) and applied this average value (0.35) to all remaining cycles ie cycles 7 to 39.

All other aspects of the model remain unchanged. The associated transition probabilities are provided in Appendix 1.

The results from these revisions are presented in the table below.

Table 3 – Cost-effectiveness results from the RPSFT analysis using the November 2008 data cut from RECORD-1 and extended economic model with PAS

	Everolimus plus BSC QALY	BSC alone QALY	Everolimus plus BSC LYG (months)	BSC alone LYG (months)	Inc LYG (months)	Inc QALY	Everolimus plus BSC cost (£)	BSC alone cost (£)	Inc cost (£)	ICER for everolimus plus BSC versus BSC alone (£/QALY)
RPSFT, extended model	0.96	0.46	1.34 (16 months)	0.66 (7.9 months)	0.68 (8.2 months)	0.50	£38,353	£13,500	£24,853	**£49,537**

The deterministic results from this analysis give an incremental cost-effectiveness ratio of £49,537 (with PAS). This is underpinned by a mean estimated survival of 7.9 months in the BSC arm and 16.1 months in the everolimus arm. In order to achieve a target threshold of £30,000 per QALY gained, a QALY weight of 1.66 would be required. This QALY weight is within previously accepted limits based on products meeting the end of life criteria.

C1. ii) Updated IPCW Analysis

The IPCW analysis presented in our original submission was based on data from the February 2008 data cut. The later November 2008 data cut demonstrated greater survival in everolimus patients than that indicated by the February 2008 analysis. In order to take account of the updated results and take into account PenTAG's criticisms the following revisions have been made to the IPCW analysis:

- data from the November 2008 data cut has been used to populate the model;
-the number of cycles in the model have been increased from 18 to 39 in order to capture the greater survival demonstrated by the November 2008 data cut;
- as suggested by PenTAG, discounting at a rate of 3.5% has been applied from cycle 2;
- as suggested by PenTAG, the HR multiplier has been applied to rates rather than the transition probabilities:

- as suggested by PenTAG, in the BSC arm, for states leading to death, rather than carry the last transition probability forward for the remaining cycles (as in our previous model), we have calculated an average of the transition probabilities from cycles 10 (0.24) and 11 (0.23) and applied this average value (0.23) to all remaining cycles ie cycles 12 to 39.
- overestimation of mortality in BSC arm is corrected by applying the same rate to all transitions leading to death ie from stable disease with adverse events, stable disease without adverse events and progressed disease to death.
- transition probabilities were calibrated to ensure an effective HR of 0.55. The effective HR was checked by running a virtual cohort of patients through the model and analysing the survival output using a Cox proportional hazards model.

All other aspects of the model remain unchanged. The associated transition probabilities are provided in Appendix 1.

The results from the updated analysis are presented in the table below.

Table 4 – Cost-effectiveness results from the IPCW analysis using the November 2008 data cut from RECORD-1 and extended economic model with PAS

	Everolimus plus BSC QALY	BSC alone QALY	Everolimus plus BSC LYG (months)	BSC alone LYG (months)	Inc LYG (months)	Inc QALY	Everolimus plus BSC cost (£)	BSC alone cost (£)	Inc cost (£)	ICER for everolimus plus BSC versus BSC alone (£/QALY)
IPCW, extended model	0.96	0.56	1.35 (16.2 months)	0.807 (9.7 months)	0.54 (6.48 months)	0.398	£37,173	£16,224	£20,949	**£52,648**

The deterministic results from this analysis give an incremental cost-effectiveness ratio of £52,648 (with PAS). This is underpinned by a mean estimated survival of 9.7 months in the BSC arm and 16.2 months in the everolimus arm. In order to achieve a target threshold of £30,000 per QALY gained, a QALY weight of 1.75 would be required. This QALY weight is within previously accepted limits based on products meeting the end of life criteria. In addition, this is likely to be a conservative estimate of cost-effectiveness as it is underpinned by an assumption of survival in the BSC arm which is optimistic based on the available evidence.

D. We do not believe that the provisional recommendations as detailed in the ACD are justified nor do they constitute a reliable basis for the provision of sound guidance to the NHS.

D1. The decision not to recommend everolimus for the treatment of patients with advanced renal cell carcinoma (aRCC), whose disease has progressed on or after treatment with VEGF-targeted therapy is inappropriate as it relies on the view that the estimates of cost-effectiveness presented by PenTAG are more plausible than those presented by Novartis. This is contrary to the available evidence base.

As detailed in Section A1 of this document, Novartis strongly believes the rejection of everolimus for aRCC is perverse in the light of the evidence for the following reasons:
- the estimate of survival for BSC patients (11.2 months undiscounted) which underpins PenTAG's estimate of cost-effectiveness is not clinically plausible. This means that the resulting estimate of £75,700/QALY is highly conservative and does not reflect the true value of everolimus;

- the estimate of cost-effectiveness of around £65,200/QALY has been shown using statistical means to overestimate survival in the BSC arm thus artificially inflating the cost/QALY.

In summary, the preliminary recommendations are perverse in the light of the evidence and accordingly, do not constitute a reasonable or sound basis on which to base guidance to the NHS. In particular, the belief that the estimates of survival for BSC, and therefore cost-effectiveness, are more plausible based on PenTAG's adjustments and exploratory analysis are not supported by the available evidence base or the views of clinical experts. We therefore respectfully request that due consideration is given to the additional evidence and revised estimates of cost-effectiveness which take into account all of PenTAG's criticisms, as well as the longer term data available from the RECORD-1 trial. The revised estimates of cost-effectiveness £49,537/QALY (RPSFT analysis) and £52,648/QALY (IPCW) analysis. These results demonstrate that everolimus is a clinically-effective treatment for aRCC patients with estimates of cost-effectiveness which are within acceptable limits based on previous appraisals for products meeting the end of life criteria.

E. Other comments

Section 3.7, page 7
This section states,

"There were more adverse events and serious adverse events (grades 3 to 4) in the everolimus plus best supportive care arm (40.1%) than the placebo plus best supportive care arm (22.6%)."

This is confusing as the section refers to both adverse events and serious adverse events. We therefore propose the following amendment,

"There were more serious adverse events in the everolimus plus best supportive care arm (40.1%) than the placebo plus best supportive care arm (22.6%)."

Section 3.18, page 13
This section states,

"This equated to a mean overall survival of 15.18 months with everolimus plus best supportive care and 7.67 months with best supportive care alone (a non-statistically significant gain of 7.51 months)."

This statement is misleading as the estimates of survival quoted are generated by the economic model which are not the subject of statistical testing. We therefore propose that the statement is amended as follows,

"Estimates of mean overall survival of 15.18 months with everolimus plus best supportive care and 7.67 months with best supportive care alone were generated by the economic model."

Section 4.8, page 17
This section states,

"Firstly it did not agree with the assumption that people starting everolimus therapy would all have stable disease without adverse events."

It is not clear what is meant by this statement. All patients enter the economic model in the stable disease state without adverse events. Once on treatment, some patients will develop adverse events. The rate at which patients move from the stable disease without adverse events health state to the stable disease with adverse events health state is calculated based on patient data from the RECORD-1 study.

Section 4.13, page 19
This section states,

" The Committee heard concerns from the ERG that the RPSFT method had been applied incorrectly by the manufacturer. The application of the transition probabilities led to overestimation of the mortality risk."

It is not clear why the ERG considered the application of the transition probabilities to be an overestimation of the mortality risk. The RPSFT analysis presented by Novartis resulted in an estimate of mean survival in the BSC arm of around 8 months. Based on the available evidence this estimate of survival is likely to be more plausible than the estimate of mean survival in PenTAG's analysis of around 11 months.

Section 4.15, page 20
This section states,

" The Committee heard that the life expectancy for people with advanced RCC receiving best supportive care alone was unlikely to be greater than 24 months and was potentially as low as 6 months."

This statement is misleading. Patients who are eligible for everolimus are those who have failed treatment with sunitinib ie everolimus is indicated for a 2nd line setting. The available evidence suggests that the life expectancy of patients on BSC following sunitinib failure is likely to be considerably less than 11 months.

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A Retrospective Review of Treatment Discontinuation and Survival in Patients With Advanced Renal Cell Carcinoma Treated With Sunitinib or Sorafenib

Zhimei Liu,[1] Ji Zheng,[1] Aylin Altan Riedel,[2] Jonathan Johnson,[2] James Burke[2]

[1]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States; [2]i3 Innovus, an Ingenix Company, Eden Prairie, MN, United States

Background

- The prognosis for patients with metastatic renal cell carcinoma (mRCC) is poor. Patients have an overall median survival of less than a year, and less than 10% survive beyond 5 years prior to the introduction of recent targeted therapies[1]
- The multitargeted tyrosine kinase inhibitors sunitinib and sorafenib have been approved for the treatment of mRCC in the United States. Both sunitinib and sorafenib inhibit vascular endothelial growth factor and platelet-derived growth factor receptors[2,3]
- Sunitinib and sorafenib have both been shown in clinical trials to increase progression-free survival in mRCC patients. However, neither drug has been shown to lead to long-term disease-free survival in significant numbers of patients[4]
- The median duration of treatment was 6 months in a large phase 3 trial of sunitinib and 5.8 months in a large phase 3 trial of sorafenib[5,6]
- A different perspective on drug effectiveness may be obtained in a real-world setting, as many clinical studies employ inclusion criteria based on disease prognosis and may not be reflective of patients in the general population

Objective

- Examine treatment patterns in a "real-world" population of advanced RCC patients receiving sunitinib and/or sorafenib therapy and evaluate survival rates following discontinuation of these therapies

Methods

Study Design

- A retrospective claims study of commercially insured and Medicare patients in the United States
- Data was obtained from an insurance claims database of a large national health plan and included medical data, pharmacy data, enrollment information, and death data

Patient Population

- A diagnosis code for RCC (ICD-9-CM code of 189.0 in any position) sometime between January 1, 2003 and December 31, 2007
- Continuous health plan enrollment for 90 days before the index date (defined as the earliest date of RCC diagnosis)
- At least 18 years of age
- Use of sunitinib and/or sorafenib during the follow-up period (lasting until death or March 31, 2008)

Outcome Measures

- Discontinuation
  - Defined as discontinuation of index therapy (sunitinib or sorafenib) with no restart of medication prior to the end of the follow-up period
  - For patients who used both sunitinib and sorafenib during the follow-up period, discontinuation from the last fill of either drug (whichever occurs latest) was identified
- Discontinuation date
  - Defined as the date of the last fill for sunitinib or sorafenib + days supply from that claim
- Treatment duration
  - For patients who discontinued therapy, duration of treatment was measured as the number of months from initiation of index therapy to discontinuation of therapy
  - For patients who did not discontinue therapy, duration of treatment was calculated as the number of months from initiation of index therapy to the minimum of the end of the follow-up period, the date at which death data was captured, or the death date
- Survival
  - Length of survival time was right-censored at the date at which death data was captured for patients who survived beyond that date
  - Median survival times were estimated by the Kaplan-Meier method

Results

Patient Cohorts

- 451 patients were identified for study inclusion
  - 222 patients were treated with sunitinib alone
  - 127 patients were treated with sorafenib alone
  - 102 patients were treated sequentially with both sunitinib and sorafenib

Patient Demographics

	Total (N=451)		Sorafenib (N=127)		Sunitinib (N=222)		Sorafenib + Sunitinib (N=102)	
	n	%	n	%	n	%	n	%
Age								
18–24	0	0.00	0	0.00	0	0.00	0	0.00
25–34	6	1.33	3	2.36	2	0.90	1	0.98
35–44	29	6.43	9	7.09	16	7.21	4	3.92
45–54	108	23.95	25	19.69	49	22.07	34	33.33
55–64	166	36.81	41	32.28	88	39.64	37	36.27
65–74	93	20.62	26	20.47	45	20.27	22	21.57
75+	49	10.86	23	18.11	22	9.91	4	3.92
Gender								
Male	323	71.62	94	74.02	154	69.37	75	73.53
Female	128	28.38	33	25.98	68	30.63	27	26.47
Insurance type								
Commercial	398	88.25	110	86.61	197	88.74	91	89.22
Medicare	53	11.75	17	13.39	25	11.26	11	10.78

- The average age (standard deviation) was 60 years (11.16) for the total group
  - Sorafenib: 61.54 (12.74)
  - Sunitinib: 60.01 (10.83)
  - Sorafenib + Sunitinib: 57.95 (9.42)

Renal Cell Carcinoma Therapies Used Prior to Sunitinib/Sorafenib Treatment Period

	Total (N=451)		Sorafenib (N=127)		Sunitinib (N=222)		Sorafenib + Sunitinib (N=102)	
	n	%	n	%	n	%	n	%
Aldesleukin (IL-2)	31	6.87	8	6.30	15	6.76	8	7.84
Interferon alfa-2a	5	1.11	1	0.79	1	0.45	3	2.94
Interferon alfa-2b	15	3.33	3	2.36	7	3.15	5	4.90
Temsirolimus	0	0.00	0	0.00	0	0.00	0	0.00
Bevacizumab	22	4.88	4	3.15	9	4.05	9	8.82

- Use of other drugs to treat RCC (including cytokine therapy) prior to sunitinib or sorafenib therapy was not common

Length of Sunitinib/Sorafenib Treatment Period

		Length of Treatment (Months)				
	n	Mean	SD	Median	Min	Max
Total	451	6.46	6.40	3.91	0.10	26.63
Sorafenib	127	5.17	5.64	2.89	0.10	26.23
Sunitinib	222	4.71	5.16	2.60	0.13	25.31
Sorafenib + Sunitinib	102	11.88	6.80	10.40	2.01	26.63

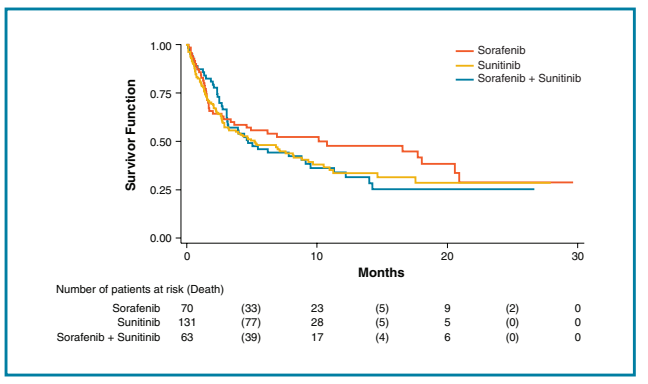
- Median treatment length was 2.9 months for patients receiving sorafenib and 2.6 months for patients receiving sunitinib
- For patients receiving both therapies, median treatment length was 10.4 months (including the gap between the 2 treatments)

Rate of Drug Discontinuation

	Total (N=451)		Sorafenib (N=127)		Sunitinib (N=222)		Sorafenib + Sunitinib (N=102)	
	n	%	n	%	n	%	n	%
Discontinuation of index drug	264	58.54	70	55.12	131	59.01	63	61.76

- In total, 58.54% of patients discontinued and did not restart therapy with sorafenib and/or sunitinib
- Rates of discontinuation were similar between sorafenib users and sunitinib users (55.12% vs 59.01%)

Survival From Discontinuation of Therapy



- Of the 264 patients who discontinued therapy, median survival following therapy discontinuation was 5.4 months
- Median survival following discontinuation of therapy was 10.8 months for patients treated with sorafenib alone, 5.2 months for patients treated with sunitinib alone, and 4.7 months for patients receiving both treatments

Conclusions

- Treatment durations of sunitinib or sorafenib alone are nearly half of that reported in clinical trials for sunitinib and sorafenib
- Patients using sunitinib and/or sorafenib had a high rate of drug discontinuation and poor prognosis following discontinuation of therapy
- Future research should investigate whether other treatment options may improve prognosis following discontinuation of sunitinib/sorafenib therapy

Data Limitations

- Claims data do not provide reason(s) why a medication was discontinued
- It is difficult to determine the precise date of discontinuation because a pharmacy claim reflects when a medication was filled

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- A different perspective on drug effectiveness may be obtained in a real-world setting, as many clinical studies employ inclusion criteria based on disease prognosis and may not be reflective of patients in the general population

Objective

- Examine treatment patterns in a "real-world" population of advanced RCC patients

- Treatment duration
  - For patients who discontinued therapy, duration of treatment was measured as the number of months from initiation of index therapy to discontinuation of therapy
  - For patients who did not discontinue therapy, duration of treatment was calculated as the number of months from initiation of index therapy to the minimum of the end of the follow-up period, the date at which death data was captured, or the death date
- Survival
  - Length of survival time was right-censored at the date at which death data was captured for patients who survived beyond that date
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- Median treatment length was 2.9 months for patients receiving sorafenib and 2.6 months for patients receiving sunitinib
- For patients receiving both therapies, median treatment length was 10.4 months (including the gap between the 2 treatments)

Rate of Drug Discontinuation

	Total (N=451)		Sorafenib (N=127)		Sunitinib (N=222)		Sorafenib + Sunitinib (N=102)	
	n	%	n	%	n	%	n	%
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- In total, 58.54% of patients discontinued and did not restart therapy with sorafenib and/or sunitinib
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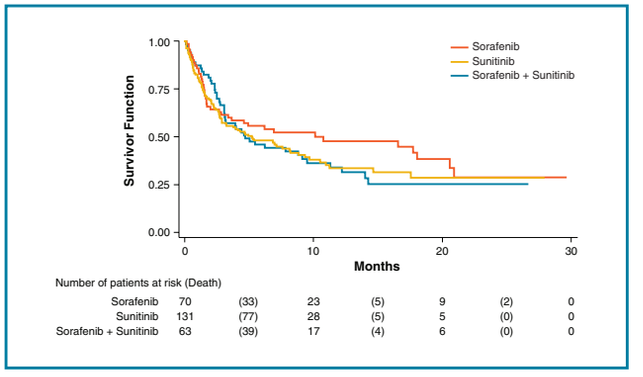

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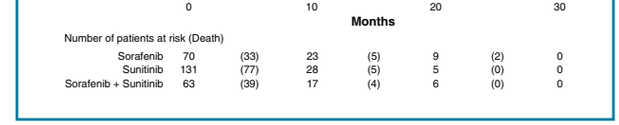

- Of the 264 patients who discontinued therapy, median survival following therapy discontinuation was 5.4 months
- Median survival following discontinuation of therapy was 10.8 months for patients treated with sorafenib alone, 5.2 months for patients treated with sunitinib alone, and 4.7 months for patients receiving both treatments

Conclusions

- Treatment durations of sunitinib or sorafenib alone are nearly half of that reported in clinical trials for sunitinib and sorafenib
- Patients using sunitinib and/or sorafenib had a high rate of drug discontinuation and poor prognosis following discontinuation of therapy
- Future research should investigate whether other treatment options may improve prognosis following discontinuation of sunitinib/sorafenib therapy

Data Limitations

- Claims data do not provide reason(s) why a medication was discontinued
- It is difficult to determine the precise date of discontinuation because a pharmacy claim reflects when a medication was filled

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase II Study of Sorafenib in Patients With Sunitinib-Refractory Metastatic Renal Cell Cancer

Giuseppe Di Lorenzo, Giacomo Cartenì, Riccardo Autorino, Gianni Bruni, Marianna Tudini, Mimma Rizzo, Michele Aieta, Antonio Gonnella, Pasquale Rescigno, Sisto Perdonà, Gianluca Giannarini, Sandro Pignata, Nicola Longo, Giovannella Palmieri, Ciro Imbimbo, Michele De Laurentiis, Vincenzo Mirone, Corrado Ficorella, and Sabino De Placido

From the Dipartimento di Endocrinologia ed Oncologia Clinica e Molecolare, and Sezione di Urologia, Università Federico II; Unità Operativa Complessa (UOC) Oncologia, Ospedale Cardarelli; Clinica Urologica, Seconda Università degli Studi; UOC Oncologia Urologica, INT Fondazione "G. Pascale", Napoli; UO Oncologia, Università Dell'Aquila, L'Aquila; Unità Operativa (UO) Oncologia Ospedale Oncologico Regionale, Rionero in Vulture, Potenza; and UO Urologia Universitaria, Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy.

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Corresponding author: Giuseppe Di Lorenzo, MD, PhD, Dipartimento di Endocrinologia ed Oncologia Clinica e Molecolare, Università Federico II, Napoli, Italy; e-mail: giuseppedilorenzoncol@hotmail.com.

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ABSTRACT

Purpose
No previous prospective trials have been reported with sorafenib in patients with sunitinib-refractory metastatic renal cell cancer (MRCC). We conducted a multicenter study to determine the activity and tolerability of sorafenib as second-line therapy after sunitinib progression in MRCC.

Patients and Methods
Between January 2006 and September 2008, 52 patients were enrolled onto this single-arm phase II study. All patients received sorafenib 400 mg orally twice a day until disease progression or intolerable toxicity. The primary end point was objective response rate (complete or partial response) evaluated every 8 weeks by use of the Response Evaluation Criteria in Solid Tumors; secondary end points were toxicity, time to progression (TTP), and overall survival (OS).

Results
All patients were included in response and safety analyses. Partial responses were observed in 9.6% of patients (five of 52 patients; 95% CI, 5% to 17%) after two cycles. Grade 1 to 2 fatigue, diarrhea, nausea/vomiting, rash, and neutropenia were the most common side effects, noted in 16 (30.8%), 19 (36.5%), 20 (38.5%), 19 (36.5%), and 20 patients (38.5%), respectively. The most common grade 3 toxicity was diarrhea, noted in six patients (11.5%). Median TTP was 16 weeks (range, 8 to 40 weeks), and median OS was 32 weeks (range, 16 to 64 weeks).

Conclusion
Although well tolerated, sorafenib shows limited efficacy in sunitinib-refractory MRCC. Further randomized trials comparing sorafenib with other drugs that target different biologic pathways are needed to define the best second-line treatment option in these patients.

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INTRODUCTION

Renal cell carcinoma (RCC) affects approximately 38,000 patients in the United States every year, with one third of patients presenting with metastatic disease.[1] Metastatic RCC (MRCC) is resistant to classical cytotoxic chemotherapy and hormonal therapy,[2,3] and the benefit of interferon alfa and interleukin-2 is modest. Interferon therapy results in responses in 10% to 20% of patients with a median duration of 3 to 16 months,[4] whereas intravenous interleukin-2 results in generally durable complete responses (CRs) in approximately 6% of patients, and only in good-risk patients.[5]

The treatment of MRCC has recently evolved from being predominantly cytokine-based to being grounded in the use of drugs targeting vascular endothelial growth factor and platelet-derived growth factor pathways.[6] Various antiangiogenic drugs have been studied for the treatment of patients with RCC and have been shown to improve survival.[7] Targeted therapies using sorafenib and sunitinib have recently been approved for use as orally administered agents for the treatment of MRCC. Sunitinib is reserved for the treatment of cytokine-naïve patients,[8] whereas sorafenib was approved for patients with disease that is refractory to cytokine therapy.[9]

However, in clinical practice, sunitinib and sorafenib are often both used as first-line and second-line treatments for MRCC. When one agent fails to produce a response in patients, the other agent is often used, resulting in sequential therapy.

Although sorafenib and sunitinib are multitarget tyrosine kinase inhibitors (TKIs), they have distinct affinities for target kinases and distinct pharmacokinetics that could explain a non–cross-resistance between the two drugs.[10] Scientific data supporting this sequence are limited and only

retrospective.[11-13] To date, no prospective trials have been published. Therefore we initiated a phase II study of sorafenib to assess its activity and safety in sunitinib-refractory MRCC.

PATIENTS AND METHODS

Patient Selection

All patients were adults with histologically confirmed RCC that was metastatic and measurable according to the Response Evaluation Criteria in Solid Tumors.[14] Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2; previous sunitinib therapy as first-line treatment; progression of disease after sunitinib; absolute neutrophil count $\geq 1{,}500/\mu L$; hemoglobin ≥ 9 g/dL; platelets $\geq 100{,}000/\mu L$, normal renal, cardiac, and liver functions; and controlled blood pressure. Patients with all subtypes of RCC were eligible. Patients who had received two previous lines of therapy and with brain metastases were excluded from the study. All patients gave informed consent for their treatment. The study complied with the provisions of the Declaration of Helsinki, Good Clinical Practice Guidelines, and local laws.

Study Design

The study was an open-label, nonrandomized, non–company-sponsored, Italian multicenter, phase II study approved by the institutional review boards at eight participating centers. The primary end point was response rate; secondary end points were safety, time to progression (TTP), and overall survival (OS).

Treatment consisted of 8-week cycles of sorafenib (Nexavar, Bayer, Milan, Italy) 400 mg orally twice a day on a continuous basis, and the patients were evaluated for tumor response at the end of week 8. In case of an objective response or stable disease (SD), the patients could receive additional cycles until occurrence of disease progression. Patients were seen on weeks 1, 4, and 8 of each cycle; blood tests to check renal and hepatic functions and blood counts were performed on patients every 2 weeks. All patients had their blood pressure measured at baseline and were required to control it every week. Left ventricular ejection fraction was evaluated with cardiovascular ultrasound at baseline and after each cycle of sorafenib.

Toxicity was assessed using the National Cancer Institute Common Toxicity Criteria (version 3.0).[15] Grade 2 nonhematologic toxicities were managed by holding the drug until resolution to $\leq$ grade 1 and then resuming without a dose reduction. If the patient experienced a second grade 2 nonhematologic toxicity, the drug was reduced by 25%. Grade 3 or 4 hematologic and nonhematologic toxicities were managed through dose interruption, followed by 50% dose reduction. Treatment was discontinued if a grade 3 or 4 toxicity did not resolve within 3 weeks or if a second dose reduction was required.

Assessment of Tumor Response

Tumor measurements were obtained by computed tomography scan, including the brain, before treatment and at the end of week 8 of each cycle. Response and progression were assessed by the treating physicians, who performed their evaluations on the basis of Response Evaluation Criteria in Solid Tumors.[14]

Statistical Design

Sample size was established by use of a two-stage minimax Simon's design to evaluate the null hypothesis that the true response was 5% and the alternative hypothesis that the objective response was 15%, with a type I error (α) of 0.05 and a type II error (β) of 0.2. Thirty patients were to be treated in the first stage. If at least two responses were observed in the first stage, 22 additional patients were to be entered onto the second stage.

Response rate (CR plus partial response [PR]) is reported with its exact 95% CI. Toxicities are tabulated by type and grade. TTP was defined as the time from registration until disease progression. OS was calculated from the date of registration to the date of death for any reason. Analyses were carried out on an intent-to-treat population, including all patients without major violations of the eligibility criteria.

RESULTS

Patient Characteristics

Between January 2006 and September 2008, 52 patients (35 men, 17 women; median age, 60 years, range 40 to 78 years) with MRCC were entered onto this phase II trial (Fig 1). Forty-eight patients (92.3%) had an ECOG PS of 0 to 1, whereas four patients (7.7%) had a ECOG PS of 2. The majority of patients had clear-cell histologic subtypes (86.5%), and the most common site of metastases was the lung (73%). Using the Memorial Sloan-Kettering Cancer Center criteria, the majority of patients fell into the favorable-risk (76.9%) or intermediate-risk (17.3%) groups. Twenty-four (46.2%), 18 (34.6%), and 10 patients (19.2%) had one, two, or more sites of metastasis (Table 1).

All patients had received prior sunitinib therapy (schedule "4/2" with a starting dose of 50 mg/d for 4 weeks, followed by a 2 week off-drug period) and had experienced progression during treatment or within 60 days of completing sunitinib. The median duration of prior sunitinib was four cycles; one (1.9%) and 21 patients (40.4%) experienced CR and PR to sunitinib, respectively. Sunitinib-dose reduction of 25% (37.5 mg) and 50% (25 mg) for grade 3 to 4 hematologic and nonhematologic toxicities was observed in 10 (19%) and five patients (9.6%), respectively. Median time between interruption of sunitinib and start of sorafenib was 4 weeks (range, 3 to 8 weeks).

Therapy Administration

At total of 109 cycles were administered. The mean number of cycles per patient was 2.17 (median, two cycles; range, one to 10 cycles). The schedule resulted in a mean received dose-intensity of 668.8 mg/d, or 83.6% of the planned dose-intensity. A dose reduction of 25% (600 mg/d) and 50% (400 mg/d) was adopted in 36 (33%) and 18 cycles (16.5%), respectively, as a result of grade 2 to 4 nonhematologic and hematologic toxicity. Treatment was delayed in eight cycles (7.3%). Reasons for delay were patient's request (five cycles), grade 1

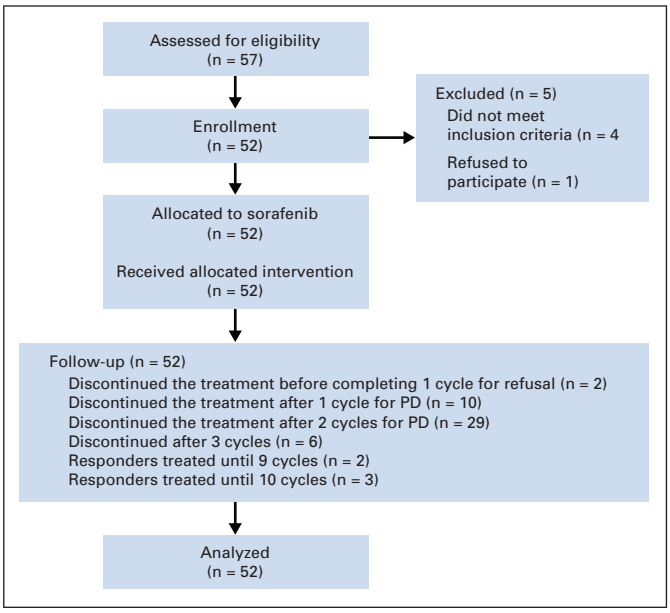

Fig 1. CONSORT diagram. PD, progressive disease.

Table 1. Patient Characteristics (N = 52)

Characteristic	No. of Patients	%
Sex		
Men	35	67.3
Women	17	32.7
Age, years		
Median	60	
Range	40-78	
ECOG performance status		
0	33	63.5
1	15	28.8
2	4	7.7
Prior nephrectomy	49	94.2
Histologic subtypes		
Clear cell	45	86.5
Papillary	5	9.6
Sarcomatoid	2	3.8
Prior adjuvant immunotherapy		
Interferon alfa	5	9.6
Interleukin-2	4	7.7
Prior systemic therapy for metastatic disease		
Sunitinib alone	50	96.1
Sunitinib plus interferon	2	3.8
Prior radiotherapy	3	5.8
Site of metastases		
Lung	38	73
Liver	12	23
Lymph nodes	12	23
Adrenal	5	9.6
Bone	4	7.7
Kidney	3	5.78
Soft tissue	2	3.8
No. of disease sites		
1	24	46.2
2	18	34.6
≥ 3	10	19.2
MSKCC risk factors		
0	40	76.9
1-2	9	17.3
≥ 3	3	5.78
Best response to first-line sunitinib		
CR	1	1.9
PR	21	40.4
SD	7	13.5
PD	23	44.2
Duration of prior sunitinib therapy, cycles		
Median	4	
Range	1-12	

Abbreviations: ECOG, Eastern Cooperative Oncology Group; MSKCC, Memorial Sloan-Kettering Cancer Center; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

nonhematologic toxicity (two cycles), and investigator's decision (one cycle).

Response and Survival

All patients receiving at least one dose of sorafenib were included in analyses. Table 2 shows responses and survival rates in 52 patients. Two patients did not complete the first cycle (because of refusal to continue the treatment after 3 and 4 weeks, respectively). After one cycle, 40 and 12 patients showed SD and progressive disease (PD),

Table 2. Responses and Survival Rates According to Follow-Up (N = 52)

Response and Survival	After 1 Cycle No.	After 1 Cycle %	After 2 Cycles No.	After 2 Cycles %
Response				
CR	0		0	
PR	0		5	9.6*
SD	40	76.9	5	9.6
PD	12	23.1	42	80.8
Time to progression, weeks				
Median			16	
Range			8-40	
Overall survival, weeks				
Median			32	
Range			16-64	
Survival in responders, weeks				
Median			48	
Range			44-64	

NOTE. One cycle is 8 weeks and two cycles is 16 weeks, as reported in Patients and Methods. Two patients did not complete cycle 1 but were included in the intent-to-treat analysis.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.
*95% CI, 5% to 17%.

respectively, whereas five cases of PR occurred after two cycles, for an overall response rate of 9.6% (95% CI, 5% to 17%). A total of 76.9% of patients had SD for at least one cycle (8 weeks), and 80.8% had PD after two cycles (16 weeks). Thirteen patients (25%) had some tumor reduction in target lesions (a reduction of 50%, 40%, 20%, and 10% in three, two, five, and three patients, respectively).

Median follow-up was 8 months (range, four to 16 months). Median TTP and median OS were 16 weeks (range, 8 to 40 weeks) and 32 weeks (range, 16 to 64 weeks), respectively (Table 3). Median survival in responders was 48 weeks (range, 44 to 64 weeks).

Note that two PRs were observed among sunitinib responders, whereas two responses were noted in patients with previous SD with sunitinib, and one response was noted in a nonresponder to sunitinib (Table 3).

All PRs were in patients with clear-cell subtypes, and the most common site of response was the lung (Table 4). The five responder patients were treated for nine (three patients) and 10 cycles (two patients), respectively. Two patients achieving response received everolimus as third-line treatment.

Table 3. Evaluation of Sorafenib Responses Compared With Previous Responses to Sunitinib (as first-line treatment)

Response	Responses to First-Line Sunitinib No.	Responses to First-Line Sunitinib %	Responses to Sorafenib No.	Responses to Sorafenib %
CR	1	1.9	0	0
PR	21	40.4	2	38.5
SD	9	17.3	2	38.5
PD	21	40.4	1	19.2

NOTE. Response criteria are as given in Patients and Methods.
Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 4. Characteristics of Responders

Histology	Best Response	Sites of Response	Total No. of Cycles	Further Therapy After Sorafenib
Clear cell	PR	Lung, liver, lymph nodes	9	Everolimus
Clear cell	PR	Lung, liver	9	Supportive care
Clear cell	PR	Lung, lymph nodes	10	Everolimus
Clear cell	PR	Lung, adrenal	9	Sunitinib
Clear cell	PR	Lung	10	Supportive care

Abbreviation: PR, partial response.

Toxicity

In general, treatment was well tolerated. No toxic deaths occurred. Grade 1 to 2 fatigue, diarrhea, nausea/vomiting, rash, and neutropenia were the most common side effects, noted in 16 (30.8%), 19 (36.5%), 20 (38.5%), 19 (36.5%), and 20 patients (38.5%), respectively. Grade 1 to 2 hand-foot reaction was observed in nine patients (17.3%).

The most important grade 3 hematologic toxicity was neutropenia in five patients (9.6%), whereas the most common grade 3 nonhematologic toxicities were diarrhea in six patients (11.5%), nausea/vomiting in five patients (9.6%), and hypertension in five patients (9.6%).

The five cases of grade 3 hypertension were noted after two cycles and were already reported with previous sunitinib treatment; in fact, during previous therapy, there were five cases of grade 3 hypertension requiring appropriate antihypertensive drugs. During sorafenib, these patients needed to add an angiotensin-converting enzyme inhibitor to previous drugs.

Table 5. Toxicity Experienced by Study Participants (N = 52)

	Grade 1-2		Grade 3		Grade 4	
Toxicity	No.	%	No.	%	No.	%
Fatigue	16	30.8	2	3.8	0	
Diarrhea	19	36.5	6	11.5	0	
Neutropenia	20	38.5	5	9.6	3	5.8
Nausea/vomiting	20	38.5	5	9.6	1	1.9
Anemia	15	28.8	4	7.7	1	1.9
Rash	19	36.5	2	3.8	0	
Alopecia	15	28.8	2	3.8	0	
Thrombocytopenia	15	28.8	4	7.7	0	
Oral mucositis	15	28.8	2	3.8	0	
Hand-foot reaction	9	17.3	1	1.9	1	1.9
Hypertension	9	17.3	5	9.6	0	
Sensory neuropathy	5	9.6	2	3.8	0	
Left ventricular ejection fraction dysfunction	5	9.6	1	1.9	0	
Headache	6	11.5	0		0	
Bleeding	6	11.5	0		0	
Creatinine elevation	5	9.6	0		0	
Hyperglycemia	4	7.7	0		0	
Hypothyroidism	4	7.7	0		0	
Lipase elevation	3	5.8	1	1.9	0	
Transaminase elevation	3	5.8	0		0	

Grade 4 hematologic toxicity was limited to neutropenia in three patients and to nausea, anemia, and hand-foot reaction in one patient each. All grade 4 toxicity resolved with appropriate therapy (Table 5).

DISCUSSION

To our knowledge, this study represents the first prospective investigation of sequential sorafenib in sunitinib-refractory MRCC. Prior retrospective studies suggested activity and tolerability with this agent in second-line treatment, but those reports are subject to several biases.[11-13]

Despite the absence of prospective information, in clinical practice, sequential therapy with sorafenib and sunitinib has become de facto a standard treatment. A prospective study to evaluate the efficacy and safety of sorafenib after sunitinib exposure is necessary to better define the clinical benefit of this algorithm.

The scientific rationale of our trial was that although sorafenib and sunitinib are multitargeted TKIs, they have similar, but not identical, targets and a substantial variety of binding specificity among drugs targeting the same kinases.[10,16]

Although sunitinib is an inhibitor of c-kit, platelet-derived growth factor receptor α and β, vascular endothelial growth factor receptors (VEGFRs), and FLT-3, sorafenib is a potent raf kinase inhibitor and targets VEGFR-2, VEGFR-3, and platelet-derived growth factor receptor β.[10,16]

Resistance to single-agent antiangiogenic therapy may develop by way of compensatory mechanisms that are driven by upregulation of vascular endothelial growth factor, fibroblast growth factors, and activation of angiogenesis by interleukin-8, RAS, or PI3K/Akt, which could activate or be activated by hypoxia-inducible factor α.[17]

Sorafenib, targeting RAF, could directly block the overexpressed VEGF pathway and indirectly block PI3K/akt and other pathways, such as apoptosis.[18] In the present study, we hypothesized that drug resistance that emerged after sunitinib would be overcome by sorafenib, which could block iperexpressed kinases and apoptosis.

Our study shows that sorafenib was well tolerated and demonstrated a similar response rate compared with that of previous trials with sorafenib in cytokine-refractory patients; however, it was less active than we expected, according our statistical design. Toxicity from treatment with sorafenib in our study was consistent with that of previous trials.[9] Grade 4 toxicity was rare and well managed with supportive care, and grade 2 to 3 toxicity was well controlled with dose modification. Fatigue, diarrhea, nausea/vomiting, and rash were higher compared with that of the study by Escudier et al,[9] but it is important to note that our patients were pretreated with another TKI with a similar toxicity profile.

Grade 3 hypertension was higher, but the number of patients who reported hypertension was related to previous treatment; in fact, all five cases of grade 3 hypertension appeared during previous sunitinib therapy. Hypertension has been noted with TKI and was expected with this class of drug.[19] Grade 3 hypertension was easily managed with antihypertensive drugs and resolved on discontinuation of the study treatment.

The study has several limitations. First, it is important to note that the responses in this study were investigator-assessed, and because independent review of scans can result in lowering of the response rate relative to the investigator-assessed response, such an effect should be taken into consideration when interpreting the results.

Another limitation is that this was a single-agent, nonrandomized study without a control arm, with limitations in determining the benefit of other agents such as bevacizumab alone or in combination with cytokines, adding two agents together, or treatment with an agent that targets different pathways (eg, everolimus or temsirolimus). It is important to note that at the start of our trial, we did not possess the selection of drugs and wealth of information we do today. Besides, the efficacy of targeted agents is better evaluated with other end points, such as tumor shrinkage, TTP, progression-free survival, and OS, than only the response rate.

Also, our statistical design could be subject to criticism. We have hypothesized a minimal response of 5%, with a 15% response required for a positive trial. At the time of protocol writing, only the results of phase III showed a 10% response to sorafenib after cytokine treatment.[9] Considering that the populations were different, with different studies (phase III *v* phase II) and different end points, speculating on an overexpression of potential targets for sorafenib after sunitinib, we have hypothesized a higher response rate than the previous phase III studies. Often the response rate in phase II studies is higher than that of phase III studies. Surely today, with much more literature examining sorafenib, we would use a different statistical design and different end points.

The development of several targeted agents means the physician is now faced with the dilemma of which agent to give, and in which order, to provide optimal benefit. Tamaskar et al[20] reported a response rate of 20% in patients receiving sorafenib or sunitinib after therapy with a variety of antiangiogenic agents. Axitinib has demonstrated promising activity in cytokine-refractory MRCC, with a response rate of 44.2% and a median TTP of 15.7 months.[21] Rini et al[22] have reported a response rate to sunitinib of 23% in patients with disease that has become refractory to bevacizumab.

A single-arm phase II study does not allow for direct comparison of sorafenib with sunitinib and axitinib. However, the reported response rate, tumor shrinkage, TTP, and OS demonstrate that sorafenib might be a less promising drug in pretreated MRCC, although a randomized controlled trial is needed to confirm this finding. Methodologic differences between trials, including trial design and patient eligibility, probably account for some differences in the results. For example, our patients received sunitinib as first-line treatment, which, to date, gives the best results in terms of OS. Prospective randomized trials will be required to provide insight into the most effective option after disease progression with a target agent.

Our data are consistent with the hypothesis that drug resistance emerging after initial use of sunitinib is not completely overcome by sorafenib, and options for overcoming resistance to antiangiogenic therapy may include novel strategies, such as blocking the mammalian target of rapamycin (mTOR). This strategy has been tested in a clinical trial with everolimus, an mTOR inhibitor that has been shown to have a progression-free survival advantage when used in patients who had experienced disease progression on prior TKI therapy.[23]

In this study, everolimus was compared with placebo, although it could be useful to compare an mTOR inhibitor with another targeted agent. This strategy is now being tested in clinical trials evaluating the efficacy of temsirolimus with sorafenib as second-line therapy in patients who have experienced treatment failure with first-line sunitinib (NCT00474786) or temsirolimus in combination with bevacizumab after TKI failure (NCT00782275).[24] Considering the multiple options for treatment of MRCC, it is important to identify the correct sequence to improve the survival of our patients.

Our results show that sorafenib has manageable toxic effects and limited efficacy in sunitinib-refractory MRCC. Further clinical trials, specially comparing a TKI with an mTOR inhibitor, will define the best second-line treatment for patients who experience treatment failure with first-line sunitinib.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Giuseppe Di Lorenzo, Giacomo Cartenì, Sabino De Placido
Financial support: Vincenzo Mirone, Sabino De Placido
Administrative support: Vincenzo Mirone, Sabino De Placido
Provision of study materials or patients: Giuseppe Di Lorenzo, Riccardo Autorino, Gianni Bruni, Marianna Tudini, Mimma Rizzo, Michele Aieta, Antonio Gonnella, Pasquale Rescigno, Sisto Perdonà, Gianluca Giannarini, Sandro Pignata, Nicola Longo, Giovannella Palmieri, Ciro Imbimbo, Michele De Laurentiis, Vincenzo Mirone, Corrado Ficorella
Collection and assembly of data: Giuseppe Di Lorenzo, Riccardo Autorino, Sisto Perdonà
Data analysis and interpretation: Giuseppe Di Lorenzo, Giacomo Cartenì, Sabino De Placido
Manuscript writing: Giuseppe Di Lorenzo, Riccardo Autorino
Final approval of manuscript: Giuseppe Di Lorenzo, Giacomo Cartenì, Sabino De Placido

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Everolimus: for treatment of Renal Cell Carcinoma (mRCC -second line metastatic)

The James Whale Fund for kidney Cancer

46-48 King Street
Cambridge CB1 1LN
Tel 01799 585 033 (Mon-Fri 10am-4pm)
Fax 01223 507095
Email - contact@jameswhalefund.org

Patient Group response to the Appraisal Consultation Document issued on 9th February 2010

The James Whale Fund for Kidney Cancer on behalf of its membership disagrees fundamentally with the preliminary N I C E decision (ACD) that Everolimus is not a cost effective use of NHS resources and will not be recommended as 2nd line treatment for advanced and/or metastatic Renal Cell Carcinoma (mRCC)

Prepared by [redacted] at James Whale Fund for Kidney Cancer. Date - 1st March 2010

nb. The kidney cancer patients, carers, families and supporters of the James Whale Fund for Kidney Cancer have given permission for their experience, opinion and patient perspective to be used in the preparation of this document.

THE NHS CONSTITUTION

1st paragraph - The NHS belongs to the people.

"It is there to improve our health and well-being, supporting us to keep mentally and physically well, to get better when we are ill and, when we cannot fully recover, to stay as well as we can to the end of our lives. It works at the limits of science – bringing the highest levels of human knowledge and skill to save lives and improve health. It touches our lives at times of basic human need, when care and compassion are what matter most."

HIGH QUALITY CARE FOR ALL – OUR JOURNEY SO FAR.

Foreword - Secretary of State Rt Hon Mr Andy Burnham

"From the cradle to the grave, the NHS is there for all of us. It supports people at those moments in life when they find themselves at their most vulnerable, providing a service to everyone that is free at the point of need. It is not just an organisation, but a cherished and ingrained part of life in our country."

INTRODUCTION.

The James Whale Fund for Kidney Cancer is the UK's leading specialist kidney cancer charity (Registered Charity No.1120146). We seek to reduce the harm caused by kidney cancer by increasing knowledge and raising awareness. We provide accurate and upto date patient information and we support kidney cancer patients, carers and their families by offering practical support, advocacy & friendship through a network of local Support Groups across the UK and an active online patient forum. The Fund actively promotes and facilitates research into the causes, prevention and treatment of Kidney Cancer.

- In this document The James Whale Fund is responding to the Appraisal Consultation Document (ACD) set out on 9th February 2010 on www.nice.org and the preliminary decision of the Appraisal Committee that Everolimus is not a cost effective use of NHS resources and is NOT recommended for the second-line treatment of advanced and/or metastatic Renal Cell Carcinoma (RCC).
- We believe that the preliminary decision not to recommend Everolimus for kidney cancer patients reaching the end of their life, fails to take account of the unmet

clinical needs for this Group of vulnerable patients for whom there are no alternative treatment options. The Fund believes it is clinically and ethically unjust to refuse rarer cancer patients active treatment which is proven to be clinically effective and proven to extend life.

- We believe the drug Everolimus, meets the criteria as an "end of life" drug as set out in the N I C E supplementary advice to be taken into account when appraising new & innovative treatments for small numbers of patients with incurable illnesses. We ask the Appraisal committee to reconsider their decision to refuse NHS funding for Everolimus and to attach the proper weight to the patient experience.
- We would ask the Appraisal Committee to take into account the following points at the second committee meeting on the 9th March 2010. These views have been collated from patient correspondence, patient surveys, notes taken during telephone conversations and online forum posts from patients, carers and survivors of kidney cancer.

Has all of the relevant evidence been taken into account?

It is our assertion that meaningful patient input is missing from the ACD. The James Whale Fund feel the evidence should be revisited and the patient perspective must be included and given due weight if N I C E wish to present a balanced and rounded appraisal.

- The spend on cancer drugs is higher in other EU Countries. A recent report from Policy Exchange states that spending on cancer medicines in England is only 60% of that spent by other advanced EU countries and our cancer death rate is 6% higher than the EU average, it would be naïve not to see the connection between those two figures. Cancer patients in England are hugely disadvantaged by this process of rationing by cost.
- The last 10 years has seen much research into innovative anti-cancer drugs come to fruition. In the case of Kidney Cancer , NICE has reviewed 5 such new drugs and has only approved one 1st line new drug (Sunitinib) and refused all 2nd line sequential treatments. The drugs refused by N I C E are widely available in all western countries and NICE's justification for denying access to innovative new cancer drugs to NHS patients are based on esoteric cost calculations and statistics which are incomprehensible to patients and the general public. Denying treatment to terminally ill cancer patients has been hugely controversial and the Department of Health, through N I C E, has been forced to react to public criticism by introducing an "End of Life" criteria to ensure that modern and comparably costly drugs, are not automatically refused when they fail the notorious and arbitrary N I C E QALY. There is no evidence that the EOL criteria have been applied to this application for Everolimus even though Everolimus fits the criteria perfectly. The consequence of this unfair approach is that mRCC patients have only 1 drug for 1st line treatment (accepting there maybe some limited use for 20 year old immunotherapy treatments such as interferon alfa), none at all for sequential 2nd line treatment leaving only, as a last resort, best supportive care. Once again kidney cancer patients in the UK are disadvantaged by the N I C E model of cost analysis.

- The figure of the £30,000 Q A L Y has not been updated since its inception – one can imagine the furore if other cost areas in the NHS i.e. salaries and expenses had remained unchanged for 9 years. A simple calculation shows if the QALY had been adjusted in line with other NHS costs, a £50/55,000 Q A L Y would be the norm and taking the figure of 1.4 quoted recently by Professor Stevens as the multiplier, the EOL Q A L Y should now be £70/75,000. N I C E appears to exist in a time warp for this one area of their work. Today's treatments for today's patients should not be judged against a set of "rules" which are nearly 10 years old.
- (patient quote) "Cancer survival rates are much higher in other EU countries especially when sequential treatment is available."

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It is apparent to us from talking and listening to patients and the general public that the majority of people do not understand the pseudo-science of mathematical models, ICER's and QALY's. Patients do not understand how an actual invoice cost of £31,000 pa can, following an appraisal by N I C E, be transformed into a cost to the NHS of £75,000 pa. If N I C E cannot find a way to explain their processes to patients denied access to clinically effective treatments that Clinicians wish to prescribe, then we suggest it is out of touch with the NHS patients it is meant to be serving.

- (patient quote) "It's so difficult to understand what they are saying, with all that gobblygook, when Sutent stops working for me, can I really expect to live another 11 or 12 months without any proper cancer treatment at all. That's not what I read on the patients forums. Do other stage 4 patients and the Oncologists agree with that I wonder?"
- NICE should take into account the wider societal benefits of access to end of life drugs for cancer patients when assessing cost effectiveness. If patients on active treatment can continue to work and support their families, is that worth nothing?
- (patient quote) " The NHS has a forecast underspend against budget this year of £1.4 billion – is it a cost effective use of NHS resources to keep that money sitting in NHS bank accounts rather than spend it on front line services like cancer treatments for patients who desperately need them."
- If this decision is not changed , NICE will have recently rejected all five 2nd line kidney cancer treatments despite promised greater flexibility from NICE for EOL drugs
- Is there a figure being used as the benchmark for "end of life" drugs? How do patients or the public know whether that figure is "reasonable"? How can we comment when the information is not made available? What is a cost effective use of resources when keeping any patient alive? Is it the cost of kidney dialysis per year; is it the cost of an organ transplant operation and ongoing drugs for life?
- (Patient quote)"Our drugs will always be more expensive as there are far fewer of us and pharmaceutical companies have to recoup R & D costs. Drugs

must cost the same to get a license whether they are prescribed to 1000 rarer cancer patients or 40,000 patients."

- (patient quote) "Everolimus is cost effective – it works, it does what it says on the tin. I know what it is worth because I'm taking the drug."
- (patient quote) "N I C E is just rationing treatments based on money, but rarer cancer patients obviously are still coming off worse".

.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

The general feeling from the kidney cancer community is that they are passionate defenders of the NHS and the principle of universal care, but do not understand why a committee set up to appraise cancer drugs would do so without a leading Oncologist on the panel and without the added value and experience of a cancer patient. To exclude both viewpoints from membership of the Appraisal committee in favour of multiple commissioning and health economics input seems perverse.

- (patient quote) "Rarer cancer patients are discriminated against & feel disenfranchised by the N I C E process"
- (patient quote) "Kidney cancer patients have paid into the NHS ; I've paid a lifetime of taxes - we have paid into the system now all we want is to have treatment options like other cancer patients"
- (patient quote) "This QALY figure is arbitrary, it is out of date and based on goodness knows what? Was it guesswork?"

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

- Do kidney cancer patients just have the "wrong type of cancer" Patients are dying prematurely because they simply have the bad luck to have been diagnosed with a rare cancer, through no fault of their own. Nothing will change until the NHS accepts that rarer cancer patients need a separate process of appraisal. A one size HTA does not fit all.
- (patient quote) "Everolimus is available in other EU countries as 2nd line treatment for mRCC, why not in Great Britain?"
- (patient quote) "KC patients have limited treatment options unlike more common cancers (chemotherapy & radiotherapy do not work for kidney cancer) Why can't similar amounts of money that other cancer patients have access to for their treatments be given to us to help pay for drugs we need. If patients with rarer cancers can't get treatment because they are in a minority surely this is a form of discrimination."

- (patient quote) "The majority of KC patients are aged 60+; not everyone has access to computers and NICE website is awful, it is not user friendly, it puts you off before you start; how we are expected to appeal properly. We only have 20 days to appeal against refusal for our drugs and yet this was referred to NICE in November 2008. The NHS and the N I C E Quango take as much time & money as they want to get their arguments marshalled, but again we get no help, no resources at all to put our case forward."
- (patient quote) "The Human Rights Act, article two, gives every human being THE RIGHT TO LIFE, denial of a proven clinically effective treatment which gives an individual that right cannot therefore be legal under the convention."

The James Whale Fund for Kidney Cancer ask the Appraisal Committee to take account of the following general points from the perspective of the hundreds of kidney cancer patients who will be affected by their ultimate decision.

We feel the principle of cost effectiveness is applied randomly – N I C E asserts it is the guardian of NHS resources by applying clinical effective evidence in a rigorous manner. It tells us that NHS funded treatments must be evidence –based. Despite this assertion cancer patients know there is striking evidence this principle is not consistant across the NHS. It is difficult for kidney cancer patients to reconcile the control N I C E exerts over clinically effective and proven cancer drugs and yet fails to apply to other NHS funded treatments –

1. Homeopathy, which is available on the NHS at huge cost and yet is unproven and felt by many to be no better than placebo.
2. Acupuncture, which is available on the NHS with very little peer reviewed evidence.
3. Alternative medicines available on the NHS and not subject to NICE scrutiny.
4. The swine flu panic now agreed to have led to the waste of huge NHS resources
5. The winter flu jab for the over 65's, now seen as failing to deliver measurable benefit.

These examples are proof to patients the NHS is not consistent and N I C E is a questionable guardian of precious NHS resources and yet N I C E persist in denying treatments to fulfil an unmet clinical need for a 2nd line treatment for terminally ill kidney cancer patients.

Patients tell us they are actively encouraged to enter clinical trials for new cancer drugs. They do so for a number of reasons; it may be the only route to active treatment, they feel they are "doing a good thing" helping to further medical knowledge and they feel their involvement may help future generations of cancer patients. Each time that N I C E deny access to effective drugs, the effect on those patients who took part on the clinical trials is immediate and diminishes their contribution; they feel let down and some feel hoodwinked. Their hopes of enabling effective treatment to be used to help other cancer patients are dashed. The knock on effect for further research and trials in the UK must be recognized as must the effect on patients whose hopes are raised when they hear first hand in their Clinics, about good results and evidence, but then discover N I C E will not allow these new compounds to be funded by the NHS.

We urge the committee on the 9th March to acknowledge the value of the patient experience, we have asked that our expert patient Mr Bill Savage should be available for

your committee to talk to about the points we have raised in our submission and we would like your agreement to that request.

In conclusion we will share with your committee the words of a stage 4 kidney cancer patient who, until disease progression 3 months ago, was taking a kidney cancer drug refused by N I C E, a cancer drug that has given him 3 years of extra life - not a few weeks as we hear quoted in the media, but 3 years during which time he has continued to work and play a full role in his family …….

"Being told you have terminal kidney cancer is not the worst thing in the world to happen to you – far worse is knowing there are proven drugs that can help you, but you can't have them."

Patients in this situation now need sequential 2nd line treatment: who is going to sit this patient down and say to him…….

"It has become too expensive for us to keep you alive."

[redacted] - Patient Advocate
The James Whale Fund for Kidney Cancer

KIDNEY CANCER UK

SUBMISSION TO NICE

HEALTH TECHNOLOGY APPRAISAL

EVEROLIMUS

Some comments on the Appraisal Consultation Document (ACD)

February 2010

Kidney Cancer UK is most disappointed with the Appraisal Committee's recommendation that the drug Everolimus should not become an NHS second-line option for advanced/metastatic renal cell carcinoma. In responding to Dr Longson's letter of 2 February we have arranged our comments under the general headings beneath which the Appraisal Committee is said to be interested.

Has all the relevant evidence been taken into account?

Not in our view.

Evidence on patient benefits has scarcely been considered in the ACD, compared with the enormous amount of space devoted to discussion of the evidence on costs. In our view the central measure of a QALY is a woefully inadequate measure of patient benefit, calibrated as it is on the basis of a number of truly heroic assumptions. Patient benefit encompasses far more than a QALY.

A more academically respectable approach to the evaluation would have involved calculation of net present values [NPVs] in a full-blown cost-benefit analysis. Admittedly, NPV calculations would be much more difficult to make, given that they would require direct valuation of patient benefits. But in this-as in everything else-there is more to be said for *rough* estimates of the *precise* concept than for *precise* estimates of some *rough* concept. An incremental cost effectiveness ratio [ICER] per QALY is a pretty rough concept; and sometimes it is, solemnly, and most precisely, given down to the last £1**.**

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

Not in our view

The summaries rest very heavily on certain assumptions regarding how long patients can survive solely on best supportive care after treatment

with Sunitinib has failed. PenTAG's ICER per QALY of £75,000 is associated with a mean survival of 11 months in the best-supportive- care arm. But there are reasons to believe that 11 months is an unrealistic estimate of survival on best supportive care. For instance, in a paper by Di Lorenzo et alia published in *The Journal of Clinical Oncology* [10.1200/JCO, 2009, August] it is shown that patients failing on Sunitinib and then going on to receive Sorafenib as second-line treatment lived for a median period of just 32 weeks [or a little less than 7.4 months]. It seems inconceivable that patients on best supportive care would survive longer than patients receiving an active drug.

A further piece of evidence is found in a study by Z. Liu et alia presented at the Joint 15th Congress of the European CanCer Organisation [ECCO] and 34th Congress of the European Society for Medical Oncology [ESMO] Berlin, 20-24 September 2009. In this study, the median overall survival for patients who received no active treatment after Sunitinib is found to be only 5.2 months.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

Not in our view

We feel that, on more realistic assumptions regarding relative survival, the ICER per QALY for Everolimus would come down to around the same level as that at which Sunitinib was approved for NHS funding, namely £54,000. We note that it is accepted that, like Sunitinib, Everolimus is deemed eligible to be designated as an end-of-life medicine. Accordingly, we suggest that the final decision on Everolimus be aligned with that on Sunitinib.

*****

National Institute for Health and Clinical Excellence

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

Royal College of Nursing

Introduction

The Royal College of Nursing (RCN) was invited to review the Appraisal Consultation Document (ACD) of Everolimus for the second-line treatment of metastatic renal cell carcinoma

Nurses caring for renal cancer patients reviewed the documents on behalf of the RCN.

Appraisal Consultation Document – RCN Response

The Royal College of Nursing welcomes the opportunity to review this document. The RCN's response to the four questions on which comments were requested is set out below:

i) **Has the relevant evidence been taken into account?**

We are unaware of any evidence that has not been included in this technology appraisal.

ii) **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?**

We agree with the interpretations of the clinical evidence. We do not have enough expertise to comment on cost- effectiveness and the methodology used.

iii) **Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?**

It is regretful that the preliminary recommendations contained in the document, mean that a second line treatment would not be available to patients but note that these recommendations are in line with the previous technology appraisal of Sorafenib.

iv) **Are there any equality related issues that need special consideration that are not covered in the ACD?**

We are not aware of any equality related issues that need special consideration which have not been covered in the ACD.

Royal College of Physicians
Setting higher medical standards

11 St. Andrews Place
Regent's Park, London NW1 4LE

Telephone +44(0) 20 7935 1174
Textphone +44(0) 20 7486 5687
Facsimile +44(0) 20 7487 5218

www.rcplondon.ac.uk

From The [redacted]

Telephone extension [redacted]
Direct facsimile [redacted]

[redacted]
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
London
WC1V 6NA

24th February 2010

Dear [redacted]

Re: Single technology appraisal (STA) - Everolimus for the second-line treatment of metastatic renal cell carcinoma - Appraisal consultation document

I write on behalf of the NCRI/RCP/RCR/ACP/JCCO with relation to this ACD consultation. We are grateful for the opportunity to respond and would like to make the following comments. Our thanks go to our clinical expert nominee, Dr Kate Fife for coordinating the response.

We are disappointed with the ACD decision not to fund everolimus for second line treatment of patients with metastatic renal cancer, after failure of sunitinib therapy. The evidence review group agreed that everolimus has been shown to be clinically effective, increasing survival by 3 months, and meets the end-of-life criteria for drug funding. However, they have declined funding for this small group of patients purely on the basis of cost. Health economic analyses are sensitive to small changes in inputted data and there is often disagreement, even amongst the experts, about interpretation of the results.

We are concerned that the committee have misunderstood the prognosis for this group of patients. Section 4.15 quotes 'life expectancy for people with advanced RCC receiving best supportive care alone was unlikely to be greater than 24 months and was potentially as low as 6 months'; this range is actually for patients receiving first line sunitinib. For patients who fail sunitinib, the likely survival without further active treatment is only in the region of 4 or 5 months (expert opinion). It is important that the committee reconsider their decision in the light of this misunderstanding.

It is also important to note that the results of the RECORD-1 clinical trial. Patients in both arms of the study received further lines of therapy after everolimus, resulting in a median overall survival of 13 months. This would not of course be the case for the British public with advanced renal cancer. They will be able to receive sunitinib (now NICE approved) but no further treatment if this ACD is ratified in the Final Appraisal Determination.

Yours sincerely

[redacted]

[redacted]

I attended the Technology Appraisal Meeting in Manchester in January regarding Everolimus and following the ACD , I would like to make the following points :

- **The rejection of Everolimus in the context of NICE's rejection of avastin, nexavar and torisel means that oncologists have only 1 drug –sutent –to treat advanced RCC in the first line and no second line treatments with the exception of old discredited drugs such as interleukin or interferon. This situation means that patients are denied modern drugs which prolong life simply on cost grounds. This is neither moral or just .**
- **Everolimus fits the EOL criteria –short like expectancy, 3 months plus life extension, ICER over £30k per annum, no available alternatives-. I can see no evidence that NICE have taken these criteria into account . They were designed specifically to cope with the problems encountered by very expensive life prolonging drugs and yet they have been ignored.**
- **RCC patients are being discriminated against by the nature of the QALY which turns a cost of £ 30000 into a fantastic figure of over £ 70000 per annum. The application of the current rule set and methodology means that it is almost certain that all modern new drugs for RCC will be rejected leaving England in a situation where these life extending drugs are denied whereas they are widely available across Europe and the USA**

There is no doubt that Everolimus is clinically effective in extending life . RCC is a lethal disease with very poor outcomes . NICE has placed patients in a situation where life extending drugs have been denied on the grounds of cost and cost alone but a cost based on the strange world of the QALY which no patient or carer can understand and is unrecognisable in the real world. Patients deserve transparency and not to be at the mercy of cold blooded health economics.

Bill Savage

(Personal Response to the ACD)

Everolimus for the Treatment of Advanced Renal Cell Carcinoma (aRCC) – Additional Sensitivity Analyses

Background

Following the Appraisal Committee meeting on the 11th August, a request was received on the 16th August to conduct further sensitivity analyses as follows:

a) Probabilistic Sensitivity Analysis (PSA) to include a plausible range of Overall Survival (OS) estimates;
b) One way sensitivity analyses to assess the impact of OS on the cost-effectiveness of everolimus;
c) Further information regarding the estimates of administration time/cost associated with the PAS scheme and inclusion of these estimates in the PSA.

Details regarding these analyses are provided below.

a) Probabilistic Sensitivity Analysis (PSA)

A probabilistic sensitivity analysis has been requested by the Appraisal Committee to, "clarify the uncertainty associated with the new evidence on the total costs of use of everolimus in the NHS."

PSA Methods

Probabilistic sensitivity analysis was performed using a second order Monte Carlo simulation. Two scenarios were explored based on the following ranges for OS:

- Scenario A) OS HR 0.06 to 1.63 representing RPSFT 95% CI (0.5, 8.5) and
- Scenario B) OS HR 0.27 to 0.87 which represents a conservative, relatively more clinically plausible range.

Each analysis comprised 100 iterations using a sample size of 1000 patients per cohort. An overview of the PSA parameters is presented in Table 1.

Table 1 - Overview of PSA Parameters

Parameter	Range	Distribution	Justification for Distribution Adopted
Resource costs	0 to infinity	Gamma	Accepted practice for varying costs in the probabilistic sensitivity analysis
PAS administration costs	Mean cost £18.33 (38.29 minutes x £28) plus or minus 1 SE (£4.15)	Gamma	Accepted practice for varying costs in the probabilistic sensitivity analysis
Health state utility values	0 to 1	Beta	Accepted practice for varying utilities in the probabilistic sensitivity analysis
Transition probabilities	Various ranges related to the individual parameter value and sample information	Dirichlet	Accepted practice for varying multinomial data (e.g. more than one possible transition) in the probabilistic sensitivity analysis
RPSFT-derived hazards ratio	Scenario A) OS HR 0.06 to 1.63 (RPSFT 95% CI (0.5,8.5)) Scenario B) OS HR – 0.27 to 0.87*	Log Normal Log Normal	Accepted practice for varying hazards ratio in the probabilistic sensitivity analysis

*see below for full description of derivation of this range.

Scenario A – RPSFT Confidence Intervals

As acknowledged in Frances Sutcliffe's email dated 16.8.10, the PSA is more complex than usual for the following reasons:

- The 95% confidence intervals are very wide because the RPSFT method preserves randomisation and does not change the level of evidence against the null hypothesis thus resulting in very wide confidence intervals and
- Survival estimates from the RPSFT method have been presented as relative survival rather than the traditional hazard ratios;

As the RPSFT results are expressed as relative survival, hazard ratios corresponding to the 95% CI (0.5, 8.5) were calculated to provide a suitable range for the PSA. In order to do this, Weibull curves were constructed for the BSC arm corresponding to the 95% CI (0.5, 8.5) from the RPSFT analysis. These curves were derived by first calculating transition probabilities using individual patient data from the RPSFT analysis, and then fitting a Weibull distribution to those transition probabilites as described by the ERG for their base-case analysis. The two resulting Weibull curves were used to calculate adjusted transition probabilities which were entered into the base case model to estimate mean life years gained. The modelled estimates of mean OS derived from these curves were then used to calculate hazard ratios (using Excel Solver) of 0.06 and 1.63 (corresponding to relative survival of 8.5 and 0.5 respectively) thus providing a range which could be explored in the PSA. NB: As the hazard ratios relate to the odds of events occurring and the RPSFT results relate to relative survival time the relationship between relative survival and the hazard ratio is not necessarily linear.

Scenario B – Analysis to Explore a Relatively More Plausible Clinical Range

Although, the wide 95% confidence intervals produced by the RPSFT analysis are statistically valid, they represent extreme values which are not necessarily clinically plausible. At the lower bound, a relative survival of 0.5 would mean that BSC patients live twice as long as patients on everolimus treatment. This is unlikely to be the case and there is no evidence to suggest that everolimus reduces life expectancy compared to BSC treated patients. The upper bound of 8.5 would mean that patients on everolimus treatment live 8.5 times as long as those on BSC and although this is possible there is no evidence as yet, that this is the case.

We have therefore attempted to define a relatively more clinically plausible range to explore in the PSA. Although there is limited clinical data on the OS of BSC patients, we have defined a range based on the best available data. For the upper limit we have used the point estimate from the November ITT analysis of the pivotal RECORD-1 trial which was described in our original submission. This gives a highly conservative result for the effectiveness of everolimus (HR 0.87) as it includes the 81% of patients randomised to BSC who crossed over to receive active treatment thus confounding the results to the disadvantage of everolimus. In the absence of any other data, it is a reasonable upper bound to use in the PSA for illustrative purposes. In order to define the lower bound we estimated a hazard ratio of 0.27 based on feedback from the clinician survey (described in our ACD response dated, 2.3.10) which suggests that patients on BSC survive on average for 6 months following failure of sunitinib as compared to a median OS of 14.78 months for patients on everolimus from the RECORD-1 trial. Evidence from actual UK clinical audit data (presented in our ACD response dated 2.3.10) suggests that actual OS in BSC patients, post-failure on sunitinib ranges from 2 to 5 months i.e incremental survival would be greater than if BSC patients live for 6 months as assumed in this analysis. A copy of the ACD response is attached as Appendix 1 for your information.

Compared to Scenario A, Scenario B therefore explores a relatively more clinically plausible range in the PSA, albeit conservative, spanning an OS HR of 0.27 to 0.87.

Scenario A PSA Results

The PSA results relating to Scenario A, are presented in Tables 2 and 3.

Table 2 - Scatterplot of Costs and Effects for Scenario A, Based on OS HR 95% CI (0.06, 1.63)

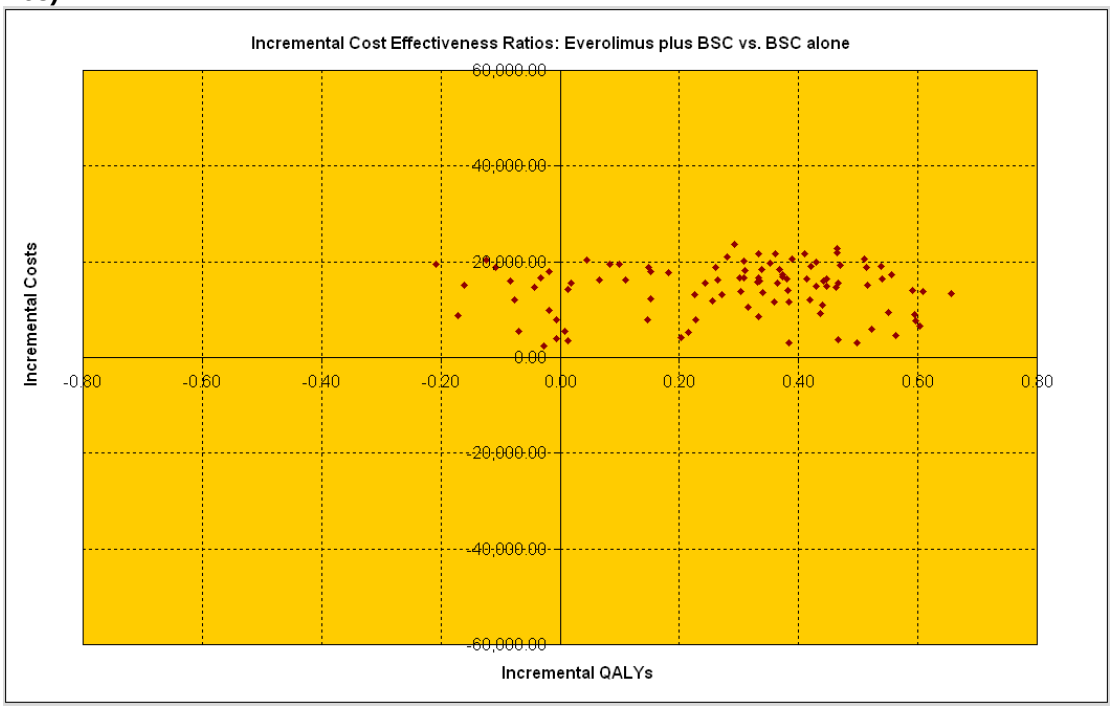
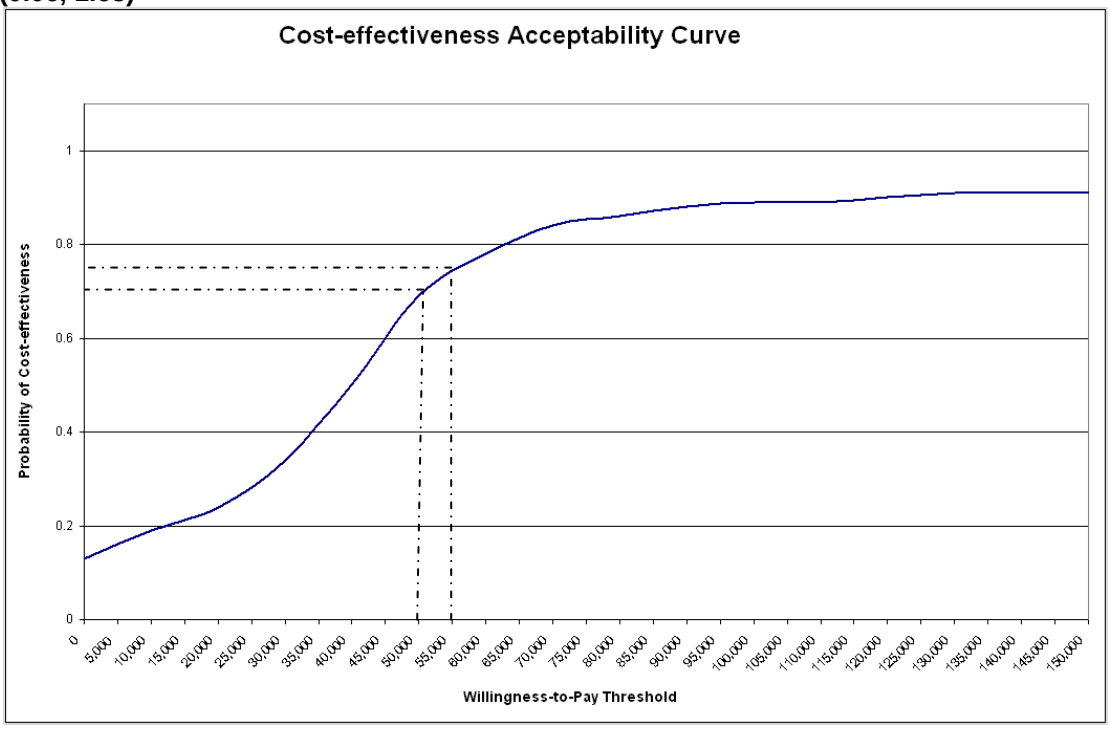


Table 3 – Cost-effectiveness Acceptability Curve for Scenario A, Based on HR 95% CI (0.06, 1.63)



The CEAC demonstrates that there is a 69% probability that the Incremental Cost-effectiveness Ratio (ICER) is below £50k and a 73% probability that the ICER is below £55k.

However as discussed previously, the wide RPSFT confidence intervals represent extremes which are statistically but not necessarily clinically plausible.

Scenario B PSA Results
The PSA results relating to Scenario B, are presented in Tables 4 and 5.

Table 4 - Scatterplot of Costs and Effects for Scenario B Based on OS HR 0.27 to 0.87

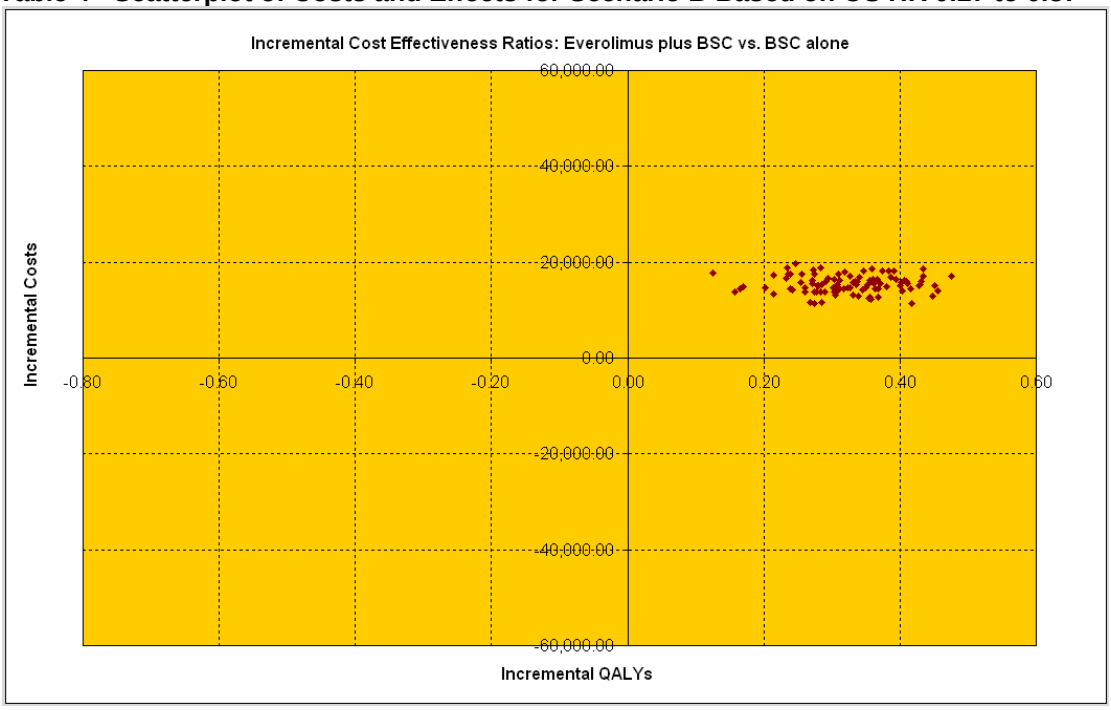
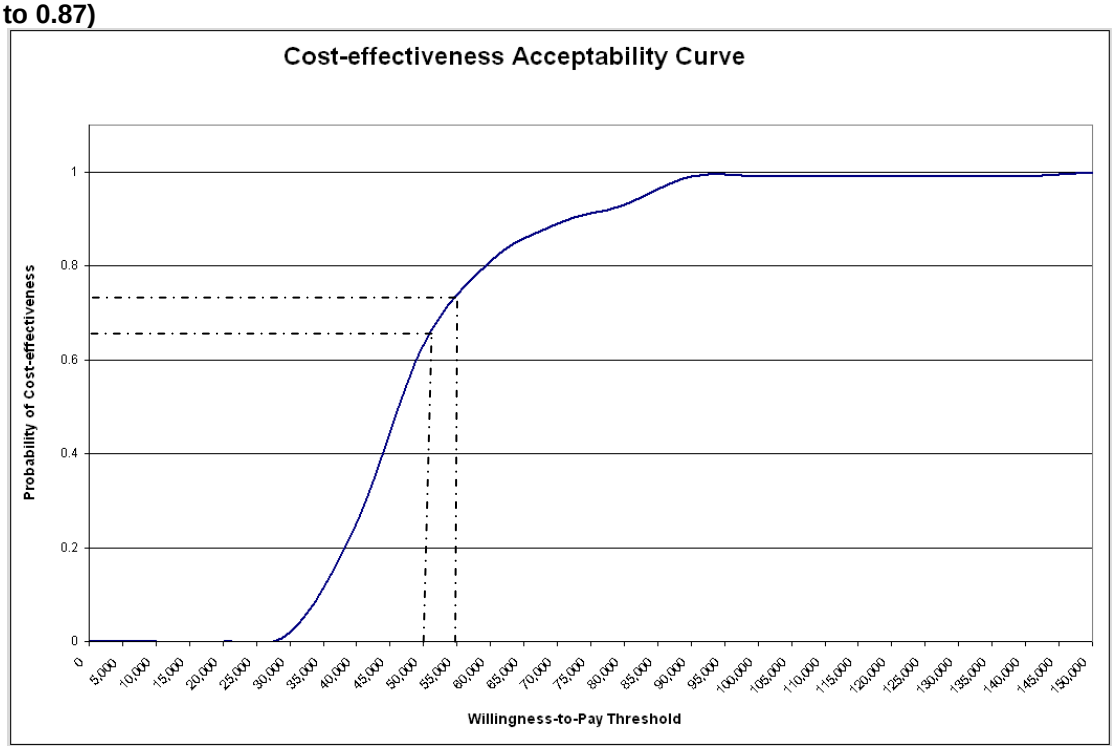


Table 5 – Cost-effectiveness Acceptability Curve for Scenario B) Based on OS HR 0.27 to 0.87)



The CEAC demonstrates that there is a 63% probability that the Incremental Cost-effectiveness Ratio (ICER) is below £50k and a 74% probability that the ICER is below £55k. This is likely to be a conservative estimate as the HR defining the upper bound (representing minimum effectiveness of everolimus in terms of effect on OS) is based on the confounded ITT results from the RECORD-1 study where 81% of patients randomised to BSC crossed over to receive everolimus. In addition, the HR defining the lower bound (representing the maximum effectiveness of everolimus in terms of effect on OS) is based on patients on BSC surviving for 6 months, although UK audit data suggests that this may be optimistic. The results demonstrate that the probability of very high ICERs is lower than that suggested by the RPSFT 95% CI.

b) One Way Sensitivity Analyses

As requested, one-way sensitivity analyses were conducted around different estimates of OS and PAS administration costs. The results from these analyses are presented in Table 6 below.

Table 6 – One-way Sensitivity Analysis Results

Variable	Incremental cost £	Incremental QALY	ICER for everolimus plus BSC versus BSC alone £
Base Case	**xx**	**xx**	**49,186**
1) Base Case Plus Admin costs (£28)	xx	xx	49,272
2) RPSFT 95% CI, 8.5 (HR = 0.06)	24,784	0.734	33,749
3) Assuming OS in BSC arm is 6 months (HR = 0.269)	19,752	0.497	39,724
4) Mean PAS admin cost assuming 2 hours (£ 56)	xx	xx	49,358

Scenario 2) above with an ICER of £33,749 is based on the RPSFT 95% CI, 8.5 which represents everolimus patients living 8.5 times as long as those on BSC. As stated previously as yet there is no evidence that this is likely to be the case and therefore the result from Scenario 2) is likely to be optimistic. Scenario 3) above is based on feedback from a survey of UK clinicians which suggested that on average BSC patients survive for around 6 months. This gives an ICER of £39,724. However, this may be a conservative estimate as data from an audit of UK centres suggested that patients on BSC survived for 2 to 5 months post-sunitinib treatment. The results from Scenario 4) demonstrate that even if the mean PAS administration cost was assumed to be 2 hours (mean time from survey = 38 minutes) the ICER would still be below £49,400.

Resource/Cost Associated with Administering the Everolimus Patient Access Scheme (PAS)

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It is not anticipated that the proposed scheme will have any additional burden over and above the current scheme as the only difference will be xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxx However, in order to evaluate NHS time and therefore cost associated with administering the PAS we conducted a survey of those who had registered patients into the scheme

In total ten centres were identified where everolimus patients have been registered using the current PAS. Telephone interviews were conducted with 8 of the pharmacists at centres participating in the PAS. Pharmacists at two of the centres were on vacation and therefore results were obtained from 8/10 of the centres. The summary results from the telephone survey are presented below.

Table of Telephone Survey Results for Time Spent (in minutes) Administering the PAS

	Time spent on Registration Form in Minutes
Mean (Median)	38.29 (30)
Range	5 to 75
Standard Error	8.89

The figures in the above table are based on 7/8 of the responses. This was because one of the seven responses was substantially different to the others which were largely consistent. In five out of eight responses the estimated total time to administer the PAS was less than one hour and in two cases around one hour. The remaining response suggested that the scheme would take around eight hours to administer. Importantly, the respondent did comment that this was unlikely to be a robust estimate, due to limited experience of administering the PAS. We therefore consider this response to be an outlier and have consequently not included it in the summary statistics or the PSA. Even if we included the outlier in the summary statistics, the mean time spent administering the PAS would be 94 minutes. Full details of the results from the survey are presented in the appendix attached. Feedback from the survey also suggested that no special qualification, or grade of pharmacist would be necessary to administer the scheme and therefore the costs of administering the PAS are based on an hourly rate of £28 for a basic grade pharmacist (PSSRU 2009). A copy of the draft PAS registration form is attached for your information in Appendix, 2.

Conclusions

Results from both PSA scenarios suggest that the probability of everolimus being cost-effective at a willingness to pay of £50k/QALY is at least 63% and at a willingness to pay of £55k/QALY is at least 73%. Furthermore the results from Scenario B, which represents a relatively more clinically plausible range, demonstrates that the probability of very high ICERs is lower than that suggested by the RPSFT 95% CI. As Scenario B, is based on conservative estimates of the effectiveness of everolimus, particularly with respect to the HR of 0.87 at the upper bound, it is likely that the true cost-effectiveness of everolimus is likely to be better than that suggested by the PSA in either scenario.

Appendix – Results from Survey to Ascertain PAS Administration Time

Respondent	At point of registration	Within 2 months of registration	Beyond 2 months of registration	Total time (mins)
1	x	x	x	x
2	x	x	x	x
3	x	x	x	x
4	x	x	x	x
5	x	x	x	x
6	x	x	x	x
7	x	x	x	x
8*	x	x	x	
			total time (mins)	**275.0**
			mean	**39.29**
			median	**30.00**
			standard deviation	**23.53**
			standard error	**8.89**
			min time	**15**
			max time	**75**

* not used in the analysis

Everolimus for the Treatment of Advanced Renal Cell Carcinoma (aRCC) – Details of Updated Patient Access Scheme (PAS) and Associated Results

Background

The decision not to recommend everolimus for advanced renal cell carcinoma, as detailed in the Final Appraisal Determination (FAD) dated June 2010, is based on a cost/QALY of £58.3k. This estimate of cost-effectiveness was generated from the ERG's adjustments to the Novartis model and the incorporation of a PAS which was approved by the Department of Health prior to the first Appraisal Committee meeting. In order to expedite the availability of everolimus to patients with advanced renal cell carcinoma, rather than submitting an appeal, we have decided to offer a revised PAS which will further reduce the cost of everolimus to the NHS. The original PAS provides the first pack free with a 5% discount on list price applied to all subsequent packs.
xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxx The net result of incorporating this updated PAS into the cost-effectiveness analysis is to reduce the cost/QALY from £58.3k to £49.1k. This substantially improved offering demonstrates our continued commitment to patients and we fervently hope that it will enable patients, who have no other treatments options, to benefit from access to everolimus.

The Updated PAS

Original PAS
1st pack (10mg or 5mg tablets x 30) at zero cost to the NHS. Subsequent packs (10mg x 30) will be offered to the NHS at a cost of £2,822.

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The list price is £2,970 per pack of 30 x 10mg tablets.

Updated Costs Applied in the Model (without dose intensity adjustment)

Everolimus Cost with Original PAS			Everolimus Cost with Updated PAS			
Unit cost (30 x 10mg tablet pack) £	Total cost per 8 week cycle £	Total cost per 8 week cycle–subsequent cycles £	Unit cost (30 x 10mg tablet pack) £	Total cost per 8 week cycle– first cycle £	Total cost per 8 week cycle– second cycle £	Total cost per 8 week cycle– subsequent cycles £
2822.00	2445.30	5266.80	xxxxx	x	xxxxxx*	xxxxxx

*xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxx.

The dose intensity adjustment of 91.8% is applied automatically within the model and therefore the associated figures are not supplied in this document.

Text or figures underlined and highlighted in yellow are designated as commercial in confidence.

Summary of Results

The results of incorporating the updated PAS are presented in the following table.

Table of Cost-effectiveness Results

	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)
ERG Model with Original PAS	0.843	0.517	0.33	33,854	14,868	18,986	**£58,316**
ERG Model with Updated PAS	0.843	0.517	0.33	30,882	xxxxxx	xxxxxx	**£49,186**
ERG Model with Updated PAS and admin cost*	.843	0.517	0.33	30,910	xxxxxx	xxxxxx	**£49,272**

*An assumed administration cost has been added to the model allowing for one hour of pharmacist time.

Description of Changes to the Model to Take Account of the Updated PAS

The transition probabilities from the ERG's model and supplied by Rebecca Trowman on 1.7.10 were applied in the Novartis model. This enabled us to reproduce the £58,316 estimate. This amended model was then used to calculate the impact of the updated PAS on the cost/QALY.

xxx

1) In the "Deterministic Results" worksheet the "Patient access scheme: 30 days Free" box was unchecked. NB: Checking this box removes the cost of 30 days treatment only, thus leaving 26 days worth of Afinitor treatment costs in cycle 1. Therefore it is important that this box is unchecked to ensure that a full 56 days worth of Afinitor treatment costs are removed from cycle 1.

2) In the "Markov Model (Afinitor)" worksheet, the formula in cell Q8 (costs, undiscounted, cycle 1) was changed from,

=IF('Deterministic Results'!$W$13=TRUE,Q7+C8*((cAfinitorTx/2.154)+cSD)+G8*((cAfinitorTx/2.154)+cSD+cAfinitorAE)+J8*$D$51+(L8-

L7)*$D$52,Q7+C8*((cAfinitorTx)+cSD)+G8*((cAfinitorTx)+cSD+cAfinitorAE)+J8*$D$51+(L8-L7)*$D$52)

to

=IF('Deterministic Results'!$W$13=TRUE,Q7+C8*((cAfinitorTx/2.154)+cSD)+G8*((cAfinitorTx/2.154)+cSD+cAfinitorAE)+J8*$D$51+(L8-L7)*$D$52,Q7+(C8*cSD)+G8*(cSD+cAfinitorAE)+J8*$D$51+(L8-L7)*$D$52)

This removes all Afinitor costs from cycle 1.

3) In the "Markov Model (Afinitor)" worksheet, the formula in cell Q9 (costs, undiscounted, cycle 2) was changed from,

=Q8+C9*$K$49+C8*D9*$D$50+G8*(1-SUM(H9:I9))*$K$50+(C8*E9+G8*H9)*$D$51+J8*(1-K9)*$K$51+(L9-L8)*$D$52

to

=Q8+C9*((cAfinitorTx/1.076)+cSD)+C8*D9*((cAfinitorTx/1.076)+cSD+cAfinitorAE)+G8*(1-SUM(H9:I9))*((cAfinitorTx/1.076)+cSD)+(C8*E9+G8*H9)*$D$51+J8*(1-K9)*$K$51+(L9-L8)*$D$52

xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxx

In order to account for the reduced cost per unit pack, in the "Treatment Costs" worksheet, the cost of Afinitor in cell D22 is reduced from £5266.8 xxxxxxxxxxxx.

No other changes were made to the ERG adjusted model. Implementation of the above changes results in a revised cost/QALY of £49,186.

The addition of a further £28 in cycle 1, to cover the cost of 1 hour of pharmacist time was added as an assumed cost of administering the scheme. This increased the ICER from £49,186 to £49,272.

Impact of Updated PAS on NHS Administration Requirements

As this is a finance based scheme, there is no requirement to track individual patients. In addition, we believe that the proposed changes to the PAS have negligible additional impact on the level of administration required. This is because we will be issuing the first two packs of Afinitor together rather than just the first pack. The discount on subsequent packs will be applied at the point of invoice. No guidance has yet been provided by the DoH or PASLU as to the likely NHS administration requirements but in view of the simplicity of the scheme an assumption of 1 hour of a pharmacist's time seems reasonable. The impact of adding

the cost of 1 hour of a pharmacist's time into the model is to increase the ICER from £49.1k to £49.2k.

Everolimus for Second-line Treatment of Advanced Renal Cell Carcinoma (aRCC)

ERG response to Additional Sensitivity Analyses.

Introduction

In response to requests from the NICE Appraisal Committee on 11th August, Novartis have presented additional sensitivity analyses. These include a Probabilistic Sensitivity Analysis (PSA), one-way sensitivity analyses, and further information relating to administration of the updated Patient Access Scheme.

The documents outlining these analyses were received by PenTAG (the ERG) on 21 Sept 2010 and a copy of the model used for the PSA was subsequently received on 28 Sept 2010. Given the clear time constraints entailed it was not possible to perform a full and thorough evaluation of the model and presented analysis before preparing this document. A summary evaluation of the Novartis submission however is given below.

Analysis of Probablistic Sensitivity Analysis

In the PSA analysis Novartis present two alternative scenarios based on the following two confidence intervals (CIs) for the hazard ratio for overall survival:

- the CIs derived from the RPSFT analysis on which the overall survival curves are based (HR 95% CI : 0.06, 1.63).
- CIs for the hazard ratio deemed more 'clinical plausible' by Novartis (HR 95% CI: 0.27, 0.87)

We examined both these sets of analysis. We were surprise to see that no summary statistics relating to the mean incremental costs and benefits in the PSA had been provided in the Novartis presentation (these were subsequently reported by email). We were also surprised to see that relatively few iterations (i.e. 100 trials) of the simulation had been used in the PSA. We therefore re-ran the model with 1000 iterations to test the model and results provided by Novartis. The results from these re-runs are presented below and are less favourable to everolimus than the results reported in the Novartis submission.

During our examination of the model we noticed a clear error in the CEAC presented for Scenario A in the Novartis submission (Table 3 in the Novartis submission). This shows a positive probability that everolimus is cost-effective at a zero willingness-to-pay threshold which would imply that in some simulation trials, treatment with everolimus plus BSC costs less than BSC alone. On examination we found that this error is cause by the fact that the Excel model sheet includes dominated trial outputs in the total of ICERs at zero (Cell: "Per Patient Model Results"!BM8). This entails in turn that they contributed to the probability of the ICER falling below £50K/QALY which falsely increases the reported probability of everolimus falling below the £50K/QALY willingness to pay threshold in Scenario A. Our results below correct for this error.

A number of other observations made from our examination of the model and documentation are listed here:

- We are not clear that all sources of potential uncertainty had been included in the model. For example we could find no evidence that the uncertainty surrounding the Weibull survival curve fit had been incorporated.
- The choice of distributions seems broadly in-line with accepted practice, however, the key parameters to determine the shape of probability distributions are not properly reported. The range information given in Table 1 is insufficient (for instance all Beta

distributions have a range of 0-1). These key parameters should ideally be specified as well as their source and justification.

- The method of implementing the PSA by applying probabilities to individual patients (i.e. a per patient approach) is unusual and we did not fully understand why the more conventional cohort based approach had not been adopted.

PSA Results from Scenario A (re-run with 1000 simulation trials)

Based on Overall Survival confidence limits derived from RPSFT analysis

Table 1 : Scenario A - summary PSA outputs

Mean inc. Costs	Mean inc. QALY	ICER £s/QALY	Mean Net benefit @ £50K/QALY	Prob. ICER < £30K	Prob. ICER < £50K
XXX	XXX	£51,661	- £440.77	24.0%	52.7%

Figure 1 : Cost Effectiveness Scatterplot for Scenario A (CIs based on RPSFT HR 95% 0.06, 1.63)

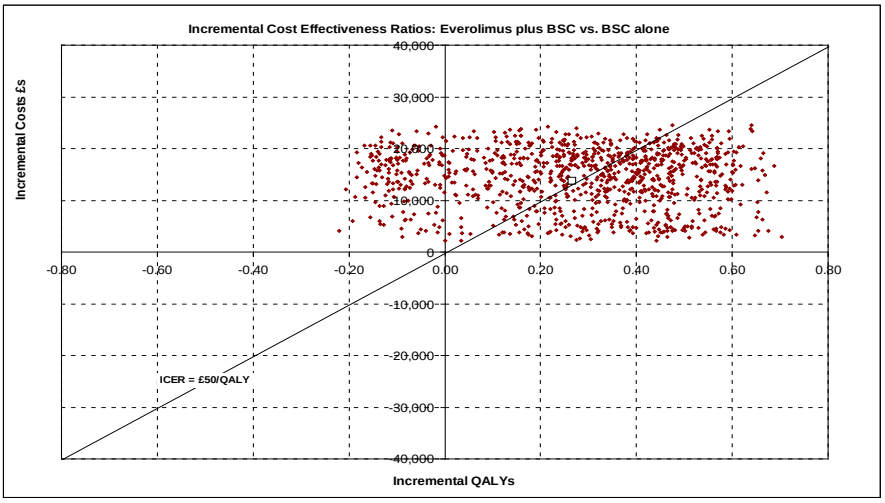
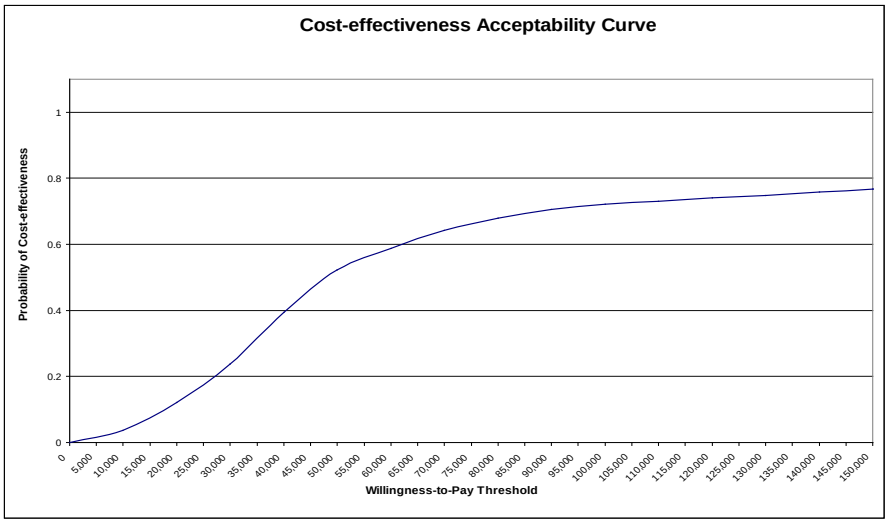


Figure 2 : Cost-effectiveness Acceptibility Curve for Scenario A (CIs based on RPSFT HR 95% 0.06, 1.63)



PSA Results from Scenario B (re-run with 1000 simulation trials)

Based on Overall Survival confidence limits suggested by Novartis

Table 2 : Scenario B - summary PSA outputs

Mean Inc. Costs	Mean inc QALY	ICER £s/QALY	Mean Net benefit @ £50K/QALY	Prob. ICER < £30K	Prob. ICER < £50K
XXX	XXX	£49,479	£152.72	28.0%	52.6%

Figure 3 : Cost Effectiveness Scatterplot for Scenario B (CIs suggested by Novartis OS HR 95% 0.27, 0.87)

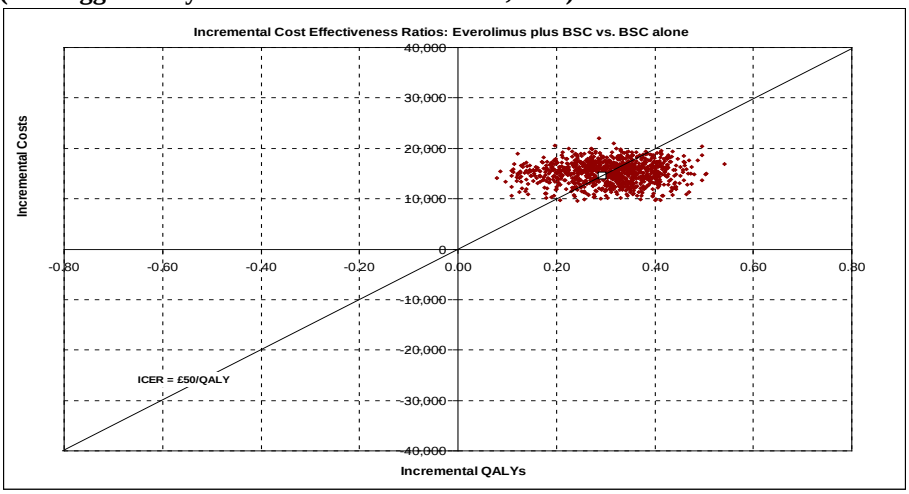
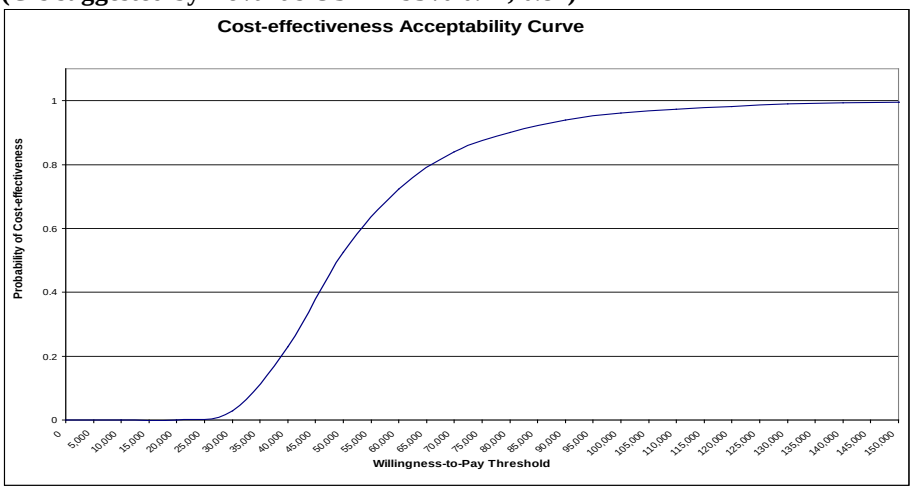


Figure 4 : Cost-effectiveness acceptibility curve for Scenario B (CIs suggested by Novartis OS HR 95% 0.27, 0.87)



One-way sensitivity analysis

In our view the one-way sensitivity analysis provided by the Novartis submission is clearly inadequate. Four separate analyses are presented but these look only at the impact of changes in one direction from the base case. Normal practice is to examine the impact of changes to each parameter of interest in both directions and typically to examine a number of different levels for each parameter value. Despite this these one-way analyses confirm once again the centrality of the overall survival hazard ratio in driving the model ICER.

Conclusion

The PSA presented by Novartis confirms the high levels of uncertainty associated with the base case estimate of cost-effectiveness for everolimus and BSC vs BSC alone for aRCC. The primary driver for uncertainty in the model outputs is the uncertainty surrounding the estimate of hazard ratio for overall survival between arms.

Two separate analyses are presented by Novartis based on different assessments of the confidence limits that should be applied to the hazard ratio for overall survival. These give slightly different levels of probability that the treatment is cost-effective at the £50,000 per QALY willingness to pay threshold as well as slightly variant mean levels for the incremental costs and benefits.

When we re-ran the Novartis model with a 1000 simulation trials and we needed to correct for an error in the CEAC calculation. We found that mean levels from the PSA analysis of incremental cost and benefit gave an ICER very close to the threshold level of £50,000 per QALY. The CEACs also show that the probability that treatment with everolimus versus BSC is cost-effective at this threshold is very close to 50% in both scenarios.

Constraints in the time available to assess the Novartis PSA analysis have meant that a thorough and in-depth evaluation has not been possible however we would point to the fact that our overview found at least one basic error (i.e. the calculation of the CEAC for Scenario A) and some clear reporting omissions in the Novartis submission (e.g. too few simulation trials, lack of PSA means, lack of detail, and lack of comprehensive one-way sensitivity outputs). These failings raise questions about the general confidence that can be given to the overall findings presented by Novartis.