BEVACIZUMAB, SORAFENIB TOSYLATE, SUNITINIB AND TEMSIROLIMUS FOR RENAL CELL CARCINOMA:

A SYSTEMATIC REVIEW AND ECONOMIC EVALUATION

Report commissioned by: NHS R&D HTA Programme

On behalf of: NICE

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Date completed: 2nd May 2008

Expiry date:

ABOUT THE PENINSULA TECHNOLOGY ASSESSMENT GROUP (PENTAG)

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- Screening for Hepatitis C Among Injecting Drug Users and in Genitourinary Medicine (GUM) Clinics - Systematic Reviews of Effectiveness, Modelling Study and National Survey Of Current Practice (2002)
- Systematic Review of Endoscopic Sinus Surgery for Nasal Polyps (2003)
- The Effectiveness and Cost-Effectiveness of Imatinib for First Line Treatment of Chronic Myeloid Leukaemia in Chronic Phase (2003)
- The Effectiveness and Cost-Effectiveness of Microwave and Thermal Balloon Endometrial Ablation for Heavy Menstrual Bleeding - A Systematic Review and Economic Modelling (2004)
- Do the Findings of Case Series Studies Vary Significantly According to Methodological Characteristics?(2005)
- The Effectiveness and Cost-Effectiveness of Pimecrolimus and Tacrolimus for Atopic Eczema - A Systematic Review and Economic Modelling (2005)
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- Inhaled Corticosteroids and Long-Acting Beta2-Agonists for The Treatment of Chronic Asthma in Adults and Children Aged 12 Years and Over: a Systematic Review and Economic Analysis (2007, In Press)
- Inhaled Corticosteroids and Long-Acting Beta2-Agonists for The Treatment of Chronic Asthma an Children Under the Age of 12 Years: a Systematic Review and Economic Analysis (2007, In Press)
- The Effectiveness and Cost-Effectiveness of Cochlear Implants for Severe to Profound Deafness in Children and Adults: A Systematic Review and Economic Model (2007, In Press)

Source of funding

This report was commissioned by the NHS R&D HTA programme as project number 07/72/01.

Competing Interests of Authors

None

Acknowledgements

We would like to acknowledge the help of Sue Whiffin and Jo Perry for their administrative support, Martin Pitt for assistance with verification of the cost effectiveness model and Gabriel Rogers for creating PenTAG's database for managing references and assisting with reference management.

We would particularly like to thank the Expert Advisory Group for their help throughout the project.

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Competing Interests of Expert Advisory Group

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	Four further UK clinical oncologists provided advice during the preparation of the report but later retracted consent to be acknowledged here. These individuals declared the following competing interests – advisory boards; speaker bureau; research funding from Bayer, Pfizer, Roche and Wyeth; received sponsorship from Bayer, Pfizer & Roche to attend meetings and honoraria for Advisory Board Meetings and sponsored lectures from Bayer, Pfizer & Roche and an honorarium for an Advisory Board from Wyeth; acted as a consultant and spoken at company sponsored events for Roche, Bayer, Pfizer and Wyeth and received honoraria for these services; has been involved with clinical studies with the agents under review; has received research support from Bayer and Pfizer; is a trustee of KCUK which is a charity dedicated to the interests of people affected by kidney cancer; is the Chair of the Medical Advisory Committee of Cancerbackup; Anti-angiogenic treatment of renal cancer is a primary academic and clinical interest; Ad-Hoc advisor to Roche, Pfizer, Bayer and Chiron; Consultant to Oxford Biomedica (unrelated vaccine being tested in renal cancer); has received research funding for unrelated project from Pfizer

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

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Colin Green	Contributed to the design of the assessment, led the cost-effectiveness aspects including the critique of submissions provided by industry. Contributed to writing and editing of the protocol and the report.
Martin Hoyle	Contributed to the design and implemented the economic model. Performed the critique of industry submissions. Contributed to the clinical effectiveness section and to writing and editing of the report.
Zulian Liu	Assessed abstracts for inclusion and exclusion. Performed the data extraction of clinical effectiveness data. Managed the reference database. Contributed to the cost effectiveness analysis and to writing and editing of the report.
Tiffany Moxham	Carried out literature searches for the systematic reviews and identification of model parameters.
Ken Stein	Contributed to the design of the assessment, the design and development of the cost effectiveness analysis and the preparation and editing of the report.
Jo Thompson Coon	Provided overall project management. Wrote the protocol. Performed the systematic review of clinical effectiveness. Contributed to writing and editing of the report. Contributed to the cost effectiveness analysis.
Karen Welch	Carried out literature searches for the systematic reviews and identification of model parameters.

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ADL	Activities of daily living
AE	Adverse event
AJCC	American Joint Committee on Cancer
ARCC	Advanced renal cell carcinoma
ASCO	American Society of Clinical Oncology
BNF	British National Formulary
BSC	Best supportive care
CEA	Cost effectiveness analysis
CEAC	Cost effectiveness acceptability curve
CI	Confidence interval
CR	Complete response
CIPFA	Chartered Institute for Public Finance and Accountancy
CNS	Central Nervous System
CRD	Centre for Reviews and Dissemination
CT	Computed tomography
CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
EAG	Expert Advisory Group
EAU	European Association of Urology
ECCO	European CanCer Organisation
ECOG	Eastern Cooperative Oncology Group
ECOG-PS	Eastern Cooperative Oncology Group – Performance Status
EORTC	European Organisation of Research and Treatment of Cancer
EQ-5D	EuroQoL Questionnaire
ERK	Extracellular signal-regulated kinase
FACT	Functional Assessment of Cancer Therapy
FACT-G	Functional Assessment of Cancer Therapy: General
FKSI	Functional Assessment of Cancer Therapy (FACT)-Kidney Symptom Index
FKSI-DRS	FKSI Disease-related Symptom subscale
HIF-1	Hypoxia-inducible factor-1
HR	Hazard Ratio
HRQoL	Health Related Quality of Life

ICD-10	International Classification of Diseases-version 10
ICER	Incremental Cost Effectiveness Ratio
IFN	Interferon-α
IL-2	Interleukin-2
ITT	Intention To Treat
i.v.	Intravenous route
KIT	Stem Cell Factor Receptor
LYG	Life year gained
LVEF	Left ventricular ejection fraction
MAPK	Mitogen-activated protein kinase
mg	Milligram
MPA	Medroxyprogesterone acetate
mRCC	Metastatic Renal Cell Carcinoma
MRCRCC	Medical Research Council Renal Cancer Collaborators
MRI	Magnetic Resonance Imaging
MSKCC	Memorial Sloan-Kettering Cancer Centre
mTOR	Mammalian Target Of Rapamycin
MU (or MIU)	Million Unit
MUGA scan	Multiple Gated Acquisition scan
NCI	National Cancer Institute
NCI-CTC	National Cancer Institute Common Terminology Criteria
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive disease
PDGF	Platelet-derived growth factor
PDGFR	Platelet-Derived Growth Factor Receptors
PFS	Progression-free survival
PR	Partial response
PSA	Probabilistic Sensitivity Analysis
IPSS	Personal Social Service
PWB	Physical Well Being subscale
QALY	Quality Adjusted Life Year
Q-TWiST	Quality-adjusted Time Without Symptoms of disease or Toxicity of treatment
QUOROM	The Quality of Reporting of Meta-analyses statement
RECIST	Response Evaluation Criteria in Solid Tumours

RCC	Renal Cell Carcinoma
RCT	Randomised controlled trial
RDI	Relative dose intensity
RDT	Randomised discontinuation trial
s.c.	Subcutaneous route
sd	Standard deviation
se	Standard error
SD	Stable disease
SG	Standard Gamble
SR	Systematic review
TNM	Tumour node metastasis
TOX	Toxicity
TTO	Time Trade-Off
TWiST	Time Without Symptoms of progression or Toxicity of treatment
VEGF	Vascular Endothelial Growth Factor
VEGFR	Vascular-Endothelial Growth Factor Receptors
VPF	Vascular permeability factor
VHL	von Hippel-Lindau

1. Executive Summary

1.1. Background

Renal cell carcinoma (RCC) is a highly vascular type of kidney cancer arising in the epithelial elements of the nephrons. The most common histological subtype of RCC is clear cell carcinoma (approx 75% of cases). RCC is often asymptomatic until it reaches a late stage. Metastatic spread may involve the lymph nodes, lung, bones, liver, brain and other organs. The main risk factors for kidney cancer include obesity, hypertension, smoking and some genetic conditions, although none of these risk factors are particularly strong. In England and Wales, kidney cancer is the eighth most common cancer in males and the fourteenth most common cancer in females. In 2004, there were 5745 registrations of newly diagnosed kidney cancer in England and Wales. Incidence begins to rise over the age of 40 and is highest in those over the age of 65. Of all those diagnosed with RCC in England and Wales, about 44% live for at least five years after initial diagnosis and about 40% live for at least 10 years. However, the prognosis following diagnosis of metastatic disease is poor and approximately 10% of people diagnosed with Stage IV RCC live for at least five years after diagnosis.

Current NHS treatment options for metastatic RCC include radical nephrectomy and IFN. There is currently no standard NHS treatment for patients with metastatic RCC who do not respond to first line immunotherapy, or those who are unsuitable for treatment with IFN.

Bevacizumab is a humanised monoclonal antibody, administered as an intravenous infusion in combination with IFN and licensed for use as first line therapy in patients with advanced and/or metastatic RCC. *Sorafenib tosylate* is an orally active bi-aryl urea, small molecule inhibitor of various tyrosine kinase receptors licensed for first line use in individuals who are not suitable for treatment with IFN and as second line therapy in those in whom treatment with cytokine based immunotherapy has failed. *Sunitinib* is a novel, oral multi-targeted inhibitor of tyrosine kinase receptors and licensed for use in the first and second line treatment of advanced and/or metastatic RCC. *Temsirolimus* is a selective inhibitor of the mammalian target of rapamycin (mTOR) and is licensed for first line treatment of patients with advanced RCC who have at least three of six poor prognostic risk factors.

1.2. Objectives

The purpose of this report is to assess the clinical and cost effectiveness of bevacizumab combined with IFN, sorafenib tosylate, sunitinib and temsirolimus in the treatment of people with advanced and/or metastatic RCC.

The objectives are:

- to identify, appraise and synthesise where appropriate, the current evidence for the clinical and cost effectiveness of the interventions in the treatment of people with advanced and/or metastatic RCC in accordance with their marketing authorisations and to
- determine what, if any, is the incremental cost-effectiveness of the interventions when compared to current standard treatment.

More fully the policy questions to be answered are:

First line therapy

(1) In those who are suitable for treatment with immunotherapy, what is the clinical and cost effectiveness of bevacizumab plus IFN and sunitinib, using IFN as a comparator?

(2) In those who are not suitable for treatment with immunotherapy what is the clinical and cost effectiveness of sorafenib tosylate and sunitinib, using best supportive care as a comparator?

(3) In those with three or more of six poor prognostic factors what is the clinical and cost effectiveness of bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and best supportive care using immunotherapy as a comparator?

Second line therapy

(4) In those in whom cytokine based immunotherapy has failed what is the clinical and cost effectiveness of sorafenib tosylate and sunitinib, using best supportive care as a comparator?

We have defined suitability for treatment with immunotherapy in terms of contraindication to treatment (e.g. autoimmune disease or a history of depression). We have not considered prognosis when assessing suitability for treatment with IFN. However, we are aware that in some

centres in the UK, people with intermediate or poor prognosis would be considered to be 'unsuitable for treatment with IFN', following the publication of several trials in which IFN was shown to be of no benefit in these patients.

1.3. Methods

The assessment comprises a systematic review of clinical and cost effectiveness studies, a review of manufacturer submissions and an economic analysis.

1.3.1. Clinical effectiveness systematic review

For the assessment of clinical effectiveness, a literature search was conducted in a number of electronic databases, up to September/October 2007 (and re-run in February 2008). Systematic reviews and randomised clinical trials that compared any of the interventions with any of the comparators in participants with advanced and/or metastatic RCC were included. The use of data from phase II studies and non-randomised clinical trials was considered where there was insufficient evidence from good quality randomised clinical trials. Conference abstracts were included if there was sufficient detail to adequately assess quality. Full papers for studies that appeared relevant were retrieved and screened in detail. All trials were fully data extracted and quality assessed. Results of the included trials were synthesised narratively. There were insufficient studies identified to consider quantitative meta-analysis. The validity of indirect comparison between interventions was considered using the method proposed by Bucher and colleagues where data from head-to-head randomised clinical trials was unavailable.

1.3.2. Review of economic evaluations, related literature and manufacturer submissions

A literature search was conducted in a number of electronic databases up to September/October 2007 (and re-run in March 2008). All titles and abstracts were assessed independently and all publications meeting the inclusion criteria were fully data extracted and discussed narratively. Searches were also performed to identify literature describing health related quality of life of people with RCC, treatment costs and resource use associated with the treatment of RCC, and modelling methods used to model disease progression and cost effectiveness in RCC. The cost effectiveness analyses reported in the manufacturer submissions were assessed against the NICE

reference case and critically appraised using the framework presented by Phillips and colleagues. A narrative summary of the company submissions is also presented.

1.3.3. PenTAG cost utility model

A decision analytic Markov-type model was developed in Excel to simulate disease progression and to estimate the cost effectiveness of the drugs under consideration. The model has three health states: progression free survival, progressive disease and death and uses estimates of effectiveness, costs and health state utilities assigned to these states to model disease progression and cost effectiveness over time in a cohort of patients. The model has a ten year time horizon and a 6-week model cycle. Future costs and benefits were discounted at 3.5% per annum. Weibull survival curves were fitted to the progression free and overall survival Kaplan Meier curves from clinical trials for the baseline comparator. Relative measures of treatment effectiveness (hazard ratios) were then used to estimate the expected disease progression compared to baseline. Costs and effects were estimated for each health state at each model cycle across the cohort of patients. One-way, multi-way and probabilistic sensitivity analyses were performed to explore structural and parameter uncertainty.

1.4. Results

1.4.1. Number and quality of effectiveness studies

The electronic searches retrieved a total of 888 titles and abstracts. Thirteen publications describing eight clinical trials were included. Of these,

- Seven were fully published randomised clinical trials and
- One was available as a protocol and a conference abstract

Data contained within a further 19 conference abstracts relating to the included trials were also considered.

Three randomised clinical trials were identified that compared either bevacizumab plus IFN (two trials, one published in abstract form only) or sunitinib (one trial) with IFN alone as first line therapy in those suitable for treatment with IFN. For the comparison of interventions in people unsuitable for treatment with IFN, preliminary results of one randomised clinical trial in which

sorafenib was compared with best supportive care, available in abstract form only was located. We found one randomised clinical trial of temsirolimus versus IFN in people with three or more of six risk factors for poor prognosis. For the final research question (second line therapy), we included a randomised clinical trial and a randomised discontinuation trial of sorafenib versus best supportive care and two phase II single arm trials of sunitinib.

We were unable to identify any data on clinical effectiveness in the following areas:

- In patients unsuitable for treatment with immunotherapy, we found no suitable data on sunitinib or best supportive care
- In patients with poor prognosis we found no data on sorafenib
- We were unable to locate any RCTs of sunitinib as second line therapy, and
- We were unable to locate any RCTs of any of the interventions in comparison with IL-2.

All the fully published included trials were large, multicentre, good quality trials. There was insufficient detail in the conference abstracts to fully appraise the quality of the trials.

1.4.2. Summary of benefits and risks

Bevacizumab plus IFN and sunitinib compared to IFN as first line therapy

The trials suggest that treatment with both interventions has clinically relevant and statistically significant advantages over treatment with IFN alone, in terms of progression free survival and tumour response, doubling median progression free survival from approximately 5 months to approximately 10 months. There is less data available to inform the effects on overall survival due to the early crossover of patients on control treatment following interim analyses; both interventions show some benefits on overall survival. Results of an indirect comparison between sunitinib and bevacizumab plus IFN suggest that sunitinib may be more effective than bevacizumab plus IFN (HR 0.67; 95% CI 0.50 to 0.89) in terms of progression free survival. Sunitinib is associated with a lower frequency of adverse events than IFN although the adverse event profile is different. Bevacizumab plus IFN is associated with slightly more adverse events than IFN alone.

Sorafenib tosylate and sunitinib compared with best supportive care as first line therapy

No trials met the inclusion criteria for the systematic review of clinical effectiveness.

Bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and best supportive care compared with IFN as first line therapy in people with poor prognosis

The available data indicates that temsirolimus has clinically relevant and statistically significant advantages over treatment with IFN in terms of progression free and overall survival, increasing median overall survival from 7.3 to 10.9 months (HR 0.73; 95% CI 0.58 to 0.92). There is also some evidence to suggest that progression free survival may be prolonged by treatment with the combination of bevacizumab plus IFN compared with IFN alone, however whether this effect would be considered clinically and statistically significant is unclear. We were unable to find any data on sorafenib tosylate in this population. A significantly lower frequency of grade 3 and 4 adverse events was reported during temsirolimus treatment than during IFN treatment in the randomised clinical trial.

Sorafenib and sunitinib compared with best supportive care as second line therapy

The trials suggest that sorafenib tosylate has clinically relevant and statistically significant advantages over best supportive care in terms of overall survival, progression free survival and tumour response. Progression free survival was doubled in the large randomised clinical trial (HR 0.51; 95% CI 0.43 to 0.60). Sorafenib tosylate is associated with an increased frequency of hypertension and hand foot skin reaction compared to placebo. We were unable to locate any comparative trials of sunitinib as second line therapy. Two single arm phase II trials suggest that sunitinib may be efficacious in this population with no greater incidence of adverse events than when used as first line therapy.

1.4.3. Summary of costs

According to the current edition of the British National Formulary (BNF), the cost of treatment with bevacizumab (10mg/kg) plus IFN (9MU three times per week) for an 80kg patient is £151.42 per day (exclusive of the costs of drug administration), sorafenib costs £89.45/day and sunitinib costs £74.74 per day. The price of temsirolimus is not yet available in the BNF, Wyeth

have advised that the cost of a 30mg vial is £618. The cost of temsirolimus is therefore £88.29 per day (exclusive of drug administration costs).

1.4.4. Summary of cost effectiveness

We were unable to locate any fully published economic evaluations of any of the interventions. Whilst there are many similarities in the methodology and structural assumptions employed by PenTAG and the manufacturers of the interventions, in all cases, the cost effectiveness estimates from the PenTAG economic evaluation are higher than those presented in the manufacturer submissions.

Bevacizumab plus IFN and sunitinib compared to IFN as first line therapy

The PenTAG economic evaluation estimated that the cost per QALY for bevacizumab plus IFN versus IFN is £171,301 per QALY. Where the NHS is willing to pay £30,000 for an additional QALY, there is zero probability that this intervention would be considered cost effective. Bevacizumab plus IFN is unlikely to be considered cost effective compared with either sunitinib or IFN at any reasonable willingness to pay threshold.

For sunitinib versus IFN, the PenTAG cost effectiveness analysis estimates a cost per QALY of £71,462 per QALY. The probability that sunitinib would be considered cost effective at a willingness to pay threshold of £30,000 per QALY is zero. Sunitinib is likely to be considered cost effective compared to both bevacizumab plus IFN and IFN alone above a willingness to pay threshold of £75,000 per QALY.

Sorafenib tosylate and sunitinib compared with best supportive care as first line therapy

We were unable to perform a cost effectiveness analysis to inform this research question due to the lack of clinical effectiveness data. The manufacturer of sorafenib (Bayer) presents an analysis of a subgroup of patients from the TARGETs second line trial of sorafenib versus best supportive care who were unsuitable for treatment with IFN. The cost per QALY for people unsuitable for treatment with IFN was [redacted] per QALY.

Bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and best supportive care compared with IFN as first line therapy in people with poor prognosis

We were unable to locate appropriate overall and progression free survival data with which to populate the economic model for bevacizumab plus IFN, sunitinib, sorafenib toylate or best supportive care.

The base case discounted incremental cost effectiveness ratio for temsirolimus versus IFN estimated from the PenTAG economic analysis is £94,385 per QALY. The probabilistic sensitivity analyses suggest that where the NHS is willing to pay £30,000 for an additional QALY, the probability that temsirolimus is likely to be considered cost effective compared with IFN is zero. Temsirolimus is likely to be considered cost effective compared with IFN only above a willingness to pay threshold of £95,000 per QALY.

The cost utility analyses performed in patient subgroups indicate cost per QALY estimates ranging from £74,184 per QALY to £154,334 per QALY, although the clinical effectiveness data on which these analyses are based is uncertain.

Sorafenib and sunitinib compared with best supportive care as second line therapy

As we were unable to locate any comparative trials of sunitinib as second line therapy, we were only able to perform economic analyses of the cost effectiveness of sorafenib versus placebo (best supportive care) in this patient population. The PenTAG model estimates a cost per QALY for sorafenib versus best supportive care of £102,498 per QALY. The probability that sorafenib would be likely to be considered cost effective compared with best supportive care at the £30,000 per QALY level is zero. Compared with best supportive care, sorafenib is only likely to be considered cost effective above a willingness to pay threshold of approximately £100,000 per QALY.

1.4.5. Sensitivity analyses

For all comparisons, the cost-effectiveness estimates are particularly sensitive to variations in the estimates of treatment effectiveness, drug pricing (including dose intensity data), and health state utility input parameters. The ICERs are insensitive to a number of assumptions and data estimates, in particular, discounting, time horizon, limiting IFN administration to one year, non-

drug costs, inclusion of estimates associated with costs of death, and estimates of adverse event costs.

1.5. Discussion

This assessment has been necessarily constrained by the marketing authorisations of the interventions under review, leading to difficulties in deriving research questions applicable to the RCC population. We felt it was important to use current standard treatment as the comparator wherever possible - considering IFN to be the comparator for first line therapy in patients suitable for treatment with immunotherapy and best supportive care the comparator in all other situations. Suitability for treatment with immunotherapy was defined in terms of clinical contraindication to treatment (e.g. autoimmune disease or a history of depression). However, we acknowledge that a large proportion of people diagnosed with RCC in the UK will be deemed unsuitable for treatment with IFN as a result of clinical markers of prognosis. Informal extrapolation of available data suggests that if it is assumed that there is no difference in the relative effectiveness of best supportive care and IFN in this population, and that the cost of best supportive care would be less than the cost of treatment with IFN, it is possible that the new interventions would be less likely to be considered cost effective at commonly used willingness to pay thresholds when compared to best supportive care.

Clinical trials suggest that all four interventions have clinically relevant and statistically significant advantages over current standard treatment (IFN or best supportive care) where data exists with which to make the comparison. The most robust clinical effectiveness data exists for progression free survival; treatment crossover following interim analyses was permitted in all but one (temsirolimus vs. IFN) of the included trials resulting in confounding of overall survival data. There is therefore a large amount of uncertainty in the estimates of overall survival used in the assessment of clinical and cost effectiveness.

The PenTAG cost effectiveness analysis estimates that if the NHS is willing to pay £30,000 for an additional QALY, the probability that any of the interventions (in the undertaken comparisons) would be considered cost effective is zero. Exploration of these results using one-way, multi-way and probabilistic sensitivity analyses indicate that the model is most sensitive to variations in the hazard ratios for overall survival, drug pricing (including assumptions made about dose intensities and drug wastage) and health state utility values. The sensitivity analyses for the hazard ratios for progression free survival have highlighted issues linked to the balancing of

incremental costs and effects. In the PenTAG analysis, improvements in progression free survival make the drugs less attractive in terms of value for money. This counter-intuitive effect is seen across all of the analyses undertaken by PenTAG, is apparent for both cost per QALY and cost per life-year analyses and can be explained partly by the relatively high incremental treatment costs (costs of the drug, drug administration and monitoring) associated with time spent in the progression free disease health state.

The cost effectiveness estimates produced in the PenTAG economic evaluation are higher than the manufacturer base case estimates in all cases (although in two of the four analyses the results are similar). Whilst there are some common aspects of methodology, in both model structure and data inputs across manufacturer and PenTAG analyses, there are also clear differences in the resulting cost effectiveness estimates.

1.5.1. Strengths and limitations of the analyses

The strengths of this assessment include comprehensive, explicit and systematic literature searches including hand searching of conference proceedings to locate evidence both for the review of clinical effectiveness and to inform the economic modelling study; work to fit the most appropriate survival curves to the empirical immature overall survival data and extensive analyses of the uncertainty of the model using one-way, multi-way and probabilistic sensitivity analyses.

Limitations include the constraint of the assessment by the marketing authorisations of the products leading to difficulties with the derivation of research questions and the subsequent applicability of these questions to the RCC population, the uncertainty of the overall survival and health state utility data, the availability of clinical effectiveness data for all potential comparisons, issues surrounding patient preference, consideration of the sequencing of treatments, some of the structural modelling assumptions used in the PenTAG model and the scarcity of available information on resource use and costs.

1.5.2. Generalisability of the findings

All the trials included in the review of clinical effectiveness were conducted in patients with predominantly clear cell, metastatic RCC, the majority of whom had undergone previous nephrectomy and many of whom were of favourable and intermediate prognosis and good performance status. None of the studies recruited patients with brain metastases (unless

neurologically stable) and few patients with bone metastases were included (20% in the trial of bevacizumab plus IFN versus IFN and 30% in the trial of sunitinib versus IFN). Whether the results of this assessment can be extrapolated to other patient groups is unclear.

1.6. Conclusions

We conclude that there is evidence to suggest that treatment with bevacizumab plus IFN and sunitinib has clinically relevant and statistically significant advantages over treatment with IFN alone in patients with metastatic RCC. There is also evidence to suggest that, in people with three of six risk factors for poor prognosis, temsirolimus has clinically relevant advantages over treatment with IFN and sorafenib tosylate is superior to best supportive care as second line therapy. The frequency of adverse events associated with bevacizumab plus IFN, sunitinib and temsirolimus is comparable with that seen during treatment with IFN, although the adverse event profile is different. Treatment with sorafenib is associated with a significantly increased frequency of hypertension and hand foot syndrome.

The PenTAG cost effectiveness analyses suggests that the probability that any of the interventions would be considered cost effective at a willingness to pay threshold of £30,000 per QALY is zero.

1.6.1. Suggested future research questions and priorities

There are clear gaps in the evidence base needed to fully appraise the clinical and cost effectiveness of these four interventions in accordance with their marketing authorisations. Further randomised clinical trials in the following areas would therefore be useful:

- in patients unsuitable for treatment with IFN either as a result of contraindications or who have been defined as having intermediate and poor prognosis and may not benefit from IFN, trials of sorafenib, sunitinib, bevacizumab and best supportive care, and
- comparative trials of sunitinib and sorafenib as second line therapy.

In the current evidence base there is large amount of uncertainty surrounding the estimates of overall survival, primarily due to early crossover of people receiving control treatment following interim analyses. It is unrealistic and perhaps unethical to expect that further randomised clinical trials would be performed using IFN or best supportive care as a comparator in these

interventions that are now widely used in Europe and the US. As the interventions provide little possibility of a cure and in the absence of unconfounded estimates of overall survival from RCTs, further understanding of the impact of the interventions on health related quality of life during progression free survival and progressed disease would facilitate the decision making process for clinicians and patients.

Research on current treatment pathways and current practice (e.g. in the use of interferon) would reduce the level of uncertainty in future studies modelling the cost-effectiveness of drugs for treatment of renal cancer.

As more agents are introduced for the treatment of metastatic RCC, the issues of treatment sequencing become more evident and raise many additional research questions surrounding the combination and order of treatments to provide maximum benefit in each patient population.

When modelling treatment of RCC there are methodological challenges when using summary data (survival analysis) from clinical trials, and research to explore the impact of using aggregated data compared to individual patient level data would be helpful

2. Background

2.1. Description of underlying health problem

2.1.1. Definition and classification (staging)

Renal cell carcinoma (RCC) is a highly vascular type of kidney cancer arising in the epithelial elements of nephrons. In England and Wales, almost 90% of kidney cancers are RCCs.[1] The most common histological types of RCC are clear cell carcinoma (also known as conventional or non-papillary RCC) (approx 75% of cases), Type I papillary RCC, Type II papillary RCC and chromophobe RCC.[2] There are differences in the characteristics of different RCC histologies e.g. clear cell carcinoma produces VEGF, spreads early and may respond to treatment with immunotherapy. Papillary cancer is less well understood.[3] Although most (>90%) cases of RCC occur sporadically, mutations in the von Hippel-Lindau (VHL) tumour suppressor gene appear to be responsible for about 60 percent of the cases of clear-cell type[3] and gene silencing by methylation for most of the remainder. The sporadic form tends to be solitary and usually occurs in and beyond the 4th decade of life. The inherited form tends to be multi-focal and bilateral and has an earlier onset. [3]

Staging of RCC uses the American Joint Cancer Committee (AJCC) Tumour-Node-Metastasis (TNM system). Tumour stage is based on the combination of tumour size (T) and extent of spread from the kidneys (Table 1, page 14). TNM classifications are combined to produce Stages I to IV (Table 2, page 15) and describe a patients' overall disease stage.[4] This report is concerned with people diagnosed with RCC at stage III and IV.

Table 1: TNM system for staging of RCC

	Tumour size (T)		**Regional Lymph nodes (N)**		**Distant metastases (M)**
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed	MX	Presence of distant metastasis cannot be assessed
T0	No evidence of primary tumour	N0	No regional lymph node metastasis	M0	No distant metastasis
T1a	Tumour is 4cm in diameter or smaller and is limited to the kidney	N1	No regional lymph node metastasis.	M1	Distant metastasis present: includes metastasis to non-regional lymph nodes and/or other organs
T1b	Tumour is larger than 4cm but smaller than 7cm and is limited to the kidney.				
T2	Tumour is larger than 7cm but is still limited to the kidney.	N2	Metastasis to more than one regional lymph node		
T3a	Tumour has spread into the adrenal gland or into fatty tissue around the kidney, but not beyond the Gerota's fascia (a fibrous tissue which surrounds the kidney and nearby fatty tissue).				
T3b	Tumour has spread into the large vein leading out of the kidney (renal vein) and/or the part of the large vein leading into the heart (vena cava) that is within the abdomen.				
T3c	Tumour has reached the part of the vena cava that is within the chest or invades the wall of the vena cava.				
T4	Tumour has spread beyond the Gerota's fascia				

Table 2: Staging renal cell carcinoma

Stage	TNM classification	Description
Stage I	T1a-T1b, N0, M0	The tumour is 7cm or smaller and limited to the kidney. There is no spread to lymph nodes or distant organs
Stage II	T2, N0, M0	The tumour is larger than 7cm but is still limited to the kidney. There is no spread to lymph nodes or distant organs
Stage III	T1a-T3b, N1, M0 or T3a-T3c, N0, M0	There are several possible descriptions for Stage III including any tumour that has spread to one nearby lymph node but not to more than one lymph node or other organs and tumours that have not spread to lymph nodes or distant organs but have spread to the adrenal glands or to fatty tissue around the kidney and/or have grown into the vena cava.
Stage IV	T4, N0-N1, M0 or any T, N2, M0 or any T, Any N, M1	There are several possible descriptions for Stage IV including any tumours that have spread directly through the fatty tissue and beyond the Gerota's fascia, any tumour that has spread to more than one lymph node near the kidney or to any lymph node distant from the kidney, or to any distant organs.

2.2. Epidemiology of renal cell carcinoma

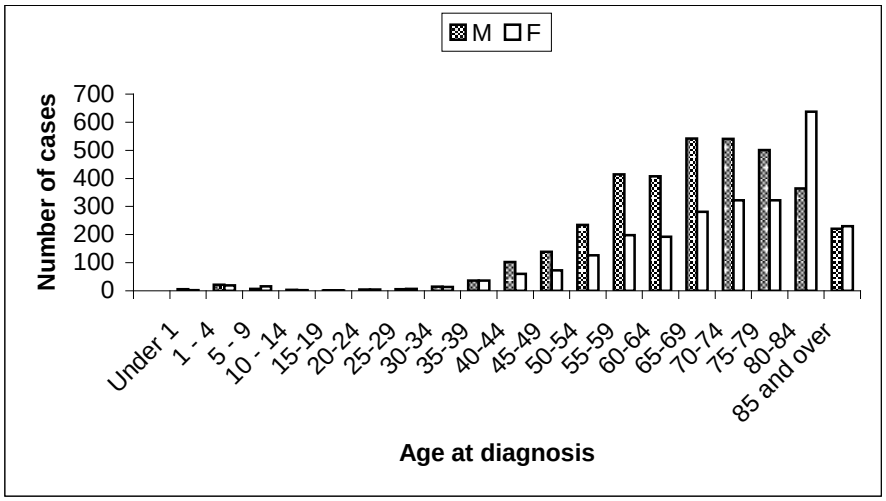
2.2.1. Incidence

In England and Wales, kidney cancer is the eighth most common cancer in males and the fourteenth most common in females. In 2004, there were 3,567 registrations of newly diagnosed kidney cancer (ICD-10 codes C64-66, C68) in men and 2,178 in women.[5,6] Figures for England are shown below in Figure 1; incidence begins to rise over the age of 40 and is highest in those aged 65 and above.

BACKGROUND

Worldwide incidence of kidney cancer has been rising steadily since the 1970's for both men and women.[7] Analysis of data from the US suggests that part of the rise is due to an increase in incidental detection as a consequence of the increased use of imaging technology such as ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI). Although, the rise in the number of cases is greatest in small, localised tumours, there has also been a rise in advanced cases of RCC which would suggest that increased detection of pre-symptomatic tumours cannot fully explain the rising incidence of RCC.[8]

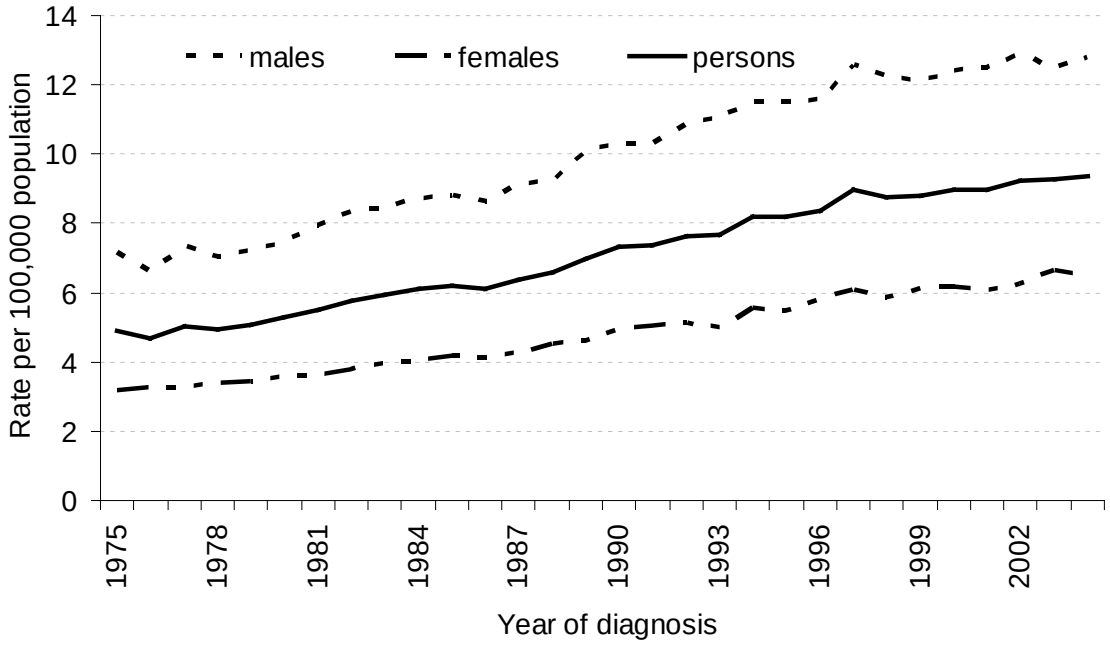
Figure 1: Number of cases of diagnosed kidney cancer by age and sex registered in England in 2004



Source: Office of National Statistics, Report MB1 35, Cancer Statistics Registrations, 2006[5]

In Great Britain, the incidence of kidney cancer in men has risen from 7.1 per 100,000 in 1975 to 12.8 per 100,000 in 2004. Over the same period, the incidence in women has increased from 3.2 to 6.5 per 100,000 (Figure 2, page 17). Increases have been greatest in men aged over 65 and women over 55 years of age.[9]

Figure 2: Age standardised (European) incidence rates of kidney cancer in Great Britain, 1975 to 2004



Source: Kidney Cancer Statistics, Cancer Research UK, 2007[9]

2.2.2. Aetiology

The main risk factors for kidney cancer include obesity [10-13], hypertension [8], smoking [14] and some genetic conditions, although none of these risk factors are particularly strong.[3] The risk of kidney cancer increases with age and is more common in men than in women (see section 2.2.1, page 15). It has been estimated that approximately 25% of the cases of kidney cancer diagnosed in Europe are attributable to obesity [12] and 25% of cases in men are attributable to smoking.[14] A recent meta-analysis of 24 studies of smoking as a risk factor for the development of RCC found the relative risk for male smokers was 1.54 (95% CI = 1.42-1.68) and for female smokers was 1.22 (95% CI = 1.09-1.36). For both men and women there was a strong dose-dependent increase in risk and a reduction in relative risk for those who had quit smoking more than 10 years previously.[15]

2.2.3. Symptoms

Renal cancer is often asymptomatic until it reaches a late stage. A large number of patients with RCC are diagnosed due to clinical symptoms, although few cases now present with the classical triad of palpable abdominal mass, flank pain and haematuria. Paraneoplastic signs and symptoms include

hypertension, cachexia, weight loss, pyrexia, neuromyopathy, amyloidosis, elevated erythrocyte sedimentation rate, anaemia, abnormal liver function and hypercalcaemia. Metastatic spread may involve the lymph nodes, bones, liver, brain and other organs.

In a retrospective analysis of 400 patients diagnosed with RCC in France between 1984 and 1999, Patard and colleagues stratified tumours into three groups. Forty-one percent of patients reported isolated local symptoms such as lumbar pain, palpable mass and haematuria; systemic symptoms (anorexia, asthenia, weight loss or symptoms associated with metastasis (bone pain, persistent cough) were reported in 22% at presentation, and the remaining 37% of patients were asymptomatic at diagnosis. [16]

The British Association of Urological Surgeons collects data on kidney cancer diagnoses in the United Kingdom. According to their figures, of those diagnosed with kidney cancer in 2006, for whom staging information was available, just over a third (40%) were diagnosed with stage 1 RCC, 18% had stage 2, 26% had stage 3 and 17% had stage 4. In just under a quarter of those diagnosed with stage 4 RCC, the primary cancer had grown out of the kidney to involve other structures (stage 4a). In three quarters of patients with Stage 4 disease the tumour had metastasised to distant sites (stage 4b).[17]

The number of incidentally diagnosed tumours appears to be increasing (see section 2.2.1, page15). Early detection and treatment of RCC may be associated with an improved outcome [18-20]. However, mortality rates are also continuing to increase (see section 2.2.5, page 20).

2.2.4. Prognosis

About 44% of people diagnosed with RCC in England and Wales live for at least five years after initial diagnosis and about 40% live for at least 10 years. However, the prognosis following the diagnosis of metastatic disease is poor and only approximately 10% of people diagnosed with Stage IV RCC live for at least five years after initial diagnosis.

Anatomical, histological, clinical and molecular factors all influence prognosis in patients with RCC.

Anatomical factors include tumour size, venous invasion, renal capsule invasion, adrenal involvement and lymph node and distant metastasis. These factors are considered in the TNM staging classification system described in section 2.1.1. *Histological factors* include Fuhrman grade, histological subtype, presence of sarcomatoid features, microvascular invasion, tumour necrosis and collecting system invasion. Fuhrman nuclear grade is a 4-tiered grading system based essentially on nuclear size and morphology and on the presence or absence of nucleoli. It is the most widely accepted histological grading system used in RCC. Although it is subject to intra and inter observer discrepancies, it remains an independent prognostic factor.[21] Several studies have shown a trend towards a better

prognosis for patients with resectable chromophobe and papillary RCC, with clear cell RCC having the worst prognosis. [22,23]

Clinical factors include patient performance status, localized symptoms, cachexia, anaemia and platelet count.[16] The Karnofsky scale [24] and ECOG-PS (Eastern Cooperative Oncology Group – Performance Status) [25] are convenient and commonly used scales which aim to take into account the overall impact of disease (Table 3 below and Table 4, page 20). These measures are used to document clinical progress and also to assess eligibility for clinical trials. The Karnofsky scale assesses ability to perform Activities of Daily Living (ADLs). There is evidence from several trials that ECOG-PS may be an independent prognostic factor of survival, with higher scores correlating with poorer survival. [16,26] There has been some work on the correlation between ECOG-PS and scores obtained on the Karnofsky scale. For example, in a study of patients with lung cancer ECOG-PS scores of 0 or 1 were equivalent to scores of 100, 90 and 80 on the Karnofsky scale; an ECOG-PS score of 2 to Karnofsky scores of 70 and 60 and an ECOG-PS of 3 or 4 to Karnofsky scores of less than 60.[27]

Table 3 Description of the Karnofsky scale

Score (%)	Description of signs and symptoms
100	normal, no complaints, no sign of disease
90	capable of normal activity, few symptoms or signs of disease
80	normal activity with some difficulty, some symptoms or signs
70	caring for self, not capable of normal activity or work
60	requiring some help, can take care of most personal requirements
50	requires help often, requires frequent medical care
40	disabled, requires special care and help
30	severely disabled, hospital admission indicated but no risk of death
20	very ill, urgently requiring admission, requires supportive measures or treatment
10	moribund, rapidly progressive fatal disease processes
0	Death

Source: Yates et al, 1980[24]

Table 4 Description of the ECOG performance status scores

Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work
2	Ambulatory and capable of self care but unable to carry out work activities. Up and about more than 50% of waking hours
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry out any self care. Totally confined to bed or chair
5	Dead

Source: Oken et al, 1982[25]

Several prognostic systems and nomograms that combine independent prognostic factors have been developed. There is some indication from studies that these systems might be more accurate at predicting survival than individual characteristics e.g. Fuhrman grade alone,[28-30], although they may be less accurate in patients with metastatic disease due to the heterogeneous nature of the disease, the patients and available treatments.[31]

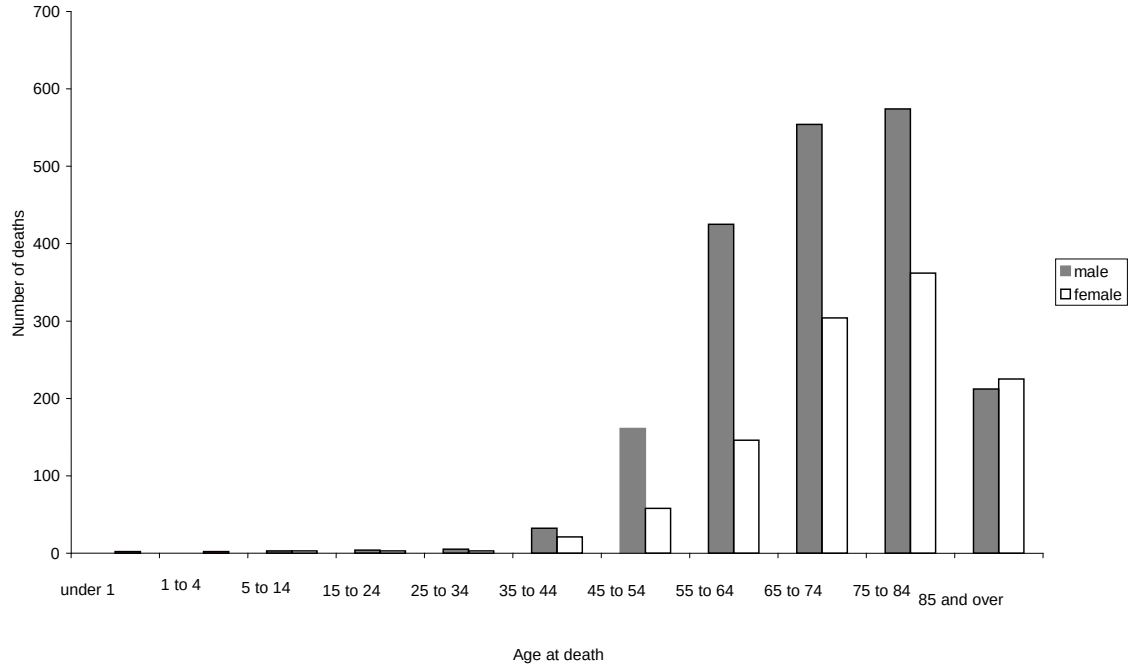
A system developed by Motzer and colleagues at the Memorial Sloan-Kettering Cancer Centre (MSKCC) in the United States is commonly used in clinical trials of advanced RCC and referred to either as the Motzer risk score or the MSKCC risk factor criteria [32,33]. Five variables are used as risk factors for short survival: low Karnofsky performance status (<80%), high lactate dehydrogenase (> 1.5 times the upper limit of normal), low serum haemoglobin, high corrected serum calcium (>10mg/dL) and time from initial RCC diagnosis to start of interferon-alpha (IFN) treatment of less than one year. Patients are then assigned to one of three risk groups according to the number of risk factors they exhibit: those with zero risk factors are deemed to have favourable risk, those with one or two risk factors are categorised as having intermediate risk and those with three or more risk factors have poor risk. In a retrospective analysis of 463 patients with advanced RCC administered IFN as first line therapy in six prospective clinical trials, progression free survival was related to risk category with median time to death ranging from 30 months in the favourable group to 14 months in the intermediate group and 5 months in the group deemed to have poor risk.[33]

2.2.5. Mortality

In 2006, there were 3,099 deaths from kidney cancer in England and Wales. Figure 3 shows the number of deaths from kidney cancer (excluding cancer of the renal pelvis) for males and females in

England and Wales in 2006.[5] Reflecting the incidence data, there were more deaths in males than in females and the mortality rate was highest in those aged between 65 and 85 years.

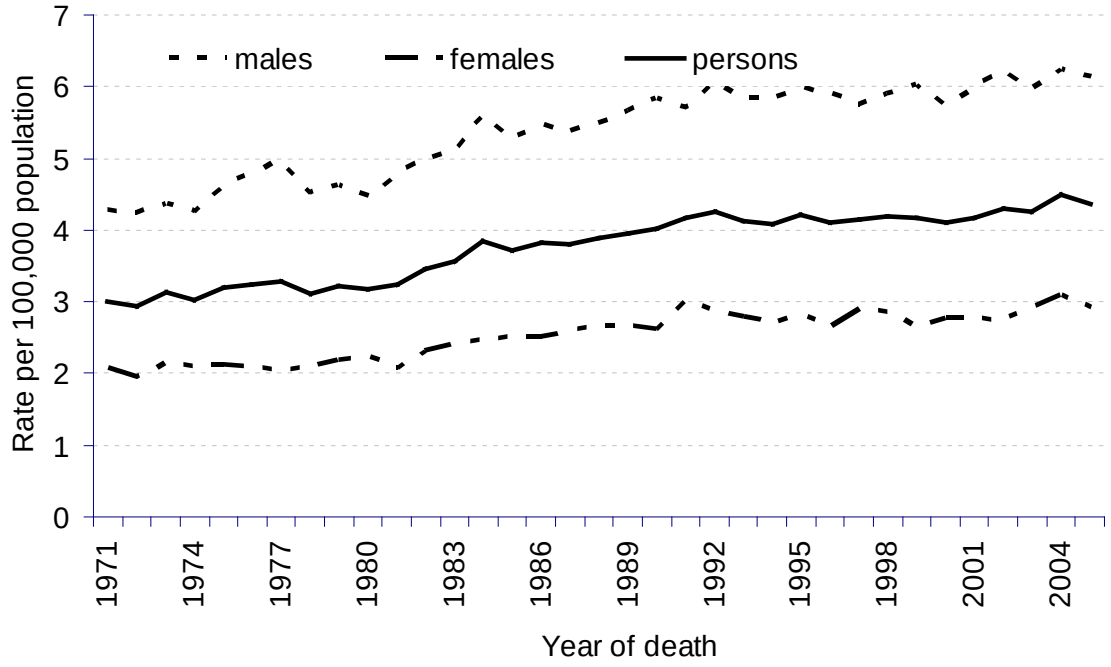
Figure 3 Number of deaths from malignant neoplasm of kidney excluding renal pelvis (ICD10 C64) by sex in England and Wales, 2006



Source: Office of National Statistics, Death Registrations, selected data tables, England and Wales, 2006

As might be expected from the patterns of incidence of diagnosis of RCC (see section 2.2.1, page15) mortality rates have also been increasing. Figure 4 (page 22) shows the age standardised (European) mortality rates for kidney cancer from 1971 to 2005. In 1971, the age standardised mortality rate for kidney cancer in men was approximately 4.3 per 100,000; by 2005 this had risen to approximately 6 per 100,000.

Figure 4 Age standardised (European) mortality rates for kidney cancer, by sex in the United Kingdom, 1971 to 2005



Source: Kidney Cancer Statistics, Cancer Research UK, 2007[9]

2.3. Treatment

2.3.1. Medical treatment

Chemotherapy and hormone therapy

High levels of expression of the multiple-drug resistance protein P-glycoprotein in renal cell carcinoma is one of the factors thought to explain the high level of resistance of RCC tumours to cytotoxic chemotherapy.[34,35]

The European Association of Urology (EAU) Guidelines on Renal Cell Carcinoma recommend that chemotherapy as monotherapy should not be considered as effective in patients with metastatic RCC. [21]

A systematic review of systemic therapy for metastatic RCC, published in 2000, identified 51 phase II trials in which 33 agents were studied in 1,347 patients.[36] The most extensively studied agents were floxuridine and fluorouracil with response rates ranging from 0 to 20%. Vinblastine and hormonal

agents such as medroxyprogesterone acetate have produced similarly disappointing results as have combinations of chemotherapy and immunotherapy.[36]

Immunotherapy

Interferon-alpha is the immunotherapy agent most commonly used in England and Wales. The preferred option in the United States is high dose interleukin-2 (IL-2). A recently updated Cochrane Review[37] identified a total of 58 randomised clinical trials (total 6880 patients) in which immunotherapies had been used in the treatment of advanced RCC. Only one study had a placebo control arm although other therapies were used as controls e.g. hormonal therapies, chemotherapy and nephrectomy. Four trials compared interferon-alpha with a non-immunotherapy control (vinblastine or medroxyprogesterone acetate) in patients with ECOG performance status 0 to 2. The pooled remission rate was 40/320 (12.5%) for interferon versus 5/324 (1.5%) for controls. The weighted average median survival was 3.8 months longer for interferon-alpha than control treatments (11.4 versus 7.6 months). [37]

A phase III study recently performed by the French Immunotherapy Intergroup (PERCY Quattro trial) in patients with intermediate prognosis (untreated patients with more than one metastatic site and a Karnofsky score of $\geq$ 80, and those with an intermediate prognosis for response to cytokine treatment) showed no improvement in median progression free survival or overall survival with use of cytokines alone or in combination when compared with a medroxyprogesterone control. Survival was 14.9 months with MPA, 15.2 months with interferon, 15.3 months with subcutaneous IL-2 and 16.8 months with interferon plus interleukin-2. Three year survival in all groups was around 20%; 5 year survival was 10%.[38] This confirms the findings of two case control studies [39,40] which also demonstrated little benefit of cytokines in those who do not have good prognosis.

Response rates of between 7 and 27% have been demonstrated for IL-2 [41-43]. Interestingly a small subgroup (about 7%) of patients achieve long term durable complete remissions with a high dose IL-2 regimen.[44] Toxicity associated with interleukin-2 is substantially higher than that of interferon-alpha; high dose IL-2 requires inpatient administration with intensive supportive care.[43] Commonly experienced adverse effects of both interferon-alpha and interleukin-2 include 'flu-like symptoms, tiredness and depression.

Various combinations of cytokines have also been studied and although there have been suggestions of improved response rates and progression-free survival times, overall survival does not appear to be better than with monotherapy regimens.[45]

2.3.2. Surgical treatment

Surgical therapy is the principle potentially curative therapeutic approach for the treatment of RCC. The standard approach is radical nephrectomy, which includes removal of the entire kidney together with Gerota's fascia. Removal of the ipsilateral adrenal gland and regional lymph nodes may also be necessary. Nephrectomy may also be performed in patients with metastatic disease. The combination of interferon-alpha and nephrectomy was shown to be superior to interferon alone in two studies in patients with metastatic RCC; one conducted in Europe [46] the other in the United States.[47] Whilst there was no significant difference in remissions between groups in either study, overall survival was prolonged in both studies. When the results of both studies were combined, the weighted mean difference in median survival was 5.8 months (13.6 versus 7.8 months) with or without initial nephrectomy respectively with a lower risk of death in the first year for those having undergone initial nephrectomy.[48]

2.4. Recurrence and progression

As described above (section 2.2.4), there are several scoring systems and algorithms which are used to stratify patients into low, intermediate and high risk groups for developing tumour recurrence or metastases, and hence predict prognosis and survival. European Association of Urology Guidelines recommend that in patients classified as having intermediate and poor prognosis, intensive follow-up including CT scans at regular time intervals should be performed.[21] A retrospective analysis of postoperative recurrence patterns, published in 2005, reported that amongst 194 patients with a diagnosis of RCC who had undergone complete surgical resection, recurrence occurred in 41 (21%). Mean time to recurrence was 17 months, with the tumour recurring within two years of surgery in 34 patients (83%). The lung was the most vulnerable site for recurrence.[49]

Clinical trials frequently measure and report progression in terms of response to treatment as partial or complete remission according to standard criteria.[50-52] The RECIST (Response Evaluation Criteria in Solid Tumours) guidelines [51,52] were developed as a result of an international collaboration between the European Organisation of Research and Treatment of Cancer (EORTC), the National Cancer Institute (NCI) of the United States and the National Cancer Institute of Canada Clinical Trials Group. The criteria provide a simplified, conservative method to compare imaging data and allow patients to be characterised within one of the following categories: complete response, partial response, progressive disease and stable disease (Table 5).

Table 5: RECIST Guidelines for categorising tumour response

Category		Description
Complete Response	CR	disappearance of all target lesions
Partial Response	PR	30% decrease in the sum of the longest diameter of target lesions
Progressive Disease	PD	20% increase in the sum of the longest diameter of target lesions or the appearance of new lesions
Stable disease	SD	small changes that do not meet the above criteria

Source: Therasse and colleagues, 2006 [51]

However, it should be noted that variability in the clinical course of metastatic RCC has been well documented and spontaneous remissions are known to occur.[53-55] In addition, the relationship between remission and overall survival is not clear[37] and there is growing support for the use of progression free survival as a better marker of anti-cancer activity in this setting.

2.5. Current service provision

The NICE manual on improving outcomes in urological cancers [56] recommends that all patients who are fit to undergo surgery (including those with metastatic disease) should be offered a radical nephrectomy (except those with small tumours). Patients with small tumours should be considered for nephron-sparing surgery. Surgery is often the only treatment needed for localised disease.

Treatment with immunotherapeutic agents (normally interferon-alpha in the UK) should be available for patients with metastatic disease. Thereafter, there is currently no standard NHS treatment for patients with metastatic RCC who do not respond to first-line immunotherapy, or those unsuitable for immunotherapy. The majority of patients diagnosed with RCC should be managed by local cancer teams. Referral to a specialist centre may be necessary for those whose tumours have or may have invaded the renal vein or vena cava, or which may involve the heart; those with limited metastatic disease which might be amenable to resection; those with bilateral disease or who require dialysis; and those with von Hippel-Lindau disease or hereditary papillary tumours.[56]

Since the publication of these guidelines, results from several trials of immunotherapy for RCC have become available which suggest that not all patients benefit equally from immunotherapy.[38-40] There is anecdotal evidence of variation in practice around the UK with some centres no longer treating patients considered to have a poor or intermediate prognosis with immunotherapy (personal communication with Expert Advisory Group).

2.6. Quality of life

Since there are currently no treatments which can reliably be expected to cure advanced RCC, relief of physical symptoms and maintenance of function are the primary objectives of medical interventions. There are several general quality of life instruments for people with cancer that can be used to assess quality of life both in clinical trials and in clinical practice e.g. the Functional Assessment of Cancer Therapy (FACT) scale [57] and the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30.[58] There are also several disease-specific instruments that have been used to evaluate symptoms of kidney cancer e.g. the Functional Assessment of Cancer Therapy – Kidney Symptom Index (FKSI) [59] and the FKSI-DRS [60] which was developed in an attempt to differentiate relief of disease-related symptoms from relief of those experienced as a result of treatment. In a national cross-sectional study of adults with RCC in the United States, the five most frequent symptoms among 31 patients with localised disease were irritability (79%), pain (71%), fatigue 71%), worry (71%) and sleep disturbance (64%). Approximately half the patients in the survey had metastatic disease and reported fatigue (82%), weakness (65%), worry (65%), shortness of breath (53%) and irritability (53%) as the five most frequently experienced symptoms.[61]

Despite the recognition that health related quality of life outcomes are important in this patient group, few clinical trials of new interventions have incorporated such measures (see section 3, page 35).

2.7. Description of new interventions

Several new therapeutic agents have recently been developed for the treatment of advanced and/or metastatic RCC. The rationale for their development stems from the discovery that an early event in the development of an RCC tumour is inactivation of the VHL tumour suppressor gene. This can result in an increased concentration of hypoxia-inducible factor-1 (HIF-1) which, in turn stimulates production of vascular endothelial growth factor (VEGF). VEGF (also known as vascular permeability factor (VPF)) is a dimeric glycoprotein and a member of the platelet-derived growth factor superfamily of growth factors, which are involved in the development of new vasculature from adjacent host blood vessels (angiogenesis) to allow for the transfer of oxygen and nutrition from the blood to the new cells that have formed. New blood vessels are essential for tumours to survive, grow and metastasise.[62] Preclinical models suggest that angiogenesis is necessary for tumour growth beyond one to two millimeters. Over-expression of VEGF, therefore, results in tumour growth and metastasis.[63-65]

The effects of VEGF are produced through activation of tyrosine kinase receptors on the cell surface, such as vascular endothelial growth factor receptors (VEGFR).[64]

Theoretically, therefore, inhibition of the VEGF and PDGF signalling pathways may reverse the pathological consequences of losing VHL protein function, disrupt the abnormal tumour blood vessels and consequently inhibit tumour progression or cause tumour cell death.[66]

The four new interventions considered in this assessment are summarised in Table 6.

Table 6: Summary of interventions

Intervention	Licensed indication
Bevacizumab	First-line therapy in combination with interferon-alpha in patients with advanced and/or metastatic RCC
Sorafenib tosylate	First-line therapy in patients with advanced and/or metastatic RCC who are unsuitable for therapy with interferon-alpha or interleukin-2 and as second line therapy in those with evidence of disease progression during cytokine-based treatment
Sunitinib	First and second line treatment of advanced and/or metastatic RCC.
Temsirolimus	First line treatment of patients with advanced RCC who have at least three of six poor prognostic risk factors

2.7.1. Bevacizumab plus interferon-alpha

2.7.1.1. Pharmacology

Bevacizumab (Avastin®) is a humanised monoclonal antibody against all biologically active isoforms of VEGF. Once bound to VEGF, bevacizumab prevents VEGF from binding to its receptors on vascular endothelial and other cells thus inhibiting angiogenesis, reducing tumour vascularisation and consequently inhibiting tumour growth and proliferation. [65,67,68]

Bevacizumab is administered as an intravenous infusion along with IFN treatment. The recommended dosage for advanced and/or metastatic RCC is 10mg/kg of body weight given once every two weeks.

The anti-tumour activity of interferon-alpha is believed to result from stimulation of the immune response, direct antiproliferative effects, anti-angiogenic effects and/or increased tumour antigen presentation.[68]

Interferon-alpha is administered by subcutaneous injection three times per week, typically at a dose of 9-10MIU, and may be self-administered by patients.

2.7.1.2. Licensing

Bevacizumab received marketing authorisation for use as first-line therapy in combination with interferon-alpha in patients with advanced and/or metastatic RCC in December 2007.[69]

2.7.1.3. Adverse events

There are few published trials of bevacizumab in patients with advanced and/or metastatic RCC. However, it has also been studied in several other conditions, including colorectal cancer, breast cancer, non-small cell lung cancer and pancreatic cancer. Such wider application provides further insight into the toxicity of the agent.

Whilst reported adverse events suggest that bevacizumab has a generally acceptable risk-benefit profile in patients with advanced cancer, severe adverse effects have been reported. Potentially severe toxicities include hypertension, gastrointestinal perforation/wound healing complications, haemorrhage, thromboembolic events, proteinuria and congestive heart failure.[65]

Further discussion of adverse events associated with bevacizumab and IFN can be found in section 3.2.2.251.

2.7.1.4. Cost

According to the current edition of the British National Formulary (BNF), the cost of treatment with bevacizumab (10mg/kg) plus IFN (9MU three times per week) for an 80kg patient is £151.42 per day (exclusive of the costs of drug administration).[70] Further discussion of the cost of bevacizumab plus IFN can be found in section 4.5.4.5 on page 143.

2.7.2. Sorafenib tosylate

2.7.2.1. Pharmacology

Sorafenib tosylate (Nexavar®) is an orally administered bi-aryl urea, which inhibits various tyrosine kinase receptors including VEGFR and PDGFR. Sorafenib may also inhibit Raf-1, a member of the mitogen-activated protein kinase (MAPK) intracellular signal transduction pathway (which comprises Raf, MAPK kinase (MEK) and extracellular signal-regulated kinase (ERK)), although whether appropriate concentrations are attained in patients is unclear. Sorafenib thus has two potential sites of action against tumour growth: by inhibiting VEGFR and PDGFR, sorafenib is able to inhibit tumour progression and angiogenesis; and by interacting with Raf-1 kinase sorafenib may interrupt the Ras/Raf/MEK/ERK cascade pathway which regulates cellular proliferation and survival.[71-75]

The recommended dose of sorafenib is 400 mg twice daily, taken either one hour before or two hours after food.

2.7.2.2. Licensing

Sorafenib tosylate has received marketing authorisation for use in patients with advanced and/or metastatic RCC as first line therapy in those who are unsuitable for therapy with interferon-alpha or interleukin-2, and as second line therapy in those with evidence of disease progression during cytokine-based treatment.

2.7.2.3. Adverse events

The most commonly reported adverse events associated with sorafenib treatment are dermatologic effects including rash and hand-foot skin reactions. Further discussion of adverse events associated with sorafenib tosylate can be found in section 3.2.5.2 on page 89.

2.7.2.4. Cost

According to the current edition of the BNF, the cost of sorafenib is £89.45/day.[70] Further discussion of the cost of sorafenib can be found in section 4.5.4.5 on page 143.

2.7.3. Sunitinib

2.7.3.1. Pharmacology

Sunitinib malate (Sutent®), formerly known as SU11248, is a novel, oral, multitargeted inhibitor of a group of closely related tyrosine kinase receptors (including VEGFR-1, -2 and -3, PDGFRα and β and KIT) with anti-tumour and anti-angiogenic activities.[66,76]

The recommended dose of sunitinib is one 50mg dose orally taken daily for four consecutive weeks with a two week rest period i.e. a complete treatment cycle of six weeks. Dose modifications based on safety and tolerability may be applied but the total daily dose should not exceed 50mg or decrease below 25mg.[77]There is also some evidence from Phase II trials that sunitinib may be effective at a continuous dose of 37.5mg per day [78].

2.7.3.2. Licensing

Sunitinib is licensed for use in the first and second line treatment of advanced and/or metastatic RCC.

2.7.3.3. Adverse events

The most commonly reported treatment-related adverse events (experienced by more than 20% of patients) in both treatment-naïve and cytokine-refractory patients with metastatic RCC include fatigue, gastrointestinal disorders such as diarrhoea, nausea, stomatitis, dyspepsia and vomiting, skin discolouration, dysgeusia (disruption of the sense of taste) and anorexia. Other adverse events include headache, hypertension, epistaxis, hand-foot syndrome, dry skin, hair colour changes, pain in extremities, mucosal inflammation, thrombocytopenia, neutropenia and decline in left ventricular ejection fraction. Further discussion of the adverse events associated with sunitinib can be found in section 3.2.2.2 on page 51.

2.7.3.4. Cost

According to the current edition of the BNF, the cost of sunitinib is £74.74 per day.[70] Further discussion of the cost of sunitinib can be found in section 4.5.4.5 on page 143.

2.7.4. Temsirolimus

2.7.4.1. Pharmacolgy

Temsirolimus (Torisel®) is a selective inhibitor of the mammalian target of rapamycin (mTOR), a serine threonine kinase that regulates a signalling cascade that controls growth factor induced cell proliferation. Temsirolimus inhibits mTOR-dependent protein translation induced by growth factor stimulation of cells. Tumour growth may also be impaired indirectly as a result of inhibition of micro-environmental factors such as VEGF.[79-81]

Temsirolimus is administered intravenously. The recommended dose is 25mg over a 30 to 60 minute period once weekly. Pre-medication with intravenous antihistamine is recommended to minimise occurrence of allergic reactions.

2.7.4.2. Licensing

Temsirolimus was granted a marketing authorisation for first line treatment of patients with advanced RCC who have at least three of six poor prognostic risk factors.

2.7.4.3. Adverse events

The most commonly reported treatment related adverse events of any grade associated with temsirolimus (experienced by more than 20% of patients) include asthenia, fever, abdominal pain,

back pain, bleeding events such as epistaxis, gastrointestinal events including nausea, anorexia, diarrhoea and constipation, cardiovascular events including chest pain, anaemia, hyperlipaemia, peripheral oedema, hyperglycaemia, hypercholesterolemia, dyspnoea and increased cough and rashes.

Further discussion of the adverse events associated with temsirolimus can be found in section 3.2.4.2 on page 70.

2.7.4.4. Cost

The price of temsirolimus is not yet available in the BNF. Wyeth have advised that the cost of a 30mg vial is £618.[70] The cost of temsirolimus is therefore £88.29 per day (exclusive of drug administration costs). Further discussion of the cost of temsirolimus can be found in section 4.5.4.5 on page 143.

2.8. Current use of new interventions in the NHS

Anecdotal evidence suggests wide variations in the current uptake and availability of these interventions. In some areas of the UK, the interventions are routinely available with all patients with metastatic RCC being offered sunitinib as first line therapy; in other areas the interventions are not currently available to any patients.

2.9. Definition of the decision problem

The purpose of this report is to assess the clinical and cost effectiveness of bevacizumab combined with IFN, sorafenib tosylate, sunitinib and temsirolimus in the treatment of people with advanced and/or metastatic renal cell carcinoma.

2.9.1. Interventions

The four interventions are considered in accordance with their marketing authorisations in two clinical settings:

- First line therapy with bevacizumab plus interferon-alpha
- First line therapy with sunitinib
- First line therapy with sorafenib tosylate
- First line therapy with temsirolimus
- Second line therapy with sorafenib tosylate
- Second line therapy with sunitinib

2.9.2. Populations including sub-groups

The relevant population for first line therapy is people with untreated advanced and/or metastatic renal cell carcinoma. The relevant population for second line therapy is people with advanced and/or metastatic renal cell carcinoma whose cancer has progressed during or after previous cytokine-based treatment. We also considered the following sub-groups:

- People who have/have not undergone surgical resection of the primary tumour
- People diagnosed with clear cell and non-clear cell carcinoma

The assessment is required to consider the interventions in relation to their marketing authorisations. Suitability for treatment with immunotherapy in this context is therefore defined in terms of contraindication to treatment with patients defined as being 'unsuitable for treatment with immunotherapy' having clinical contraindications to therapy e.g. autoimmune disease or a history of depression. We are aware that there is variation around the UK in the consideration of people with intermediate and poor prognosis for treatment with IFN. In some centres, these people are offered treatment with IFN, in others they are considered to be 'unsuitable' for treatment with IFN and best supportive care becomes their only treatment option. We have not considered that patients defined as having an intermediate or poor prognosis are 'unsuitable' for treatment with immunotherapy.

2.9.3. Relevant comparators[a]

The interventions are compared with current standard treatments. The relevant comparators are therefore as follows:

First line therapy

In patients who are suitable for treatment with immunotherapy:

- Immunotherapy (interferon-alpha) alone

[a] This represents a deviation from the protocol (26/10/07) in which we proposed to compare first line therapies with best supportive care in patients who are suitable for treatment with immunotherapy. Following extensive appraisal of existing literature we re-evaluated the potential benefit of performing this analysis (which would have netailed a full analysis of the clinical and cost effectiveness of IFN compared with best supportive care) and concluded that to use current standard treatment as the relevant comparator in all cases was more appropriate. We had intended to consider both interferon-alpha and interleukin-2 as potential immunotherapy treatments. However, due to a lack of published evidence and anecdotal evidence that interleukin-2 is not widely used in the UK, we have considered only interferon-alpha.

In patients who are not suitable for treatment with immunotherapy:

- Best supportive care

In patients with three or more of six poor prognostic factors

- Immunotherapy (interferon-alpha) alone

Second line therapy

- Best supportive care

For all indications, we have also considered the validity of indirect comparisons between interventions where appropriate.

2.9.4. Outcomes

Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus are assessed in terms of the following outcomes:

- Overall survival (OS)
- Progression free survival (PFS)
- Tumour response rate
- Adverse events/toxicity
- Health related quality of life (HRQoL)
- Cost effectiveness and cost utility

2.10. Overall aims and objectives of the assessment

This project will review the evidence for the effectiveness and cost-effectiveness of bevacizumab plus interferon-alpha, sorafenib tosylate, sunitinib and temsirolimus in the treatment of people with advanced and/or metastatic renal cell carcinoma according to their marketing authorisations. The assessment will look at first and second line use of the interventions (where appropriate) and will draw together the relevant evidence to try and determine what, if any, is the incremental cost-effective benefit of the interventions when compared to current standard treatment.

More fully the policy questions to be addressed are:

First line therapy

(1) In those who are suitable for treatment with immunotherapy, what is the clinical and cost effectiveness of bevacizumab plus interferon-alpha and sunitinib as first line therapy, using interferon-alpha as a comparator?

(2) In those who are not suitable for treatment with immunotherapy what is the clinical and cost effectiveness of sorafenib tosylate and sunitinib as first line therapy, using best supportive care as a comparator?

(3) In those with three or more of six poor prognostic factors what is the clinical and cost effectiveness of bevacizumab plus interferon-alpha, sorafenib, sunitinib, temsirolimus and best supportive care as first line therapy, using interferon-alpha as a comparator?

Second line therapy

(4) In those in whom treatment with cytokine based immunotherapy has failed, what is the clinical and cost effectiveness of sorafenib tosylate and sunitinib as second line therapy, using best supportive care as a comparator?

3. Assessment of clinical effectiveness

3.1. Methods for reviewing effectiveness

The clinical effectiveness of bevacizumab, sorafenib tosylate, sunitinib and temsirolimus was assessed by a systematic review of published research evidence. The review was undertaken following the general principles published by the NHS Centre for Reviews and Dissemination. [82]

3.1.1. Identification of studies

The Cochrane Library (Issue 3) (including CDSR, CENTRAL and HTA), MEDLINE, Embase, (ISI Web of Science) Science Citation Index, (ISI Web of Science) Proceedings and Biosis were searched for systematic reviews of RCTs and single RCTs in September/October 2007. Bibliographies of included studies were searched for further relevant studies. Individual conference proceedings from 2006 and 2007 (ASCO and ECCO) were searched using their online interface. All searches were re-run in February 2008. Full details of the search strategies are presented in Appendix 1: Literature search strategies (page 208). All references were managed using Reference Manager (Professional Edition Version 11; Thomson ISI ResearchSoft) and Microsoft Access 2003 software.

Relevant studies were identified in two stages. Two reviewers (JTC and ZL) independently examined all titles and abstracts. Full texts of any potentially relevant studies were obtained. The relevance of each paper was assessed (JTC and ZL) independently according to the inclusion and exclusion criteria and any discrepancies resolved by discussion.

3.1.2. Inclusion and exclusion criteria

RCTs were included if they compared any of the interventions (see section 2.9.1, page 31) with any of the comparators detailed in section 2.9.3 in participants with advanced and/or metastatic RCC. Primary outcomes were overall survival (OS) and progression free survival (PFS). Secondary outcomes were tumour response rate, adverse events/toxicity and health related quality of life (HRQoL). Only trials which reported at least one of the primary outcomes were included in the review. In trials in which patients were allowed to cross from comparator to active treatment following demonstration of efficacy in interim analyses, we have only considered data collected prior to treatment crossover as this provides the least biased estimate of treatment effect size. The use of data from phase II studies and non-randomised studies was only considered where there was insufficient evidence from good quality randomised controlled studies. Conference abstracts were

included if there was sufficient detail to assess quality or if they reported updated results of included trials.

3.1.3. Data extraction strategy

Data were extracted by one reviewer (ZL) using a standardised data extraction form in Microsoft Access 2003 and checked independently by a second (JTC). Disagreements were resolved by discussion, with involvement of a third reviewer if necessary. Data extraction forms for each included study are included in Appendix 2 (page 214).

3.1.4. Quality assessment strategy

The methodological quality of the studies was assessed according to criteria specified by the Centre for Reviews and Dissemination (CRD).[82] Quality was assessed by one reviewer and judgements were checked by a second. Any disagreement was resolved by discussion, with involvement of a third reviewer as necessary.

3.1.5. Methods of data synthesis

Details of the extracted data and quality assessment for each individual study are presented in structured tables and as a narrative description. Any possible effects of study quality on the effectiveness data are discussed. Survival data (overall survival and progression free survival) are presented as hazard ratios (HRs) where available.

Where data on head-to-head comparisons between interventions were not available we considered the feasibility of performing adjusted indirect comparisons using an adaption of the method described by Bucher and colleages.[83] This method aims to overcome potential problems of simple direct comparison (i.e. comparison of simple arms of different trials), in which the benefit of randomisation is lost leaving the data subject to the biases associated with observational studies. The method is only valid when the characteristics of patients are similar between the different studies being compared. Further details of the methods used can be found in Appendix 3 (page 215).

3.1.6. Handling company submissions to NICE

All the clinical effectiveness data included in the company submissions was assessed. Where these met the inclusion criteria and had not already been identified from published sources, they were included in the systematic review of clinical effectiveness.

3.1.7. Understanding the results from the clinical trials

Most of the clinical trials in which the efficacy of these interventions have been evaluated, report results in terms of hazard ratios (HR): the ratio of hazard rates in two groups. The hazard rate describes the number of events per unit time per number of people exposed (i.e. the slope of the survival curve, or the instantaneous rate of events in the group). The treatment group hazard rate divided by the control group hazard rate is called the hazard ratio. A hazard ratio of one suggests that there is no difference between the two groups of patients. A hazard ratio of greater than one indicates that the event is happening faster in the treatment group than in the control group and a hazard ratio of less that one indicates that the event of interest is happening more slowly in the treatment group than in the control group.

Most trials report toxicities using the National Cancer Institute Common Terminology Criteria (NCI-CTC) (Table 7, page 37). For each adverse event, grades are assigned using a scale from 0 to 5. Grade 0 is defined as absence of adverse event or within normal limits for values. Grade 5 is defined as death associated with an adverse event.[84]

Table 7 National Cancer Institute Common Terminology Criteria (NCI-CTC) for adverse events

Grade	Description
0	No adverse event or within normal limits
1	Mild adverse event
2	Moderate adverse event
3	Severe and undesirable adverse event
4	Life threatening or disabling adverse event
5	Death related to an adverse event

Source: Common Terminology Criteria for Adverse Events, National Cancer Institute, 2006[84]

3.2. Results of clinical effectiveness

The results of the assessment of clinical effectiveness will be presented as follows:

(i) An overview of the quantity and quality of available evidence including a table summarising all included trials and a summary table of key quality indicators,

(ii) A critical review of the available evidence for each of the stated research questions, including

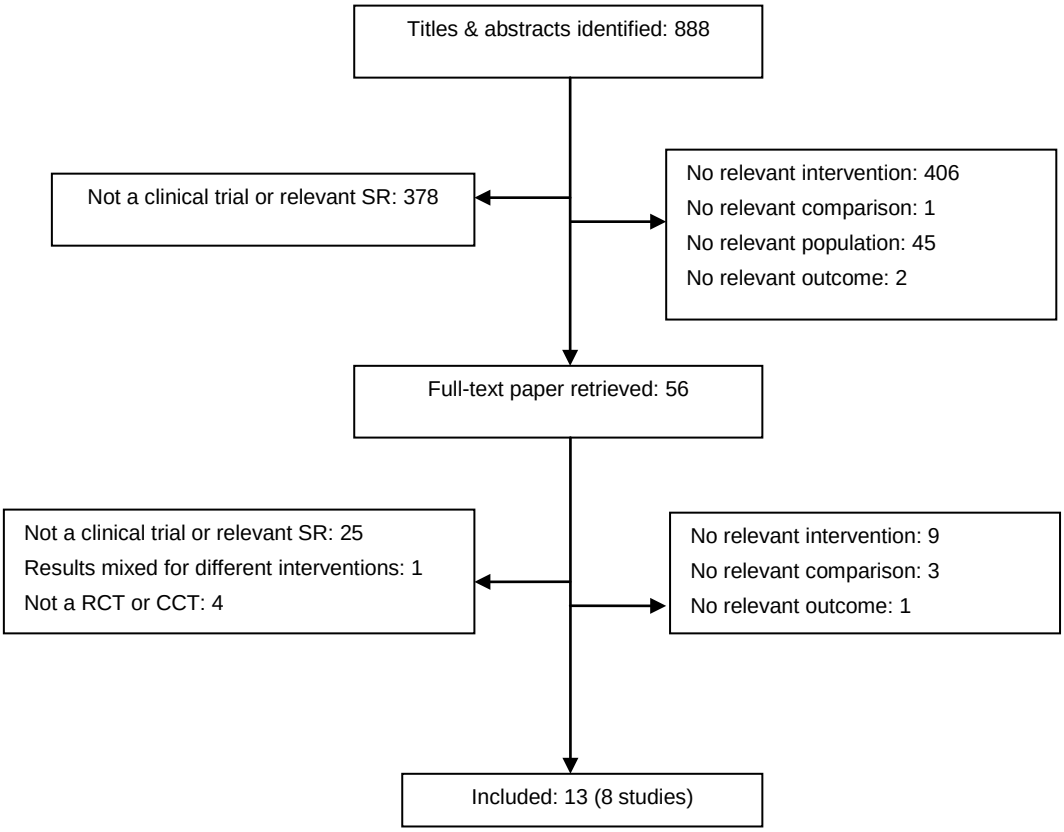
- the quantity and quality of available evidence,
- a summary table of the study characteristics,
- a summary table of the baseline population characteristics,
- comparison of the baseline populations in the included trials,
- study results presented in narrative and tabular form,
- comparison of the results in terms of effectiveness and safety

3.2.1. Quantity and quality of research available

Number of studies identified

The electronic searches retrieved a total of 888 titles and abstracts. Twenty conference abstracts updating the results of included studies were located following hand searching of individual conference proceedings. No additional papers were found by searching the bibliographies of included studies. Eight hundred and thirty-two papers were excluded on title and abstract. Full text of the remaining 56 papers was requested for more in-depth screening. The updated searches retrieved an additional 166 titles and abstracts. No further full-text trials were identified; we found one paper updating the results of an included trial.[85]. The process of study selection is shown in Figure 5.

Figure 5: Summary of study selection



Number of studies excluded

Papers were excluded for at least one of the following reasons: duplicate publications, narrative reviews, uncontrolled studies (where evidence from controlled trials was available for the research question) and publications (systematic reviews and individual studies) not considering relevant intervention, population, comparison or outcomes. The bibliographic details of studies retrieved as full papers and subsequently excluded, along with the reasons for their exclusion are detailed in Appendix 4 (page 216).

Number and description of included studies

Eight clinical trials reported in 13 publications met our inclusion criteria. A total of 20 conference abstracts relating to the included trials were also located by hand searching and considered.[86-104] [105] All included citations are detailed in Table 8 (page 41). A summary of the quality assessment of the studies is shown in Table 9 (page 42).

We were unable to identify any suitable data on clinical effectiveness in the following areas:

- in patients unsuitable for treatment with immunotherapy, we found no suitable data on sorafenib, sunitinib or best supportive care,
- in patients with poor prognosis, we found no data on sorafenib,
- we were unable to locate any randomised clinical trials of sunitinib as second line therapy, and
- we were unable to locate any randomised clinical trials of any of the interventions in comparison with interleukin-2.

Due to the lack of evidence on the use of interleukin-2 in these patients and following consultation with our Expert Advisory Group, who confirmed that interferon-alpha is the predominant immunotherapy treatment in use in the UK, we have assumed that treatment with immunotherapy will be with interferon-alpha.

Table 8: Summary information of all included studies, by research question

Study	Year published	Study type	N	Intervention	Comparator	Supplementary publications
Bevacizumab plus IFN and sunitinib compared with IFN as first line therapy						
Escudier, et al[106]	2007	R, DB, PC, phase III, international, multicentre	649	bevacizumab (BEV) plus interferon alpha - 2α (IFN)	placebo plus interferon alpha - 2α (IFN)	107 108 109 86 110
Motzer, et al[111]	2007	R, BR, C, phase III international, multicentre	750	sunitinib	IFN-2α (IFN)	91 92 93 87 88 104
Rini, et al[101]	2008	RCT, no further details available	732	bevacizumab plus IFN-α (IFN)	IFN-2α	68
Bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and best supportive care compared with IFN as first line therapy in people with poor prognosis						
Hudes, et al[112]	2007	R, O, C phase III, international, multicentre	626	temsirolimus, temsirolimus plus IFN-2α (IFN)	IFN-2α (IFN)	94 95 96 97 89
Sorafenib and sunitinib compared with best supportive care as second line therapy						
Escudier, et al[113]	2007	R, DB, PC, phase III, international, multicentre	903	sorafenib	placebo	114 98 99 102 103
Ratain, et al[115]	2006	RDT, retrospective BR, phase II, multicentre, international	202 (65 randomly assigned)	sorafenib	placebo	
Motzer, et al[116]	2006	O, single arm, phase II, multicentre, US	106	sunitinib	NA	100 85,90
Motzer, et al[117]	2006	O, single arm phase II, multicentre, US	63	sunitinib	NA	100

R – randomised, DB – double blind, C - controlled, PC – placebo controlled, BR – independent (blind) central review of radiological images used to assess primary outcome, RDT: randomised discontinuation study, O - open.

Table 9: Summary of quality assessment – all included trials

	Escudier, et al. 2007[106]	**Motzer, et al. 2007[111]**	**Rini, et al. 2004[68,101]**	**Hudes, et al. 2007[112]**	**Escudier, et al. 2007[113]**	**Ratain, et al. 2006[115]**	**Motzer, et al. 2006[116]**	**Motzer, et al. 2006[117]**
Study design	RCT	RCT	RCT	RCT	RCT	RDT	single arm	single arm
Is a power calculation provided?	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes
Is the sample size adequate?	Yes	Yes	?	Yes	Yes	?	Yes	Yes
Was ethical approval obtained?	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes
Were the study eligibility criteria specified?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the eligibility criteria appropriate?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were patients recruited prospectively?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Was assignment to the treatment groups really random?	Yes	Yes	?	Yes	Yes	Yes	NA	NA
Was the treatment allocation concealed?	Yes	NA	?	NA	?	?	NA	NA
Were adequate baseline details presented?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Were the participants representative of the population in question?	Yes	Yes	?	Yes	Yes	Partial	Yes	Yes
Were the groups similar at baseline?	Yes	Yes	?	Yes	Yes	Yes	NA	NA
Were baseline differences adequately adjusted for in the analysis?	No	Yes	?	No	Yes	No	NA	NA
Were the outcome assessors blind?	Yes	Yes	?	Yes	Yes	Yes	NA	NA
Was the care provider blind?	Yes	No	?	No	Yes	Yes	NA	NA
Are the outcome measures relevant to the research question?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Is compliance with treatment adequate?	?	Yes	?	Yes	?	?	?	?
Are withdrawals/dropouts adequately described?	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
Are all patients accounted for?	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes

Is the number randomised reported?	Yes	Yes	No	Yes	Yes	Yes	NA	NA
Are protocol violations specified?	Yes	Yes	No	Yes	No	Yes	No	No
Are data analyses appropriate?	Yes	Yes	?	Yes	Yes	Yes	Yes	Yes
Is analysis conducted on an ITT basis?	Partial	Partial	?	Partial	Yes	Partial *	Yes	Yes
Are missing data appropriately accounted for?	?	Partial	?	Partial	Partial	Partial	Yes	Yes
Were any sub-group analyses justified?	Yes	Yes	?	Yes	Yes	Yes	NA	NA
Are the conclusions supported by the results?	Yes	Yes	?	Yes	Yes	Yes	Partial	Partial

?: unclear or unknown; **NA**: not applicable; * for the randomly assigned patients.

3.2.2. Bevacizumab plus IFN and sunitinib compared with IFN as first line therapy

In this section we address Research Question 1: In those who are suitable for treatment with immunotherapy what is the clinical effectiveness of bevacizumab plus IFN, sunitinib and IFN as first line therapy, using IFN as a comparator?

3.2.2.1. Quantity, quality and characteristics of included studies

We identified three RCTs that are relevant to this question. A summary of the quality assessment of the studies is shown in Table 9 (page 42); study characteristics are summarised below and in Table 55 in Appendix 5 (page 218).

Study characteristics

Bevacizumab plus IFN versus IFN

Escudier and colleagues report the results of the AVOREN study, an international[a,] and the United Kingdom], multicentre, double blind and placebo controlled phase III RCT, in which 649 patients with confirmed clear cell metastatic RCC were randomised to receive either bevacizumab and interferon or placebo and interferon. The trial has been reported in one full publication [106] and five abstracts.[86,107-110] The aim of the study was to determine whether first-line bevacizumab plus IFN improves efficacy compared with interferon alone. Primary outcomes were overall survival and progression-free survival. Overall response rate and safety were secondary outcomes. The study was designed to have 80% power for the log rank test to detect an improvement in overall survival with an HR of 0.76, assuming an improvement of median survival from 13 months to 17 months, at a two sided alpha level of 0.05. One interim analysis was planned, based on 250 deaths, after which the study was unblinded and patients in the IFN arm who had not progressed were offered bevacizumab plus IFN.[106]

To be eligible for entry into the trial participants had to have a diagnosis of predominantly (>50%) clear cell renal cell carcinoma based on routine assessment of tumour histopathology and were also required to have undergone nephrectomy or partial nephrectomy (if resection margins were clearly negative of disease), to have a Karnofsky performance score of 70% or more, normal hepatic, haematopoietic and renal function and to have received no previous systemic therapy for RCC.

[a] Australia, Belgium, Czech Republic, Finland, France, Germany, Hungary, Italy, Israel, Netherlands, Poland, Singapore, Spain, Switzerland, Taiwan

Randomisation was performed centrally and patients were stratified according to country and MSKCC risk group. Patients were randomly assigned to receive bevacizumab (10mg/kg body weight, delivered intravenously once every two weeks) (n=327) or placebo (n=322) plus IFN-α-2a (9 MIU, delivered subcutaneously three times per week for a maximum of 52 weeks). Treatment was continued until evidence of disease progression, the patient experienced unacceptable toxicity, or withdrawal of consent. No dose reduction of bevacizumab/placebo was allowed. A starting dose of IFN of less than 9 MIU was permitted as long as the full dose was reached within the first two weeks of treatment. Dose reduction to 6MIU or 3MIU was allowed to manage adverse events of grade 3 or higher that were attributable to IFN.

Median follow-up at data cutoff was 13.3 months (range 0 - 25.6) in the bevacizumab plus IFN group and 12.8 months (range 0 - 24.2) in the control group. Median duration of bevacizumab treatment was 9.7 months (range 0 - 24.4) in the bevacizumab plus IFN group, and median duration of placebo treatment was 5.1 months (range 0 - 24.0) in the control group. Median duration of IFN treatment was 7.8 months (range 0 - 13.9) in the bevacizumab plus IFN group and 4.6 months (range 0.2 - 12.6) in the control group.

Median bevacizumab/placebo dose intensity was 92% (range 24 – 112%; mean 88%) in the bevacizumab plus IFN arm and 96% (39 – 110%; mean 89%) in the IFN only arm.

No substantial additional clinical effectiveness data was located in the related conference abstracts on this study [86,107-109,109,110] or the company submission for bevacizumab.[118]

Rini and colleagues report the results of the Cancer and Leukaemia Group B (CALGB 90206), phase III, open-label trial of bevacizumab plus IFN versus IFN conducted in 732 patients with previously untreated metastatic clear cell RCC. Patients were randomised to receive either bevacizumab (10mg/kg i.v. every two weeks) plus IFN (9 MIU s.c. three times weekly) or IFN alone. Randomisation was stratified by prior nephrectomy and MSKCC risk category. The primary endpoint was overall survival. Secondary endpoints were progression free survival, response rate (according to RECIST criteria) and safety. The trial was designed with 86% power to detect a difference in the hazard ratio of 30% assuming a two-sided significance level of 0.05. Preliminary results were reported at the American Society of Clinical Oncology Genitourinary Cancers Symposium in February 2008.[68,101]

We considered the validity of pooling the data from the two studies of bevacizumab plus IFN, however as the study by Rini and colleagues is only available in abstract form, several key pieces of information are missing (e.g. the number of patients randomised to each group, the method for assessing progression, whether the analysis was carried out on an ITT basis) and we were unable to

fully assess the quality of the study. The authors were contacted to request additional data, but were unwilling to comply. We were, therefore, unable to pool the data.

Sunitinib versus IFN

Motzer and colleagues report the results of an international (Australia and United States) multicentre phase III RCT, in which 750 patients with metastatic RCC were randomised to receive either sunitinib or IFN. The trial has been reported in one full publication [111] and five abstracts.[87,88,91-93]

The aim was to assess the efficacy of first-line treatment with sunitinib compared with interferon-alpha in the treatment of metastatic RCC. The primary outcome was progression free survival, defined as the time from randomisation to the first documentation of objective disease progression or to death from any cause, whichever came first. Secondary endpoints included the objective response rate, overall survival, quality of life outcomes and safety. The study was designed to have 90% power for the log rank test to detect a clinically relevant increase in progression free survival from 4.7 to 6.2 months in patients treated with sunitinib, at a two-sided alpha level of 0.05.

To be eligible for entry into the trial, participants had to have a diagnosis of metastatic RCC with a clear cell histological component confirmed by the participating centres. Patients also had to have measurable disease, an ECOG performance status of 0 or 1 and adequate haematological, hepatic, renal and cardiac function.

Patients were stratified according to baseline levels of lactate dehydrogenase, ECOG performance status and previous nephrectomy and randomly assigned to receive sunitinib (50mg once daily; orally) in six week cycles (four weeks on, two weeks off) or interferon-alpha-2α (Roferon-A, Roche) (9MIU three times per week, subcutaneously). Treatment was continued until evidence of disease progression, the patient experienced unacceptable toxicity, or withdrawal of consent. Dose reductions (sunitinib to 37.5mg and then 25mg per day and IFN to 6MIU and then 3MIU three times per week) were permitted to allow management of severe adverse events.

Three scheduled interim analyses were planned. The paper by Motzer and colleagues published in 2007 provides the results of the second analysis, after which the study was unblinded. This paper states that at that time-point, patients in the IFN group with progressive disease were allowed to crossover into the sunitinib group. This analysis therefore provides the most complete results for the randomised population. It is not clear why patients with progressive disease were offered further treatment as according to the protocol all treatment would be stopped on evidence of disease progression.

The median duration of treatment was 6 months (range 1 to 15) in the sunitinib group and 4 months (range 1 to 13) in the IFN group. Reasons for discontinuing treatment were: progressive disease (25%

and 45% in the sunitinib and IFN groups respectively); adverse events (8% and 13% respectively); withdrawal of consent (1% and 8% respectively); and protocol violation (< 1% in each group). Dose intensity was not reported in the full text paper. In the company submission, Pfizer report a relative dose intensity (total dose administered / total dose assigned multiplied by 100) of 86.40% for sunitinib and 83.10% for interferon which is cited as originating from the trial of sunitinib versus IFN.[111] No further details are provided.

Assessment of study quality

Bevacizumab plus IFN versus IFN

The AVOREN trial reported by Escudier and colleagues is a good quality randomised phase III trial.[106] The evaluation of the trial in relation to study quality is shown in Table 9 (page 42). Allocation concealment, details of randomisation methods and withdrawals were all adequately reported. The study is described as 'double-blind' although it is unclear whether all members of the study team were blinded (e.g. patient, pharmacist, doctor and assessor).

The CALGB trial has only been reported in abstract form and as such there are not sufficient details to adequately assess the quality of the data.[101]

Sunitinib versus IFN

This is a large, good quality, international, multicentre, randomised phase III study.[111] Although it was not possible to double blind the study due to the differences in route of administration, the assessment of the primary outcome measure and objective response rate were performed by a central and blinded review of radiological images. Further details of the quality assessment can be found in Table 9 (page 42).

Population baseline characteristics

Bevacizumab plus IFN versus IFN

At baseline, in the AVOREN study, the two treatment groups were well matched in terms of demographic characteristics and disease status (Karnofsky performance status, MSKCC risk group and the location of metastases) (Table 10).[106]

As the trial by Rini and colleagues has only been reported in abstract format, few details of the population characteristics at baseline are available. Overall, 85% of patients had undergone prior nephrectomy, 26% were assessed as having favourable prognostic risk; 64% had intermediate risk and 10% poor risk. No further details are provided.[101]

Sunitinib versus IFN

At baseline, the two treatment groups were well matched in terms of demographic characteristics and disease status (ECOG performance status, MSKCC risk factors, the number of patients with a previous nephrectomy and the number and sites of metastases) (Table 10, page 49).[111]

Comparability of baseline population characteristics between trials

Participants in the two main trials [106,111] were similar in terms of age, gender distribution, RCC pathology (predominantly clear cell), the proportion that had previously undergone nephrectomy or partial nephrectomy (100% vs. 90% for the bevacizumab plus IFN and sunitinib trials respectively), the number of patients with metastatic RCC and the profile of prognosis according to MSKCC criteria (approximately 30% of patients have favourable prognosis, 60% intermediate and 10% poor prognosis). Although, performance status was evaluated using different instruments, patients appear comparable with the majority of patients (61%) in the bevacizumab plus IFN trial being assessed as ECOG performance status 0, which equates to 'fully active, able to carry on all pre-disease performance without restriction'. Similarly, 69% of patients in the sunitinib trial had a Karnofsky performance status of 100 (normal, no complaints, no sign of disease) or 90 (capable of normal activity, few symptoms or signs of disease).

Table 10: Population baseline characteristics: bevacizumab plus IFN and sunitinib versus IFN as first line therapy

Study	**Escudier, et al. 2007[106]**		**Motzer, et al. 2007[111]**	
Intervention	**Bevacizumab + IFN**	**IFN + placebo**	**Sunitinib**	**IFN**
Number randomised	**327**	**322**	**375**	**375**
Diagnosis	Predominantly (>50%) clear cell renal cell carcinoma		Metastatic clear cell renal-cell carcinoma	
Age, median yrs (range)	61 (30-82)	60 (18-81)	62 (27-87)	59 (34-85)
Male	222 (68)	234 (73)	267(71)	267(72)
ECOG performance status: 0 1	Not reported	Not reported	 231(62) 144(38)	 229(61) 146(39)
Karnofsky performance status: n (%)			Not reported	Not reported
100	144 (44)	124 (39)		
90	105 (32)	126 (39)		
80	58 (18)	50 (16)		
70	20 (6)	22 (7)		
MSKCC risk factors: n (%)				
0 (favourable)	87(27)	93(29)	143 (38)	121(32)
1-2 (intermediate)	183(56)	180(56)	209(56)	212(57)
≥ 3 (poor)	29(9)	25(8)	23(6)	25(7)
Not available	28(9)	24(7)	NR	17(5)
n (%) patients with a previous nephrectomy	327(100)	322(100)	340(91)	355(89)
n (%) patients with previous radiation therapy	Not reported	Not reported	53(14)	54(14)
n (%) patients with metastatic renal cell carcinoma	327 (100)	322 (100)	375(100)	375(100)

Number of metastases sites: n (%)	Not reported	Not reported		
1			55(15)	72(19)
2			106(28)	112(30)
≥ 3			214(57)	191(51)
Location of metastases sites: N (%)				
Bone	58(18) *	65(20) *	112(30)	112(30)
Liver	57(18) *	56(19) *	99(26)	90(24)
Lung	192(62) *	179(59) *	292(78)	298(79)
Lymph nodes	107(34) *	107(36) *	218(58)	198(53)

ECOG: Eastern Cooperative Oncology Group score; **MSKCC**: Memorial Sloan-Kettering Cancer Centre criteria. * Based on n = 312 in bevacizumab plus IFN group and n = 301 in placebo plus IFN group

3.2.2.2. Assessment of clinical effectiveness

Overall survival (Table 11)

Bevacizumab plus IFN versus IFN

Overall survival, defined as the time between the date of randomisation and death from any cause, was the primary endpoint in the AVOREN trial.[106] The analysis was performed on an intention-to-treat basis with patients without an event being censored on the day of last follow-up assessment or the last day of study drug administration if no follow-up assessment was done. At the time of data cut-off, only 251 (56%) of the 445 deaths required for the final analysis of overall survival to be powered adequately had occurred. Median overall survival had not been reached in the bevacizumab plus IFN group and was 19.8 months in the IFN group, with a hazard ratio (HR) of 0.79 (95% CI 0.62 to 1.02; p=0.0670). A pre-planned exploratory analysis stratified by MSKCC risk group and region produced a similar result (hazard ratio of 0.75 (95% CI 0.58 to 0.97); p=0.02670). Analysis of overall survival stratified according to baseline MSKCC risk groups was similar to the unstratified analysis with HRs of 0.69 (95% CI 0.36 to 1.33), 0.74 (95% CI 0.53 to 1.02) and 0.87 (95% CI 0.48 to 1.56) for the favourable, intermediate and poor prognosis groups respectively.

Data on overall survival from the CALGB trial are still pending.[101]

Sunitinib versus IFN

At the time of analysis, median overall survival had not been reached in either group: 13% of patients in the sunitinib group and 17% in the IFN group had died. There was an improved overall survival with sunitinib, with a HR for death of 0.65 (95% CI 0.45 to 0.94; p=0.02); the comparison did not meet the pre-specified level of significance for the interim analysis.[111]

Table 11: Summary of overall survival: Bevacizumab plus IFN and sunitinib versus IFN as first line therapy

Study	Intervention	N	median OS (months)	HR	95% CI for HR	p value
Escudier, et al. 2007 [106]	bevacizumab plus IFN	327	not reached	0.79†	0.62 to 1.02†	p = 0.0670†
	placebo plus IFN	322	19.8			
Motzer, et al. 2007 [111]	sunitinib	375	not reached	0.65	0.45 to 0.94	p=0.02*
	IFN	375	not reached			

† These results are for the unstratified analysis. A pre-planned exploratory analysis stratified by MSKCC risk group and region produced a similar result.

* Did not reach the pre-specified level of significance for the interim analysis

Progression-free survival (Table 12)

In all three studies, progression-free survival was defined as the time between randomisation and first documented disease progression or death due to any cause and was reported as median duration.

Bevacizumab plus IFN versus IFN

In the AVOREN study, according to a ITT analysis, there was a statistically significant benefit in terms of median progression free survival observed for the bevacizumab plus IFN group (10.2 months) compared with the IFN and placebo group (5.4 months) with HR = 0.63 (95% CI 0.52 to 0.75; p = 0.0001). An analysis stratified by MSKCC risk group and region confirmed these results, with HR = 0.61 (95% CI 0.51 to 0.73; p< 0·0001). A test of interaction indicated that the treatment effect was consistent across the MSKCC risk groups (p=0.508).[106]

In the CALGB study, the method of assessing progression was not reported in the abstract. Median time to progression was 8.5 months in patients receiving bevacizumab plus IFN and 5.2 months in the group receiving IFN alone. The stratified estimate of the hazard ratio was 0.71 (95% CI 0.61 to 0.83; p<0.0001). Further details of the analysis are not yet available.[101]

Sunitinib versus IFN

Progression-free survival (primary endpoint) was assessed by blinded central review of imaging studies.[111] There was a statistically significant difference in progression-free survival in patients receiving sunitinib (11 months; 95% CI 10 to 12 months) compared with those receiving IFN (5 months; 95% CI 4 to 6 months) corresponding to a hazard ratio of 0.42 (95% CI 0.32 to 0.54:

p<0.001). Similar results from the investigator's un-blinded assessment of radiological images (4 months vs. 11 months; HR 0.42 (95% CI 0.33 to 0.52; p<0.001) are also reported.

Table 12: Summary of progression free survival: bevacizumab plus IFN and sunitinib versus IFN as first line therapy

Study	Intervention	N	median PFS (months)	HR	95% CI for HR	p value
Escudier, et al. 2007 [106]	bevacizumab plus IFN	327	10.2	0.63	0.52 to 0.75	p<0.0001
	placebo plus IFN	322	5.4			
Rini, et al. 2008 [101]	bevacizumab plus IFN	NR	8.5**	0.71**	0.61 to 0.83**	p<0.0001**
	IFN	NR	5.2**			
Motzer, et al. 2007 [111]	sunitinib	375	11*	0.42*	0.32 to 0.54*	p<0.001*
	IFN	375	5*			

*Results from independent central review of imaging studies; ** Preliminary results available in abstract form only, total number of patients in trial = 732; NR – not reported

Tumour response (Table 13)

In all three studies, tumour response was assessed according to RECIST criteria, based on patients with measurable disease at baseline. Responses were confirmed by a second assessment four weeks or more after the first response was recorded.

Bevacizumab plus IFN versus IFN

In the AVOREN trial, tumour response was assessed by the investigator every eight weeks up to 32 weeks and every 12 weeks thereafter until disease progression. At the time of analysis, the overall number of patients in whom a tumour response was measured was significantly greater (p=0.0001) in the bevacizumab plus IFN group (n = 96; 31%) than the IFN group (n=37; 13%). A small number of patients in both groups were assessed as having a complete response to treatment (4 vs. 6 in the bevacizumab plus IFN and IFN groups respectively) and ninety-two patients (30%) receiving bevacizumab plus IFN and 31(11%) in the IFN group experienced a partial response to treatment (defined as a 30% decrease in the sum of the longest diameters of target lesions).

Few details are provided in the abstract of the CALGB study.[101] The objective response rate was significantly ($p \leq 0.0001$) higher in patients receiving bevacizumab plus IFN (25.5% (95% CI 20.9 to 30.6)) than IFN (13.1% (95% CI 9.5 to 17.3)).

Sunitinib versus IFN

Tumours were assessed both by independent central review and by the treating physicians at baseline, at day 28 of cycles 1 through 4 and every two weeks thereafter until the end of treatment. Assessments were also made if disease progression was suspected clinically. The objective response rate, assessed by blinded imaging studies, was significantly higher in the sunitinib group (n=103; 31%) than in the interferon group (n=20; 6%) ($p < 0.001$). No patients in either group were assessed as having a complete response. Results obtained from investigator review of images were similar (137 (37%) vs. 33 (9%) patients in the sunitinib versus IFN groups respectively; $p < 0.001$).

Table 13: Summary of tumour response rate: bevacizumab plus IFN and sunitinib versus IFN as first line therapy

Study	Intervention	N	Objective response rate % (n)			P value
			overall	**complete**	**partial**	**for overall response**
Escudier, et al. 2007 [106†]	bevacizumab plus IFN	306	31 (96)	1 (4)	30 (92)	p = 0.0001
	placebo plus IFN	289	13 (37)	2 (6)	11 (31)	
Motzer, et al. [111*]	sunitinib	335	31 (103)	0	31 (103)	p<0.001
	IFN	335	6 (20)	0	6 (20)	

* Results from independent central view of radiological images; † Only patients with measurable disease at baseline are included in the analysis of response rate

Health related quality of life (Table 14)

Health related quality of life was not reported in either of the trials of bevacizumab plus IFN versus IFN.[101,106]

Sunitinib versus IFN

Health related quality of life was assessed using the Functional Assessment of Cancer Therapy – General (FACT-G) and FACT – Kidney Symptom Index (FKSI) questionnaires (see section 2.6, page 26), which were administered before randomisation, on days 1 and 28 of each cycle and at the end of treatment. No data is available on the comparability of the groups at baseline on these measures. Using data from all post-randomisation assessments, least-square means were estimated for each treatment group. A higher score indicates a better outcome. Overall differences between the two groups were tested using repeated-measures mixed effects models controlling for the assessment time, treatment-by-time interaction and the baseline score. Table 14 shows overall results (total score and all subscales of the FACT-G and total score and the Disease Related Symptoms subscale) were all significantly better for patients in the sunitinib group than in the IFN group.

Table 14: Summary of health related quality of life results: bevacizumab plus IFN and sunitinib versus IFN as first line therapy

Study	**Motzer, et al. 2007[111]**		
Intervention	**Sunitinib**	**IFN**	**P-value**
Number of patients	Not clear	Not clear	-
FACT-G total score	82.34	76.76	<0.001
· Physical Well-Being subscale	21.28	19.87	<0.001
· Social/Family Well-Being subscale	23.54	22.34	<0.001
· Emotional Well-Being subscale	18.32	17.54	<0.001
· Functional Well-Being subscale	18.98	17.00	<0.001
FKSI total score	45.34	42.07	<0.001
· Disease Related Symptoms subscale	29.36	27.37	<0.001

FACT-G: Functional Assessment of Cancer Therapy-General scale. **FKSI**: FACT-Kidney Symptom Index. A higher score indicates a better outcome.

Indirect comparison of bevacizumab plus IFN and sunitinib

In order to perform an adjusted indirect comparison of the two competing interventions, the internal validity and similarity of the two main trials [106,111] was examined (Table 15). As described above, the

baseline population characteristics of individuals in the trials were comparable in terms of demographics and disease status. IFN, the treatment common to both trials, was administered at the same dose (9MIU) and according to the same schedule (s.c three times weekly) in both trials with dose reductions to 6MIU and 3MIU for management of adverse events allowed in both trials. The median treatment duration of IFN and the reported dose intensity were also similar. In addition, median progression free survival in patients treated with IFN was similar in both trials (5.4 months in the bevacizumab plus IFN trial and 5 months in the sunitinib trial). We therefore concluded that the two trials were suitably similar to indicate that an adjusted indirect comparison of bevacizumab plus IFN versus sunitinib was appropriate, although, as explained earlier (section 3.1.5) results of indirect comparison may not be as robust or as reliable as direct comparison obtained from head-to-head randomised clinical trials and these results should therefore be treated with some caution.

Table 15: Summary of study and population characteristics for indirect comparison: bevacizumab plus IFN versus sunitinib versus IFN as first line therapy

Intervention	**Bevacizumab plus IFN vs. IFN**	**Sunitinib vs. IFN**
Study	Escudier, et al 2007[106]	Motzer, et al 2007[111]
N	649	750
Prognosis profile according to MSKCC criteria (favourable:intermediate:poor) (%)	27:56:9 (unavailable for 9% of patients)	38:56:6
Proportion of patients with clear cell carcinoma (%)	100	100
Proportion of patients having undergone previous nephrectomy (%)	100	90
Proportion of patients with metastases (%)	100	100
Dose of IFN (MIU)	9 (s.c. 3 times weekly)	9 (s.c. 3 times weekly)
Median (range) treatment duration for IFN (months)	4.6 (0.2 to 12.6)	5 (1 to 13)
Mean dose intensity of IFN (range)	89% (28 to 120%)**	83.1%*
Response to IFN (in terms of median PFS) (months)	5.4	5

* Reported in the company submission from Pfizer as relative dose intensity (total dose administered / total dose assigned multiplied by 100); ** Dose intensity was calculated as the amount of drug administered versus the amount that should have been administered over the course of treatment.

The results (Table 16) suggest that in terms of progression free survival sunitinib may be superior to bevacizumab plus IFN (HR 0.67; 95% CI 0.50 to 0.89). A similar result was seen for overall survival

(HR 0.82; 95% CI 0.53 to 1.28), although the point estimate of effect is smaller and, as the confidence intervals cross unity, the result is not statistically significant.

Table 16: Indirect comparison: bevacizumab plus IFN versus sunitinib versus IFN as first line therapy

Study	Intervention	HR for OS	95% CI for OS HR	HR for PFS	95% CI for PFS HR
Escudier, et al. 2007 [106]	bevacizumab plus IFN versus IFN	0.79	0.62 to 1.02	0.63	0.52 to 0.75
Motzer, et al. 2007 [111]	sunitinib versus IFN	0.65	0.45 to 0.94	0.42	0.33 to 0.52
Indirect comparison	sunitinib versus bevacizumab plus IFN	0.82	0.53 to 1.28	0.67	0.50 to 0.89

Adverse events

In the two main studies [106,111], data on adverse events and laboratory abnormalities were collected from the "safety population". That is, patients were assigned to treatments in the analysis based on what they actually received e.g. patients in the placebo arm receiving one or more doses of bevacizumab were assigned to the bevacizumab arm. Non-fatal adverse events reported up to 28 days after the last dose of study drug were included. Deaths were reported irrespective of when they occurred. Adverse events were measured according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Table 56 in Appendix 5 (page 221) shows adverse events of any grade reported in the course of the two studies. Some additional information obtained from a conference abstract [107] of the AVOREN trial regarding the reasons for discontinuation of study drugs are shown in Table 57 in Appendix 5 (page 223). In Table 17 (page 61), only those adverse events classified as grade 3 or above are included.

Bevacizumab plus IFN versus IFN

In the AVOREN trial [106], in both groups the most commonly reported 'any grade' adverse events in either group were pyrexia (in 45% and 43% of patients treated with bevacizumab plus IFN and IFN alone respectively), followed by anorexia (in 36% and 30% of patients respectively), fatigue (in 33% and 27% respectively), asthenia (in 32% and 28%), and influenza-like illness (in 24% and 25%). There were 203 grade 3 or worse adverse events reported by patients who received one or more doses of bevacizumab compared with 137 reported by those who did not receive the drug. The frequency of grade 3 and 4 adverse events was low, being between <1% and 12%, with most grade 3 or 4 adverse events occurring at a frequency of 3% or less. The mean number of grade 3 or worse adverse events

per patient was 1.3 in the intervention group and 0.9 in the control group. Details of statistical analyses are not provided. Adverse events that led to treatment discontinuation occurred more frequently in patients who received bevacizumab (n=95; 28%) than in those who did not (n=37; 12%). Proteinuria, hypertension and gastrointestinal perforation were the most common reasons (Table 56 in Appendix 5, page 221). Adverse event-related deaths were reported in eight (2%) patients who received bevacizumab and in seven (2%) patients who did not. Three of the deaths in patients who received bevacizumab (two bleeding events and one gastrointestinal perforation) were believed to be possibly related to bevacizumab.

The abstract of the CALGB study states that overall toxicity in the bevacizumab plus IFN group was greater than in the IFN only group, with significantly more patients reporting grade 3 hypertension (9% vs. 0%), anorexia (17% vs. 8%), fatigue (35% vs. 28%) and proteinuria (13% vs. 0%).[101]

Sunitinib versus IFN

The most commonly reported 'any grade' adverse events and laboratory abnormalities in the sunitinib group were diarrhoea (53% of patients), fatigue (51% of patients), nausea (44% of patients), leukopenia, neutropenia, anaemia, increased creatinine, thrombocytopenia and lymphopenia (which all occurred in more than 50% of the patients treated with sunitinib). A similar adverse event profile was seen in the interferon group with fatigue (51%), pyrexia (34%), nausea (33%) and chills (29%) being the most frequently reported adverse events and anaemia, lymphopenia and leukopenia the most commonly reported laboratory abnormalities (all occurring in more than 50% of patients treated with IFN). There were statistically significant differences ($p<0.05$) between groups in the frequency of reporting of the following adverse events at grade 3 and above: diarrhoea, fatigue, vomiting, hypertension, hand-foot syndrome, leukopenia, neutropenia, thrombocytopenia, lymphopenia, increased lipase and increased amylase, with all but fatigue, anaemia and lymphopenia occurring more often in the sunitinib group than the interferon group. Approximately 12% of patients in the IFN group experienced grade 3 or 4 adverse events compared with 7% in the sunitinib group; this difference was statistically significant ($p<0.05$). Treatment discontinuation as a result of unacceptable adverse events occurred more frequently in the IFN group than the sunitinib group (13% vs. 8%; $p=0.05$); no further details are provided. A total of 38% of patients in the sunitinib group and 32% in the IFN group had a dose interruption because of adverse events and in a similar proportion dosage was reduced (32% and 21% in the sunitinib and IFN groups respectively).

It is not clear from the paper whether any deaths occurred during the trial which may have been attributable to the study medication.

Summary of safety data

From the adverse events reported in these trials, the safety profile of both interventions appears to be comparable to IFN, with some adverse events particularly associated with bevacizumab plus IFN (proteinuria, hypertension, bleeding events) and sunitinib (hypertension, hand and foot syndrome). However, randomised clinical trials are not designed to detect rare adverse events and we therefore briefly reviewed additional literature, obtained from the results of our initial and updated searches, to identify any further potential safety issues.

Sunitinib

The most commonly reported treatment-related adverse events reported in an expanded access trial of sunitinib in 4000 patients in 36 countries were diarrhoea (39%), fatigue (35%) and nausea (33%).[119] A systematic review of toxicities associated with the administration of sorafenib, sunitinib and temsirolimus in phase I, II and III clinical trials found that all three interventions are associated with a large number of adverse events, although grade 3 or 4 events are less common (<1% to 16% of patients experience grade 3 or 4 adverse events with sunitinib). The most commonly reported grade 3 and 4 adverse events associated with sunitinib across all trials were elevated lipase (16%), lymphopenia (12%), neuropenia (12%), hypertension (8%), fatigue (7%) and thrombocytopenia (8%).[120]

Post-marketing surveillance has resulted in several reports of cardiac failure associated with sunitinib, occurring at a frequency classed as uncommon (1/1000 to 1/100).[77]

In a paper describing a systematic review and meta-analysis of the risk and incidence of hypertension in patients treated with sorafenib[121], the authors also discuss an unpublished meta-analysis of the risk of hypertension associated with sunitinib treatment. In this analysis, sunitinib was associated with a 22.5% (95% CI 19.5 to 25.9) incidence of hypertension with a relative risk of 3.89 (95% CI 2.6 to 5.9) compared with control treatments. No further details are provided.

We identified several conference abstracts in which reviews of the adverse events experienced by cohorts of patients treated with sunitinib were reported. These suggest that sunitinib treatment may also be associated with an increased incidence of macrocytosis [122] and thyroid dysfunction.[123] Further study is required to confirm these associations.

Bevacizumab

In a systematic review and meta-analysis of the risk and incidence of proteinuria and hypertension associated with bevacizumab treatment a significantly increased risk of both proteinuria (relative risk 2.2 (95% 1.6 to 2.9) and hypertension (relative risk 7.5 (95% CI 4.2 to 13.4) were reported.[124] Patients in the included trials were all receiving treatment with bevacizumab for metastatic cancer (including

lung, breast, colorectal and kidney) at doses of 10 or 15mg/kg. In some trials patients were also receiving treatment with other chemotherapeutic agents such as fluorouracil, carboplatin and cisplatin.

Table 17: Adverse events grade 3 and 4: Bevacizumab plus IFN and sunitinib versus IFN as first line therapy

Study	**Escudier, et al. 2007[106]***		**Motzer, et al. 2007[111]¶**	
Intervention	**BEV+ IFN**	**IFN + Placebo**	**Sunitinib**	**IFN**
N	**337**	**304**	**375**	**375**
	% of patients		**% of patients**	
Diarrhoea	2	<1	5	0†
Fatigue	12	8	7	12†
Asthenia	10	7	4	4
Nausea			3	1
Stomatitis			1	1
Vomiting			4	1†
Hypertension	3	<1	8	1†
Hand–foot syndrome			5	0†
Mucosal inflammation			2	1
Rash			2	1
Dry skin			1	0
Epistaxis			1	0
Pain in a limb			1	0
Headache	2	1	1	0
Dry mouth			0	1
Decline in ejection fraction			2	1
Pyrexia	2	<1	1	0
Chills			1	0
Myalgia			1	1
Influenza-like illness	3	2	0	1
Dyspnoea	<1	2		
Bleeding	3	<1		
Venous thromboembolic event	2	<1		
Gastrointestinal perforation	1	0		
Arterial thromboembolic event	1	<1		
Wound healing complications	<1	0		
Congestive heart failure	<1	0		

Anorexia	3	3		
Depression	3	1		
Leukopenia			5	2†
Neutropenia	4	2	12	7†
Anaemia	3	6	4	5
Increased creatinine			1	1
Thrombocytopenia	2	<1	8	0†
Lymphopenia			12	22†
Increased lipase			16	6†
Increased aspartate aminotransferase			2	2
Increased alanine aminotransferase			3	2
Increased alkaline phosphatase			2	2
Increased uric acid			12	8
Hypophosphatemia			5	6
Increased amylase			5	3†
Increased total bilirubin			1	0
Proteinuria	7	0		

*Grade 3 or 4 adverse events that occurred with a frequency of 2%; ¶ Grade 3 or 4 adverse events and selected laboratory abnormalities that occurred in at least 10% of patients in the sunitinib group. † Statistically significant difference between sunitinib and IFN ($p<0.05$).

Subgroup analyses

In the protocol we specified that, depending on the availability of data, we would consider the following subgroups of people with RCC: (1) people who had/had not undergone surgical resection of the primary tumour and (2) people diagnosed with clear cell and non-clear cell carcinoma. For the assessment of clinical effectiveness of bevacizumab plus IFN and sunitinib as first line therapy for the treatment of RCC, the following subgroup data were available:

(1) People with clear cell RCC compared with those with non-clear cell RCC

Only patients with predominantly clear cell pathology were eligible for entry to the studies. Neither study therefore provides any indication as to the relative effectiveness of the interventions amongst patients with clear cell RCC compared with those with non-clear cell RCC.

(2) People who have undergone surgical resection of the primary tumour compared with those who have not

The AVOREN study only included people who had undergone total or partial nephrectomy prior to entry to the study.[106] This trial therefore cannot provide any information on the relative effectiveness of these treatments in people who have or have not undergone surgical resection of the primary tumour.

In the trial by Motzer and colleagues [111], a small proportion of people who had not had a previous nephrectomy were included ((n=35; 9%) in the sunitinib group and (n=40; 11%) in the IFN group). Progression free survival for these subgroups using data from the independent central review of radiological images is reported (Table 18, page 64). The hazard ratio for patients who had undergone a previous nephrectomy (n=673) is 0.38 (95% CI 0.30 to 0.53) and the hazard ratio for patients who have not undergone a previous nephrectomy (n=77) is 0.58 (95% CI 0.24 to 1.03). These results may indicate that sunitinib is relatively more effective than IFN in patients who have undergone a previous nephrectomy than those who have not. However, the 95% confidence intervals for the latter comparison includes no difference. This indicates that the interventions could be equally effective in these populations although the small number of patients involved in the comparison also makes a type II error possible. Interestingly, the 95% confidence intervals for people who had undergone surgical removal of the primary tumour (0.30 to 0.53) are not distinct from that obtained for people who have not (0.24 to 1.03) which may suggest that for this outcome, it is inappropriate to divide the population according to this characteristic. It is possible that this division of the population is confounded by other factors related to the reasons for some patients not having surgery e.g. the position of the primary tumour and the performance status of the patient.

Table 18: Summary of progression free survival for patients with and without prior nephrectomy: sunitinib versus IFN as first line therapy

Study	**Motzer, et al. 2007[111]**		
Comparison	**Sunitinib vs. IFN**		
	N	**HR for PFS**	**95% CI**
Prior nephrectomy	673	0.38	0.30 to 0.53
No prior nephrectomy	77	0.58	0.24 to 1.03
Total trial population	750	0.42	0.32 to 0.54

3.2.2.3. Overall conclusion: bevacizumab plus IFN and sunitinib versus IFN

From the limited clinical data available, treatment with both interventions (bevacizumab plus IFN and sunitinib) appears to have clinically relevant and statistically significant advantages over treatment with IFN alone in terms of progression free survival and tumour response. In both trials, median progression free survival was doubled from approximately 5 months to approximately 11 months with the interventions (HR for sunitinib 0.42; 95% CI 0.32 to 0.54 and HR for bevacizumab plus IFN 0.63; 95% CI 0.52 to 0.75). Although promising, data on overall survival from these trials is not fully mature. Treatment crossover has now occurred in two of the trials [106,111] and further information from the randomised population will therefore not be available. It is not clear whether treatment crossover has occurred in the CALGB study yet and overall survival data are pending.[101]

Data on adverse events suggest that the interventions are not associated with a greater frequency of adverse events than IFN alone although the adverse event profile is different and there is some emerging concern in the published literature relating to the frequency of cardiovascular events associated with sunitinib.

All three trials were conducted predominantly in patients with metastatic clear cell carcinoma, with MSKCC risk factors suggestive of a favourable or intermediate prognosis, who had undergone a previous nephrectomy. Whether these results can be extrapolated to other groups of patients with RCC (e.g. people diagnosed with non clear cell RCC or defined as having a poor prognosis according to the MSKCC criteria) is unclear. As there is no head-to-head comparison data available for bevacizumab plus IFN versus sunitinib, we carried out an indirect comparison to consider which intervention might be the most clinically effective. The results suggest that, in terms of progression free survival, sunitinib may be superior to bevacizumab plus IFN (HR 0.82; 95% CI 0.55 to 0.89).

3.2.3. Sorafenib and sunitinib compared with best supportive care as first line therapy

In this section we address Research Question 2: In those who are unsuitable for treatment with immunotherapy what is the clinical effectiveness of sorafenib tosylate and sunitinib as first line therapy, using best supportive care as a comparator?

3.2.3.1. Quantity and quality of included studies

We were unable to locate any fully published randomised clinical trials of these interventions in people with a diagnosis of advanced and/or metastatic RCC who are deemed unsuitable for treatment with immunotherapy.

3.2.4. Bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and best supportive care compared with IFN as first line therapy in people with poor prognosis

In this section we address Research Question 3: In those with three or more of six poor prognostic factors what is the clinical effectiveness of bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus, immunotherapy and best supportive care as first line therapy, using IFN as a comparator?

3.2.4.1. Quantity, quality and characteristics of included studies

We identified one RCT relevant to this question, in which treatment with temsirolimus, temsirolimus plus IFN or IFN alone were compared in patients deemed to have poor prognosis.[112] A summary of the quality assessment of this study is shown in Table 9 (page 42); study characteristics are summarised below and in Table 58 in Appendix 5 (page 224).

We were unable to locate any eligible studies of sorafenib, sunitinib or bevacizumab plus IFN in patients with poor prognosis, nor any trials in comparison with best supportive care. However, approximately 10% of the people included in the studies described above in section 3.2.2 were defined as having poor prognosis according to similar criteria. A summary of the study characteristics and quality assessment of these trials can be found in section 3.2.2.1 (page 44) and Appendix 5 (page 218).

Study characteristics

Temsirolimus versus IFN

Hudes and colleagues report the results of the Global ARCC trial. An international[a] multicentre, 3-way parallel group, randomised phase III trial in which 626 people with previously untreated metastatic RCC, deemed to have poor prognosis according to criteria based on MSKCC risk score, received either temsirolimus, IFN or a combination of temsirolimus and IFN. The study has been published in one full paper [112] and five abstracts [89,94-97]. The primary outcome was overall survival. Progression free survival, objective response rate and the "clinical benefit rate" (defined as the proportion of people with stable disease for at least 24 weeks or an objective response) were secondary outcomes. The study (with 200 patients per group) was designed to have 80% power to detect an improvement in overall survival of 40% for each comparison with the use of a two-sided stratified log-rank test at an overall 2.5% level of significance. Two interim analyses were planned after approximately 164 and 430 deaths and a final analysis, if necessary, after a total of 504 deaths had occurred; this paper [112] provides the results of the second analysis (after 446 patients had died).

Trial eligibility is defined in Table 58 in Appendix 5 (page 224). Participants were required to have a diagnosis of histologically confirmed RCC, a Karnofsky performance status of 60 or more and measurable disease according to RECIST criteria. All patients had to fulfil pre-specified criteria for poor prognosis in order to be eligible. Although based on the MSKCC classification of prognosis, the criteria used in this trial were slightly different. The MSKCC classification includes ***five*** predictors of survival, of which a patient with poor prognosis needs to exhibit three. Participants in this trial were required to exhibit three of ***six*** features in order to be defined as having 'poor prognosis'; the additional feature being 'metastases in multiple organs'.

Randomisation was performed centrally and patients were stratified according to the geographic location of the centre and whether they had undergone previous nephrectomy. Patients were randomly assigned to receive temsirolimus (25 mg, delivered intravenously, weekly) (n=209), IFN (18MIU, delivered subcutaneously three times per week) (n=207) or a combination of both treatments (n=210). Treatment was continued until evidence of disease progression, symptomatic deterioration or intolerable adverse events. IFN was started at a dose of 3MIU for the first week, increased to 9MIU for the second week and 18MIU for the third week. Treatments were withheld if grade 3 or 4 adverse events occurred and restarted at a reduced dose after recovery to grade 2 or lower.

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[a] Argentina, Australia, Canada, Czech Republic, Germany, Greece, Hungary, Italy, Latvia, Lithuania, The Netherlands, Poland, Russia, Serbia and Montenegro, Slovakia, South Africa, Spain, Sweden, Taiwan, Turkey

The results reported in the full publication [112] were obtained from the second interim analysis after 446 deaths. At the time of data analysis, median treatment duration for temsirolimus was 3.92 months (range 0.23 to 29.08) in the temsirolimus alone group and 3.46 months (range 0.23 to 31.85) in the group receiving combination treatment. For IFN, the respective figures were 1.85 months (range 0.23 to 28.62) in the IFN group and 2.77 months (range 0.23 to 31.85) in the combination group.

The mean dose intensity of temsirolimus was 23.1mg per week or 92% of the planned dose; corresponding figures for IFN are 30.2 MU per week or 56% of the maximum planned dose in the first eight weeks of treatment. No further details are provided.

Data from the final analysis were available from a conference abstract [89] and were presented in the company submission to NICE[125,125]. Median treatment duration at this analysis is not reported in either source.

Additional data relating to HRQoL, reported in a conference abstract [97] and the company submission are also included (see Section 3.2.4.2, page 70).

Sunitinib versus IFN

See section 3.2.2.1, page 44.

Bevacizumab plus IFN versus IFN

See section 3.2.2.1, page 44.

Quality Assessment

Temsirolimus versus IFN

This is a large, international, multicentre randomised clinical trial. Although, on the whole, methods are clearly reported, several aspects are not clear in the paper, making the assessment of quality somewhat difficult. Details of randomisation methods and withdrawals were adequately reported, but details on how the randomisation code was generated were omitted. Site investigators were not blind to treatment allocation, although radiological scans used for assessment of progression free survival and response rate were assessed both by site investigators and by central blinded review. Only the analysis of the primary endpoint (overall survival) was conducted on an intention to treat basis. Further details can be found in Table 9 (page 42).

Sunitinib versus IFN

See section 3.2.2.1, page 44.

Bevacizumab versus IFN

See section 3.2.2.1, page 44.

Population baseline characteristics

Temsirolimus versus IFN

In this assessment we are interested in two of the three patient groups in this trial, temsirolimus alone and IFN alone as the combination of temsirolimus and IFN is not licensed for use in people with advanced and/or metastatic RCC. At baseline, these two treatment groups were well matched in terms of demographic characteristics (age, gender, RCC histology) and disease status (Karnofsky performance status, MSKCC risk group and proportion of patients having undergone a previous nephrectomy) (Table 19, page 68). Most tumours had clear cell histology (approx. 80%), and most patients had Karnofsky performance scores of < 70 (approx. 80%) and had undergone a previous nephrectomy (approx 65%). It is interesting to note that according to MSKCC risk classification, approximately 30% of patients in both treatment groups would have been classified as having intermediate prognosis rather than poor prognosis, and about 5% of patients in both treatment groups did not meet the criteria for entry into the study (i.e. three or more of six factors suggestive of poor prognosis).

Table 19: Population baseline characteristics: temsirolimus versus IFN as first line therapy in people with poor prognosis

Study	**Hudes, et al. 2007[112]**		
Intervention group	**Temsirolimus N (%)**	**IFN N (%)**	***Temsirolimus plus IFN N (%)***
Randomised	**209**	**207**	***210***
Diagnosis	Advanced renal cell carcinoma (stage IV or recurrent)		
Age, median yrs (range)	58 (32-81)	60 (23-86)	*59 (32-82)*
Male	139(66)	148(71)	*145(69)*
Karnofsky performance score			
> 70	41(20)	34 (16)	*33 (16)*
≤ 70	168(80)	171 (83)	*177 (84)*
MSKCC risk factors			
1-2 (intermediate)	64(31)	50 (24)	*50 (24)*
≥3 (poor)	145(69)	157 (76)	*160 (76)*
Patients with a previous nephrectomy	139(66)	139 (67)	*141 (67)*
Number of patients with clear cell histology	169(81)	170(82)	*163(78)*

Patients with poor prognostic features			
≥3 of 6	195(93)	196 (95)	*198 (94)*
<3 of 6	14(7)	11 (5)	*12 (6)*
Patients with protocol defined poor prognostic features:			
• Lactate dehydrogenase level >1.5 times upper limit of normal	36(17)	48 (23)	*33 (16)*
• Haemoglobin level < lower limit of normal	172(82)	168 (81)	*178 (85)*
• Corrected serum calcium level > 10mg/dl (2.5 mmol/L)	54(26)	72 (35)	*58 (28)*
• Time from initial diagnosis to randomization <1yr	174(83)	164 (79)	*179 (85)*
• Karnofsky performance score ≤ 70	168(80)	171 (83)	*177 (84)*
• ≥ 2 sites of organ metastasis	166(79)	165 (80)	*168 (80)*

Percentages may not total 100 because of rounding.

Sunitinib versus IFN

In the study by Motzer and colleagues [111], 23 (6%) patients receiving sunitinib and 25 (7%) patients receiving IFN had three or more MSKCC risk factors and were therefore classified as having poor prognosis. As described above, this classification is slightly different from that used in the trial of temsirolimus. The baseline population characteristics of the entire trial population are described in Section 3.2.2.1, page 44.

Bevacizumab plus IFN versus IFN

Nine percent (n=28) of the patients who received bevacizumab plus IFN and 7% (n=24) of the patients receiving IFN in the trial by Escudier and colleagues had three or more MSKCC risk factors for poor prognosis. Again, the definition of poor prognosis differs from that used in the trial of temsirolimus. The baseline population characteristics of the entire population are described in Section 3.2.2.1.

Comparison of population baseline characteristics between trials

As population baseline characteristics are not presented separately for the poor prognosis subgroups in the trials of sunitinib and bevacizumab, comparison between the studies is problematic. However, assuming that the people with poor prognosis were characteristic of the trial populations as a whole,

the demographics (median age, gender mix) of patients included in all three studies appear similar. There are, however, differences between trials in terms of the proportion having undergone previous nephrectomy (100% vs. 90% vs. 65% in the trials of bevacizumab plus IFN, sunitinib and temsirolimus respectively) and the proportion of patients with clear cell carcinoma (100% vs. 100% vs. 80% in the trials of bevacizumab plus IFN vs. sunitinib vs. temsirolimus).

3.2.4.2. Assessment of clinical effectiveness

Overall survival (Table 20)

Temsirolimus versus IFN

Overall survival was the primary outcome measure of the trial and analysed on an ITT basis. [112] At the time of the interim analysis, median overall survival was 7.3 months (95% CI 6.1 to 8.8 months) in the IFN group and 10.9 months (95% CI 8.6 to 12.7 months) in the temsirolimus group, producing a hazard ratio of 0.73 (95% CI 0.58 to 0.92; p=0.008).

In the final analysis, median overall survival in the IFN group was 7.3 months (95% CI 6.1 to 8.8 months) and in the temsirolimus group was 10.9 months (8.6 to 12.7 months), producing a slightly higher hazard ratio of 0.78 (95% CI 0.63 to 0.97; p=0.0252) indicating that temsirolimus reduced the hazard of death by 22%.[89]

These results suggest that temsirolimus may be superior to IFN in this patient group. However, the 95% confidence intervals surrounding the estimates are reasonably wide and approach unity at the upper limit (which would indicate no difference between treatments) highlighting the degree of imprecision of these results.

Bevacizumab plus IFN versus IFN and sunitinib versus IFN

Data on overall survival were not presented separately for the poor prognosis subgroup in these trials.

Table 20: Summary of overall survival: temsirolimus versus IFN as first line therapy in people with poor prognosis

Study	Intervention	N	median OS (months)	HR	95% CI for HR	p value
			Results of the second interim analysis[112]			
Hudes et, al. 2007 [112]	**temsirolimus**	209	10.9 (95% CI 8.6 to 12.7)	0.73	0.58 to 0.92	p = 0.008
	IFN	207	7.3 (95% CI 6.1 to 8.8)			
			Results of the final analysis[89]			
D'Souza et, al. 2008 [89]	**temsirolimus**	209	10.9 95% CI 8.6 to 12.7	0.78	0.63 to 0.97	p = 0.0252
	IFN	207	7.3 95% CI 6.1 to 8.8)			

Progression-free survival

Bevacizumab plus IFN versus IFN

Median progression free survival (defined as time between randomisation and first documented disease progression or death due to any cause) for patients in the poor prognosis subgroup was 2.2 months for those receiving bevacizumab plus IFN and 2.1 months for those treated with IFN, producing a hazard ratio of 0.81 (95% CI 0.46 to 1.42). As the 95% confidence interval crosses unity this result would not be considered statistically significant but could be interpreted as indicating a possible benefit of treatment with bevacizumab plus IFN compared with IFN in this patient subgroup. The lack of statistical significance could be because bevacizumab plus IFN is not more effective than IFN in patients with a poor prognosis or it may reflect the small number of patients (n=52) in this subgroup.

Sunitinib versus IFN

This paper includes results for progression free-survival for subgroups according to baseline factors. For all subgroups, the hazard ratio favours sunitinib. However, data for the group of patients with three or more MSKCC risk factors are not presented separately. This trial therefore does not provide any additional information about the effectiveness of sunitinib versus IFN in this particular population. A later analysis of the trial (following the decision to allow patients in the IFN group to receive sunitinib) is available as a conference abstract [91] and suggests that the benefit of sunitinib over IFN in terms of progression free survival (by investigator assessment) extends over all MSKCC risk groups.

Temsirolimus versus IFN

Progression-free survival (not formally defined in the paper[112]) was assessed both by the site investigators (who were not blind to treatment allocation) and by independent blinded evaluation of the radiological images. In the interim analysis, as determined by the site investigators, median progression free survival was 1.9 months (95% CI 1.9 to 2.2 months) in the IFN group and 3.8 months (95% CI 3.6 to 5.2 months).[112] Radiological images from 153 patients (74%) in the IFN group and 192 patients (92%) in the temsirolimus group were evaluated in the independent blinded review, the results of which suggest that median progression free survival was 3.1 months (95% CI 2.2 to 3.8 months) and 5.5 months (95% CI 3.9 to 7.0 months) for the IFN and temsirolimus groups respectively. The authors suggest that the reason for the discrepancy in these results is the inclusion of patients with symptomatic deterioration that had begun before scheduled radiological measurements of the tumour, in the evaluation by site investigators. Hazard ratios are not provided in the paper, nor is there any indication of the results of statistical testing. However, the abstract of the paper states that patients who received temsirolimus alone had longer progression free survival than did patients who received IFN alone ($p<0.001$).

In the final analysis, median progression-free survival by independent assessment was 5.6 months (95% CI 3.9 to 7.2) in the temsirolimus group and 3.2 months (95% CI 2.2 to 4.0) in the IFN group, with a hazard ratio of 0.74 (95% CI 0.60 to 0.91; $p = 0.0042$).[125] Again, the investigator-evaluation resulted in slightly lower estimates of PFS (3.8 months vs. 1.9 months for temsirolimus and IFN respectively). Interestingly the hazard ratio was almost identical (0.74; 95% CI 0.60 to 0.90; $p = 0.0028$).[89]

Table 21: Summary of progression-free survival: temsirolimus versus IFN as first line therapy in people with poor prognosis

Study	Intervention	N	Median PFS (months)	HR	95% CI for HR	p value
Results of the second interim analysis*[112]						
Hudes, et al. 2007 [112]	**Temsirolimus**	209	3.8 (95% CI 3.6 to 5.2)	NR	NR	NR
	IFN	207	1.9 95% CI 1.9 to 2.2)			
Results of the final analysis*[89]						
d'Sousa, et al. 2008 [89]	**Temsirolimus**	209	3.8 (95% CI 3.6 to 5.2)	0.74	0.60 to 0.90	0.0028
	IFN	207	1.9 (95% CI 1.9 to 2.2)			
Escudier, et al. 2007 [111]	**Bevacizumab plus IFN**	28	2.2	0.81	0.46 to 1.42	NR
	IFN	24	2.1			

* As assessed by site investigators – results from an independent review of images are also available for a reduced number of patients (see text above); NR – not reported

Tumour response

Bevacizumab plus IFN versus IFN and sunitinib versus IFN

Tumour response results were not presented separately for the poor prognosis subgroup in these trials.[106,111]

Temsirolimus versus IFN

Prior to the start of treatment, the following imaging studies were performed: computed tomography scans of the chest, abdomen and pelvis, a radionuclide bone scan and a magnetic resonance imaging or CT scan of the brain. Scanning was repeated at 8-week intervals to evaluate tumour size. Response to treatment was assessed using the RECIST criteria. Objective response rates in the IFN and temsirolimus groups were 4.8% (95% CI 1.9 to 7.8%) and 8.6% (95% CI 4.8 to 12.4%) respectively and did not differ significantly.

Health related quality of life

Bevacizumab plus IFN versus IFN and sunitinib versus IFN

No additional information on the effect of these treatments on health related quality of life in patients with poor prognosis was available from these trials.[106,111]

Temsirolimus versus IFN

No health related quality of life outcomes were reported in the full-text paper.[112] In a subsequent conference abstract presented in 2007, results for quality-adjusted survival (a pre-defined endpoint) are presented. Quality adjusted survival and toxicity (Q-TWiST) was estimated by partitioning overall survival into three distinct health states: time with serious toxicity, time with progression and time without symptoms and toxicity (TWiST). Survival was value-weighted when patients completed EQ-5D questionnaires at weeks 12 and 32, when a grade 3 or 4 adverse event was reported, upon relapse or progression, or upon withdrawal from the trial. All 626 randomised patients in the trial were included in the computation of health state durations. This includes patients in all three treatment groups – temsirolimus alone, IFN alone and the combination of temsirolimus and IFN. EQ-5D questionnaires were obtained from 260 of 300 patients upon progression and 230 of 570 after a grade 3 or 4 adverse event. Patients receiving temsirolimus had 38% greater TWiST than those receiving IFN (6.5 months vs. 4.7 months for temsirolimus and IFN respectively; p=0.00048) and 23% greater Q-TWiST than those receiving IFN (7.0 months vs. 5.7 months for temsirolimus and IFN respectively; p = 0.0015). Median EQ-5D scores for the total trial population are shown in Table 22.

Table 22: Summary of HRQoL: temsirolimus versus IFN as first line therapy in people with poor prognosis

Study		n	Median EQ-5D
Parasuraman, et al. 2007[97]	**At baseline**	601	0.689
	On progression	260	0.587
	During a grade 3 or 4 adverse event	230	0.585
	During stable disease (obtained at weeks 12 and 32 of treatment)	NR	0.689

NR – not reported; some data obtained from the slide presentation

Indirect comparison of first line therapy options in people with poor prognosis

No comparison with sorafenib is possible in this patient group as we were unable to locate any trials of sorafenib as first line therapy.

In order to ascertain whether an indirect comparison of bevacizumab plus IFN, sunitinib and temsirolimus was valid we examined the internal validity and similarity of the three trials. Participants in all three trials were similar in age and gender distribution and were all undergoing first line therapy for RCC. However, there were some important differences between the patient populations in terms of disease status, definitions of poor prognosis, dose of IFN used and dose intensity of IFN received, and

the treatment duration and response to IFN in the comparator arms. These are detailed in Table 23 (page 75).

Table 23: Summary of study and population characteristics for indirect comparison: bevacizumab plus IFN, sunitinib, temsirolimus or IFN for first line therapy in people with poor prognosis

	Bevacizumab plus IFN vs. IFN	Sunitinib vs. IFN	Temsirolimus vs. IFN
Study	**Escudier, et al[106]**	**Motzer, et al.[111]**	**Hudes, et al.[112]**
Proportion of patients with poor prognosis (%)	8.3	6.4	94
Definition of poor prognosis used	≥ 3 of 5 risk factors (MSKCC)	≥ 3 of 5 risk factors (MSKCC)	≥ 3 of 6 risk factors (5 MSKCC plus evidence of multiple metastases)†
Proportion of patients with clear cell carcinoma (%)	81	100	100
Proportion of patients having undergone previous nephrectomy (%)	100	93*	67
Proportion of patients with metastases (%)	32*	100	100
Dose of IFN (MIU)	9	9	18
Response to IFN (in terms of median progression-free survival [months])	2.1	Not reported	3.1
Mean dose intensity of IFN (%)	89	Not reported	73
Median (range) treatment duration for IFN (months)	4.6 (0.2 to 12.6)	4 (1 to 13)	2.77 (0.23 to 31.85)

* proportion of patients in the entire trial with these characteristics; baseline characteristics for the subgroup with poor prognosis are not available; † 73% of patients in this trial were classified as 'poor prognosis' using the alternative definition

We concluded that there were sufficient differences between the trials to render an indirect comparison between interventions inappropriate.

As many patients with poor prognosis will be managed with best supportive care rather than being considered for treatment with IFN, we also considered the validity of an indirect comparison between IFN and best supportive care in order to provide an estimate of the relative effectiveness of interventions compared with best supportive care. However, there are very few trials of IFN versus a control treatment,[37] and although some authors have considered treatments such as medroxyprogesterone and vinblastine to be equivalent to placebo or best supportive care we do not

consider this a valid assumption. In addition, none of the available trials uses the MSKCC prognostic criteria to define prognosis. We therefore concluded that a formal indirect comparison between IFN and BSC should not be carried out.

Adverse events

Bevacizumab plus IFN versus IFN

See 3.2.4.2 (page 70). No additional data were provided for those in the poor prognosis subgroup.

Sunitinib versus IFN

See section 3.2.4.2 (page 70). No additional data were provided for those in the poor prognosis subgroup.

Temsirolimus versus IFN

Adverse events were defined and graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0. No further details were provided. Table 59 in Appendix 5 (page 226) details all adverse events of any grade reported by at least 20% of patients in any group. The tables include all adverse events, not only those considered to be drug-related. Asthenia was the most commonly reported adverse event amongst patients in all treatment groups. Anaemia, nausea, anorexia, fever and chills were also commonly reported in all treatment groups. Patients treated with temsirolimus experienced more rashes, hyperlipidemia, infection, peripheral oedema, hyperglycaemia, cough, hypercholesterolemia and stomatitis than patients receiving IFN although whether these differences were statistically significant is unclear.

Table 24 (page 77) shows adverse events classified as grade 3 or 4, (based on the list of adverse events which occurred in more than 20% of patients in any group (shown in Table 59 in Appendix 5, page 226). For simplicity, only data for the temsirolimus and IFN groups are presented. More patients in the interferon group than in the temsirolimus group reported grade 3 or 4 adverse events (78% vs. 67%; p=0.02). The most commonly occurring grade 3 or 4 adverse event in the temsirolimus group was anaemia (in 20% of patients). Events which occurred more frequently in the temsirolimus group than the IFN group include dyspnoea (in 9% and 6% of patients respectively) and rash (in 4% and 0% of patients respectively), although the number of patients affected is relatively small and whether these differences were considered statistically significant is unclear. Treatment was discontinued as a result of adverse events in twice as many people receiving IFN as temsirolimus, although the number of people involved was again `small (n=29 [14%] and n=15 [7%] in the IFN and temsirolimus groups respectively). The number of deaths as a result of adverse events was not reported.

Table 24: Proportion of patients (%) reporting adverse events (grade 3 or 4): temsirolimus versus IFN as first line therapy in people with poor prognosis

Study	**Hudes, et al.**[112]	
Intervention	**Temsirolimus**	**IFN**
Number of patients	**208**	**200**
Anaemia	20	22
Asthenia	11	26
Hyperglycaemia	11	2
Dyspnoea	9	6
Pain	5	2
Infection	5	4
Rash	4	0
Abdominal pain	4	2
Anorexia	3	4
Hyperlipidemia	3	1
Back pain	3	4
Increased creatinine level	3	1
Neutropenia	3	7
Nausea	2	4
Peripheral oedema	2	0
Vomiting	2	2
Diarrhoea	1	2
Cough	1	0
Hypercholesterolemia	1	0
Fever	1	4
Stomatitis	1	0
Weight loss	1	2
Headache	1	0
Thrombocytopenia	1	0
Chills	1	2
Increased aspartate amino-transferase level	1	4
Leukopenia	1	5
Constipation	0	1

Patients who underwent randomisation but received no treatment were not included: seven in the IFN group, one in the temsirolimus group, and two in the combination-therapy group.

Summary of safety data

The frequency of treatment-related toxic events associated with bevacizumab plus IFN, sunitinib and temsirolimus appears to be comparable or slightly better than IFN, based on the data reported in these trials. There are some particular adverse events associated with each of the three interventions – bevacizumab plus IFN (proteinuria, hypertension, bleeding events), sunitinib (hypertension, hand and foot syndrome) and temsirolimus (e.g. hyperglycaemia, hyperlipidemia, hypercholesterolemia, peripheral oedema, rash). However, randomised clinical trials are not designed to detect rare adverse events and we therefore briefly reviewed additional data sources to identify any further potential safety concerns. The results of this review are detailed in section 3.2.4.2 for bevacizumab plus IFN and sunitinib. A systematic review of toxicities associated with the administration of sorafenib, sunitinib and temsirolimus in phase I, II and III clinical trials found that between 1% and 20% of patients experience grade 3 or 4 adverse events with temsirolimus treatment. The most commonly experienced grade 3 and 4 adverse events across all included trials of temsirolimus were anaemia (20%), fatigue/asthenia (11%), hyperglycaemia (11%) and dyspnoea (9%).[120]

Subgroup analyses

In the protocol we specified that, depending on the availability of data, we would consider the following subgroups of people with RCC: (1) people who had/had not undergone surgical resection of the primary tumour and (2) people diagnosed with clear cell and non-clear cell carcinoma. For the assessment of clinical effectiveness of bevacizumab plus IFN, sorafenib, sunitinib and temsirolimus as first line therapy in people with poor prognosis, the following subgroup data were available:

(1) People with clear cell RCC compared with those with non-clear cell RCC

Only patients with predominantly clear cell pathology were eligible for entry to the studies of bevacizumab plus IFN and sunitinib. Neither study, therefore provides any indication as to the relative effectiveness of the interventions amongst patients with clear cell RCC compared with those with non-clear cell RCC.

Hazard ratios for overall and progression free survival for patients with and without clear cell RCC are presented for temsirolimus versus IFN in Table 25 and Table 26, and while the results suggest that temsirolimus may be more effective that IFN in people diagnosed with clear cell carcinoma and with non clear cell carcinoma, there is a large amount of uncertainty in the estimates. It is not clear from the report whether the results were considered statistically significant.

Table 25: Summary of overall survival for patients with clear or non clear cell renal cell carcinoma: temsirolimus versus IFN as first line therapy in people with poor prognosis

Study	**Hudes, et al. 2007[96,96,112]**		
Comparison	**Temsirolimus vs. IFN**		
	n	**HR for overall survival**	**95% CI**
Clear cell	339	0.85	0.64 to 1.06
Non clear cell	73	0.55	0.33 to 0.90
Total trial population	412	0.73	0.58 to 0.92
Data missing for four patients.			

Table 26: Summary of progression free survival for patients with clear or non-clear cell renal cell carcinoma: temsirolimus versus IFN as first line therapy in people with poor prognosis

Study	**Hudes, et al. 2007[112] ***		
Comparison	**Temsirolimus vs. IFN**		
	n	**HR for PFS**	**95% CI**
Independent assessment			
Clear cell	339	0.84	0.67 to 1.05
Non clear cell	73	0.36	0.22 to 0.59
Investigator's assessment			
Clear cell	339	0.82	0.66 to 1.02
Non clear cell	73	0.40	0.25 to 0.65
* Data from Wyeth submission [125]			

(2) People who have undergone surgical resection of the primary tumour compared with those who have not

The study of the combination of bevacizumab and IFN compared with IFN alone only included people who had undergone total or partial nephrectomy prior to entry to the study.[106] This trial therefore cannot provide any information on the relative effectiveness of these treatments in people who have or have not undergone surgical resection of the primary tumour.

In the trial by Motzer and colleagues,[111] a small proportion of people who had not had a previous nephrectomy were included (n=35 (9%) in the sunitinib group and n=40 (11%) in the IFN group). However, no additional information is provided on the MSKCC risk factor status of these patients. This trial is therefore not able to provide any further evidence as to the relative effectiveness of sunitinib and IFN in patients with poor prognosis who have or have not undergone previous nephrectomy.

Overall survival for people who have and have not undergone prior nephrectomy in the trial of temsirolimus versus IFN is shown in Table 27 (page 80). Patients in both subgroups appear to respond better to temsirolimus than IFN which is consistent with the overall result. Examination of the uncertainty around the results suggests that surgical removal of the primary tumour is not an important factor in predicting the likely response to these treatments, although a type II error remains possible.

Table 27: Summary of overall survival for patients with and without prior nephrectomy: temsirolimus versus IFN as first line therapy in people with poor prognosis

Study	**Hudes, et al. 2007[112]**		
Comparison	**Temsirolimus vs. IFN**		
	n	**HR for overall survival**	**95% CI**
Prior nephrectomy	278	0.84	0.65 to 1.12
No prior nephrectomy	138	0.62	0.42 to 0.93
Total trial population	416	0.73	0.58 to 0.92

Progression-free survival data from the trial of temsirolimus versus IFN for people who have and have not undergone prior nephrectomy was not reported in the published paper, but was reported in the Wyeth submission[125] (see Table 28, page 81). Hazard ratios for progression-free survival, assessed by either investigators or independent assessors, favoured poor prognostic patients who were treated with temsirolimus compared with those treated with IFN, irrespective of whether the patients had prior nephrectomy.

Table 28: Summary of progression free survival for patients with and without prior nephrectomy: temsirolimus versus IFN as first line therapy in people with poor prognosis

Study	**Hudes, et al. 2007[112,125,125]**			
Comparison	**Temsirolimus vs. IFN**			
	n	**HR for PFS**	**95% CI**	**p value***
Investigator's assessment				
Prior nephrectomy	278	0.74	0.58 to 0.95	0.4204
No prior nephrectomy	138	0.63	0.44 to 0.91	
Independent assessment				
Prior nephrectomy	278[¶]	0.72	0.55 to 0.93	0.4735
No prior nephrectomy	138[¶]	0.62	0.43 to 0.88	

* Interaction analysis

[¶] The number of patients for which the results of independent assessment of radiological images was available is not reported in the industry submission; we assume that there was no missing data.

3.2.4.2.1. Overall conclusion: first line therapy in people with poor prognosis

There is limited data available to draw clear conclusions about the most effective first line therapy for people with RCC regarded as having poor prognosis.

We were unable to find any data on the use of sorafenib in this population, nor any head-to-head randomised trials of the new interventions, nor any comparisons with best supportive care.

Unfortunately, due to differences in study and baseline population characteristics we were unable to perform any indirect comparisons using the trials of the interventions versus IFN.

Bevacizumab plus IFN versus IFN

There is some evidence to suggest that the combination of bevacizumab plus IFN is more effective in terms of prolonging progression free survival than IFN alone (2.2 months vs. 2.1 months; HR 0.81 95% CI 0.46 to 1.42) in the poor prognosis subgroup; consistent with the results obtained from the entire trial population. No additional safety data were available for this subgroup but there is also nothing in the trial report to suggest that the adverse event profile would be any different than that seen in the whole trial population.

Sunitinib versus IFN

Although some of the patients included in the trial of sunitinib versus IFN were characterised as having poor prognosis, the results of the trial were not reported according to prognosis and so this trial is also not able to offer any substantial evidence.

Temsirolimus versus IFN

From the limited clinical data available, treatment with temsirolimus appears to have clinically relevant and statistically significant advantages over treatment with IFN in people with poor prognosis, in terms of overall survival, progression free survival and tumour response. Median progression free survival was approximately doubled from 1.9 months with IFN to 3.8 months with temsirolimus (HR 0.74; 95% CI 0.60 to 0.90). Data on adverse events suggest that temsirolimus may be associated with a lower frequency of grade 3 or 4 adverse events than IFN, although the overall frequency of adverse events is still relatively high.

Data on patients with and without clear cell carcinoma and prior nephrectomy suggest that temsirolimus is more effective than IFN in all these subgroups. Whether the results are sufficiently distinct from each other to suggest that people in these subgroups respond differently to temsirolimus is not clear.

3.2.5. Sorafenib and sunintinb compared with best supportive care as second line therapy

In this section we address Research Question 4: In those who have failed treatment with cytokine based immunotherapy what is the clinical effectiveness of sorafenib tosylate, sunitinib and best supportive care as second line therapy, using best supportive care as a comparator?

3.2.5.1. Quantity, quality and characteristics of included studies

We were unable to find any useful definitions of 'best supportive care' in this population in the literature, or any trials which compare sorafenib or sunitinab with 'best supportive care'. We identified two trials of sorafenib tosylate as second line therapy, an RCT of sorafenib versus placebo [113] and a randomised discontinuation trial (RDT) of sorafenib versus placebo.[115] We have therefore assumed that treatment with placebo is equivalent to 'best supportive care'.

We were unable to locate any randomised controlled trials of sunitinib as second line therapy. However, we did identify two single arm, phase II trials.[85,116,117]

Study characteristics are summarised below and in Table 60 in Appendix 5 (page 227). A summary of the quality assessment of these studies is shown in Table 9 (page 42);

Study characteristics

Sorafenib versus best supportive care

Escudier and colleagues report the results of the TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial) study, an international[a], multicentre, double blind and placebo controlled phase III RCT in which 903 patients with histologically confirmed metastatic clear cell RCC were randomised to receive either sorafenib (400mg orally twice daily; n=451) or matched placebo (n=452). Results of this trial have been reported in two full publications [113,114] and five abstracts.[98,99,102,103,114] The primary outcome was overall survival. Progression free survival and overall response rate were amongst the secondary outcome measures. Data on safety and health related quality of life were also collected. The study was designed to have 90% power to detect a 33.3% difference in survival between the two groups at a two-sided alpha level of 0.04 after 540 patients had died. Patients were stratified according to country and MSKCC prognostic score (low or intermediate).

Eligility criteria included the presence of histologically confirmed metastatic clear cell RCC which had progressed after one systemic treatment within the previous eight months, an ECOG performance status of 0 or 1, an intermediate or low risk according to the MSKCC prognostic score and a life expectancy of at least 12 weeks.

Treatment was continued until evidence of disease progression or withdrawal from the study due to adverse events occurred. Dose reductions (to 400mg once daily and then to 400mg every other day) were permitted to manage adverse events.

Enrolment of patients took place between November 23 2003 and March 31 2005. From November 2003 until April 2005, the sponsor and investigators were unaware of the study group assignments in the evaluation of data. In January 2005, a protocol defined independent review of the status of 769 patients (384 in the sorafenib group and 385 in the placebo group) was conducted. In April 2005, a decision was made by the independent data and safety monitoring committee that study-group assignments should be revealed and that sorafenib should be offered to patients receiving placebo. The initial analysis of overall survival which is presented in the main publication[113] is based on data obtained before treatment crossover. A further analysis of overall survival was performed six months later.

The median duration of treatment (at the time of the interim analysis) was 23 weeks in the sorafenib group and 12 weeks in the placebo group. Dose intensity was not reported.

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[a] Argentina, Australia, Belgium, Brazil, Canada, Chile, France, Germany, Hungary, Israel, Italy, the Netherlands, Russia, South Africa, Ukraine, United Kingdom and United States

No supplementary additional data were identified in conference abstracts. In the company submission to NICE, effectiveness data are presented for two sub-groups of patients within the trial; those who had received previous cytokine based therapy and those who were unsuitable for such therapy. These analyses are presented as commercial in confidence and are not available in the published paper.[113]

In 2006, Ratain and colleagues reported the results of a randomised discontinuation trial (RDT) of sorafenib versus placebo in a total of 202 patients with metastatic clear cell RCC.[115] In an RDT (a study design which was developed in an attempt to assess the clinical activity of a drug whilst minimising exposure to placebo) all patients receive the study drug for an initial run-in period followed by random assignment of potential responders to either the active drug or placebo. The design creates a controlled trial without upfront randomisation and decreases the heterogeneity of randomised patients, resulting in increased statistical power with smaller patient numbers. The study initially permitted enrolment of patients (n=502) with a variety of tumour types including metastatic RCC and metastatic colorectal cancer. Early indications of activity in patients with RCC caused a refocus on this patient population and resulted in 40% of patients in the overall trial having a diagnosis of metastatic RCC. This paper [115] describes only the RCC population. The primary outcome measure was the percentage of randomly assigned patients who remained progression free at 12 weeks following random assignment. Other endpoints included progression free survival after random assignment (randomised subset only), overall PFS (from start of treatment), tumour response rate and safety. The study was designed to have 81% power to detect a drug effect that corresponded to a reduction in the progression rate from 90% to 70% 12 weeks after randomisation.

Sorafenib (400mg twice a day) was administered to all patients in a 12-week open-label run-in period after which disease status was assessed based on changes in bidimensional tumour measurements from baseline. Patients with ≥ 25% tumour shrinkage continued to receive sorafenib until disease progression or toxicity. Patients with progressive disease (≥ 25% tumour growth or other evidence of progression) discontinued treatment. Patients who had a change in tumour size of less than 25% were randomly assigned to either sorafenib (at the same dose) or matched placebo using centrally allocated allocation via a telephone randomisation system. Treatment was stopped on disease progression.

No additional supplementary data were identified either in abstract form or as part of the company submission for sorafenib.

Sunitinib

Motzer and colleagues report the results of two similar open-label, single arm trials of sunitinib as second line therapy in patients with metastatic clear cell RCC. In both trials, conducted in multiple centres in the United States and reported in 2006 [537][542], patients received treatment with sunitinib (50mg per day, self administered, orally, in repeated six week cycles (four weeks on treatment

followed by two weeks off) until evidence of disease progression, unacceptable toxicity or withdrawal of consent.

In the earlier trial (n = 63), which we refer to as Motzer and colleageues 2006a, eligible patients had a diagnosis of histologically confirmed metastatic RCC (of any subtype), evidence of failure of one cytokine-based therapy because of disease progression or unacceptable toxicity, and an ECOG status of 0 or 1[117]. Entry criteria for the larger trial (n = 105), which is referred to as Motzer and colleagues 2006b, were similar, but restricted entry to patients with histologically confirmed clear cell typology who had undergone previous nephrectomy. The primary outcome measure in both trials was objective response rate according to the RECIST criteria.[116] A later publication providing overall survival data is also available.[85]

No additional supplementary data were identified within the relevant conference abstracts or the company submission for sunitinib.

Quality assessment

Sorafenib versus best supportive care

The quality assessment of these trials is summarised in Table 9 (page 42). Both are well conducted and well reported large, multi-centre trials. In the report of the RCT of sorafenib versus placebo [113], the authors state that the final planned analysis of overall survival (which was undertaken after treatment crossover) was conducted on an intention to treat basis. It is not clear whether the unplanned analysis of overall survival (prior to treatment crossover) was also performed under these conditions. Methods for censoring in these analyses are also not provided.

The company submission to NICE from Bayer includes commercial in confidence sub-group analyses from this trial. Within this analysis participants have been divided into two groups; those who have received prior treatment with cytokine based immunotherapy and those who were unsuitable for such therapy. For several reasons, we have not considered the results of this analysis further. The clinical basis underlying an expected difference in response to treatment in these two groups of people is not immediately evident. It is also not clear whether the subgroups were conceived a priori and the sample size calculations were based on the entire trial population meaning that the number of patients deemed unsuitable for treatment with immunotherapy is small.

In order to be considered eligible for the study, patients were required to have disease that had progressed after one systemic treatment within the previous eight months; in 17% of patients the nature of this systemic therapy is not reported in the paper. The company submission suggests that these individuals were unsuitable for treatment with cytokines; whether sorafenib represents second line therapy in this group of patients is therefore not clear.

It appears from the details of the sample size calculation provided in the RDT that the investigators were aiming to recruit 50 randomly assigned patients to each group. In practice a total of 65 patients were randomly assigned in the study.

Sunitinib

We have applied a similar list of quality assessment criteria to these two trials as used in other critical appraisals in this assessment (Table 9, page 42), with obvious exceptions (e.g. methods of randomisation and concealment etc), they appear to be well designed and reported.

Population baseline characteristics

Sorafenib versus best supportive care

In the study by Escudier and colleagues[113], population characteristics at baseline were well balanced between the groups in terms of demographic factors (age and gender distribution) and disease status (ECOG performance status and MSKCC prognostic risk score, the proportion of patients with multiple metastatic sites, the location of metastases, previous systemic therapy, the proportion of patients with previous nephrectomy and the median duration of disease) (Table 29). Approximately half the people in the trial had an ECOG performance status of 0, most (83%) had had previous cytokine-based treatment and the majority (94%) had undergone previous nephrectomy. In order to be considered eligible for the study, patients were required to have disease that had progressed after one systemic treatment within the previous eight months; in 17% of patients the nature of this systemic therapy is not reported in the paper.

A similar group of patients were entered into the RDT[115], and again the groups were well balanced at baseline. There were slightly more females in the placebo group but this difference was not statistically significant.

Sunitinib

As described above, the two trials of sunitinib [85,116,117] included patients with similar baseline characteristics, the main differences between trials being the proportion of patients with clear cell RCC and the proportion of patients with previous nephrectomy. (Table 29, page 87)

Comparability of baseline population characteristics between trials

Participants in all four trials were similar in terms of age, gender distribution and disease status. Approximately 50% of people in all four trials had an ECOG status of 0 and a favourable prognostic score according to MSKCC criteria. Cytokine-based therapies had failed to halt disease progression in the majority of patients and most had undergone a prior nephrectomy. Almost all patients had two or more sites of metastatic disease with the lung being the most common site for metastases in all trials.

Table 29: Baseline population characteristics: sorafenib and sunitinib versus best supportive care as second line therapy

Study	**Escudier, et al. 2007[113]**		**Ratain, et al. 2006[115†]**		**Motzer, et al. 2006b[85,116]**	**Motzer, et al. 2006a[117]**
Intervention	**Sorafenib**	**Placebo**	**Sorafenib**	**Placebo**	**Sunitinib**	**Sunitinib**
Number randomised	**451**	**452**	**32**	**33**	**106**	**63**
Diagnosis	Metastatic clear cell renal-cell carcinoma		Metastatic renal-cell carcinoma		Metastatic clear cell renal-cell carcinoma	Metastatic renal-cell carcinoma
Age, median (range) yrs	58 (19-86)	59 (29-84)	58 (32-76)	60 (23-74)	56 (32-79)	60 (24-87)
Male	315 (70)	340 (75)	21 (64)	26 (81)	67 (63)	43 (68)
Median duration of disease, yrs (range)	2 (<1-19)	2 (<1-20)	3.3 (0-21.2)	2.8 (0-11.7)	NR	NR
ECOG performance status						
0	219 (49)	210 (46)	18 (56)	18 (55)	58 (55)	34 (54)
1	223 (49)	236 (52)	14 (44)	15 (45)	48 (45)	29 (46)
2	7 (2)	4 (1)	0	0	0	0
Data missing	2 (<1)	2 (<1)	0	0	0	0
MSKCC risk factors						NR
0 (favourable)	233 (52)	236 (52)	13 (41)	14 (42)	61 (57.5)	
1-2 (intermediate)	218 (48)	223 (49)	18 (56)	15 (45)	41 (38.7)[‡]	
≥ 3 (poor)	0	0	0	3 (9)	4 (3.8)[§]	
Missing data	0	1 (<1)	1 (3)	1 (3)	0	
Previous systemic therapy						
Cytokine-based	374 (83)	368 (81)	26 (81)	28 (85)	NR	NR
Interleukin-2	191 (42)	189 (42)	NR	NR	50 (47)	19 (30)
Interferon	307 (68)	314 (69)	NR	NR	47 (44)	35 (56)
Both interleukin-2 and interferon	124 (27)	135 (30)	NR	NR	9 (9)	9 (14)

Radiotherapy	124 (27)	108 (24)	9 (28)	11 (33)	20(19)	25 (40)
Number of patients with a previous nephrectomy	422 (94)	421 (93)	29 (91)	29 (88)	106 (100)	58 (92)
Number of metastatic sites						
1	62 (14)	63 (14)	8 (25)	4 (12)	13 (12)	8 (13)
2	131 (29)	129 (29)	7 (22)	15 (45)	38 (36)	NR
>2	256(57)	258 (57)	17 (53)	14 (42)	55 (52)	55 (87)
Missing data	2 (<1)	2 (<1)	0	0	0	0
Sites of metastases						
Lung	348 (77)	348 (77)	28 (88)	23 (70)	86 (81)	52 (81)
Liver	116 (26)	117 (26)	5 (16)	10 (30)	29 (27)	10 (16)
Bone	NR	NR	NR	NR	27 (26)	32 (51)
Lymph nodes	NR	NR	14 (44)	16 (48)	62 (59)	NR
Kidney	NR	NR	12 (38)	15 (45)	NR	NR
Histology type						
Clear cell	451 (100)*	452 (100)*	27 (84)	25 (76)	106 (100)	55 (87)
Papillary	0	0	0	3 (9)	0	4 (6)
Sarcomatoid variant	0	0	1 (3)	2 (6)	0	1 (2)
Missing data	0	0	4 (13)	3 (9)	0	3 (5)

Data presented as number (%) of patients, unless otherwise specified.

* Although it was a criteria for entry into this study that patients must have a diagnosis of clear cell RCC, the authors state in the paper that 99% of patients had clear cell RCC – no further details are provided. † Data presented are from the randomization period only. ‡ Number (%) of patients with MSKCC score =1. § Number (%) of patients with MSKCC score ≥2.

3.2.5.2. Assessment of clinical effectiveness

Overall survival (Table 30)

Sorafenib versus best supportive care

Overall survival (defined as the time between the date of randomisation until the date of death) was the primary endpoint in the RCT of sorafenib versus placebo.[113] In the analysis performed prior to treatment crossover, 220 of the 540 deaths required for the comparison to be adequately powered had occurred; 97 deaths in the sorafenib group and 123 deaths in the placebo group. Median actuarial overall survival had not been reached in the sorafenib group and was 14.7 months in the placebo group with a hazard ratio of 0.72 (95% CI 0.54 to 0.94; p = 0.02). This result was not considered statistically significant as it did not reach the O'Brien-Fleming threshold of 0.0005.

Overall survival was not an outcome measure in the RDT.[115]

Sunitinib

Overall survival was 23.9 months in the larger trial of 105 pts (Motzer and colleagues 2006b) (95% CI 14.1 to 30.7 months)[85,116] and was 16.4 months (95% CI 10.8 to not yet attained) in the smaller trial (n=63) (Motzer and colleagues 2006a).[117] Interpretation of these results is difficult due to the lack of a comparator group.

Table 30: Summary of overall survival: sorafenib and sunitinib versus best supportive care as second line therapy

Study	Intervention	n	median OS (months)	HR	95% CI for HR	p value
Escudier, et al. 2007[113]	sorafenib	451	not reached	0.72	0.54 to 0.94	p = 0.02
	placebo	452	14.7			
Motzer, et al. 2006a[117]	sunitinib	63	16.4 95% CI 10.8 to not attained	NA	NA	NA
Motzer, et al. 2006b[85,116]	sunitinib	105	23.9 95% CI 14.1 to 30.7			

Progression free survival (Table 31)

Sorafenib versus best supportive care

Escudier and colleagues determined disease progression on the basis of computed tomography (CT) or magnetic resonance imaging (MRI), clinical progression or death. Imaging studies were performed every eight weeks and assessed according to the RECIST criteria. Investigators and independent radiologists who were unaware of treatment assignments assessed progression free survival. No information on the method of censoring of values is provided. Median progression free survival (defined as the time from the date of randomisation to the date of progression) based on 769 patients at the first pre-planned interim analysis was 5.5 months in the sorafenib group and 2.8 months in the placebo group; it is unclear from the paper, but we assume that this analysis was based on assessment by independent radiologists. Investigator-assessed PFS at the same time point was 5.9 months in the sorafenib group and 2.8 months in the placebo group, with a hazard ratio of 0.44 (95% CI 0.35 to 0.55; p<0.001).

A similar result was obtained at treatment crossover when investigator-assessed progression free survival in 903 patients was found to be 5.5 months in the sorafenib group and 2.8 months in the placebo group (hazard ratio 0.51; 95% CI 0.43 to 0.60; p<0.001). It is unclear why the authors have chosen to present results based on investigator assessment rather than assessment by independent radiologists or if there were any differences in the results obtained by the two methods of assessment.

In the RDT of sorafenib versus placebo,[115] at 12 weeks post randomisation (24 weeks from study entry), there was a statistically significant (p = 0.0077) difference in the proportion of patients in whom disease progression was evident between groups (50% of patients treated with sorafenib vs. 82% treated with placebo). Median PFS from the date of randomisation was also significantly longer in the sorafenib group (24 weeks vs. 6 weeks; p= 0.0087).

Sunitinib

The two trials of sunitinib produced similar results for progression free survival. In the smaller trial (Motzer and colleagues 2006a), median progression free survival was 8.7 months (95% CI 5.5 to 10.7 months)[117]. Based on independent third party assessment of response, median progression free survival in the larger trial (Motzer and colleagues 2006b) [85,116] was 8.8 months (95% CI 7.8 to 13.5 months). Interpretation of these results is difficult due to the lack of a comparator group.

Table 31: Summary of progression-free survival: sorafenib and sunitinib versus best supportive care as second line therapy

Study	Intervention	n	median PFS (months)	HR	95% CI for HR	p value
Escudier, et al. 2007[113]	**Assessment by independent radiologists – first planned interim analysis**					
	sorafenib	384	5.5	0.44	0.35 to 0.55	p<0.001
	placebo	385	2.8			
	Assessment by investigators – first planned interim analysis					
	sorafenib	384	5.9	NR	NR	p<0.001
	placebo	385	2.8			
	Assessment by investigators – unplanned analysis prior to treatment crossover					
	sorafenib	451	5.5	0.51	0.43 to 0.60	p<0.001
	placebo	452	2.8			
Motzer, et al. 2006a[117]	sunitinib	63	8.7 (95% CI 5.5 to 10.7)	NA	NA	NA
Motzer, et al. 2006b[85,116]	sunitinib	105	8.8 (95% CI 7.8 to 13.5)	NA	NA	NA

Tumour response (Table 32)

Sorafenib versus best supportive care

In the RCT of sorafenib and placebo [113], at the initial planned interim analysis, tumour response was assessed (by independent reviewers according to RECIST criteria) in 672 patients although data were missing for 87 (approximately 13%). Data were available for 297 patients in the sorafenib group and 288 in the placebo group. In the sorafenib group, seven patients (2%) had a partial response, 261 (78%) patients had stable disease and 29 patients (9%) had progressive disease. In the placebo group, no patients were assessed as having a partial response, 186 (55%) had stable disease and 102 patients (30%) had progressive disease. At the unplanned analysis prior to treatment crossover, according to blinded investigator assessment, one patient in the sorafenib group exhibited a complete response, 43 had a partial response and 333 had stable disease. In the placebo group the corresponding figures were none, eight and 239. Significantly ($p<0.001$) more patients in the sorafenib group than the placebo group had a complete or partial response.

Tumour response was not an outcome measure in the RDT.[115]

Sunitinib

In the two trials of sunitinib, objective tumour response, defined according to RECIST, was the primary end point. Assessments of tumour response were made using CT or MRI and bone scans (if bone metastases were present at baseline) at least after every two cycles (the assessment intervals were slightly different in the two trials) until the end of treatment. In the smaller trial (n=63)[117], partial responses were achieved in 25 patients (40%; 95% CI 28% to 53%). Best response of stable disease for three or more months was observed in a further 17 patients (27%). The remaining patients (n=21; 33%) had either progressive or stable disease of less than three months duration or were not assessable. In the larger trial (Motzer and colleagues 2006b)[116], tumour response was assessed both by treating physicians and a third party imaging laboratory (with two radiologists). According to third party assessment of images, 33% of patients (n= 35) had a partial response, and a further 31 patients (30%) had stable disease for three or more months. The remainder (n=39; 37%) were assessed as having progressive disease or stable disease for less than three months. These results are difficult to interpret as there was no comparator group.

Table 32: Summary of tumour response: sorafenib and sunitinib versus best supportive care as second line therapy (presented as n (%) of patients)

Study	Intervention	n	Complete response	Partial response	Stable disease	Progressive disease	Not assessed
Escudier, et al. 2007[113]*	sorafenib	451	1 (<1)	43 (10)	333 (74)†	56 (12)	18 (4)
	placebo	452	0	8 (2)	239 (53)†	167 (37)	38 (8)
Motzer, et al. 2006a[117]	sunitinib	63	0	25 (40)	17 (27)‡	21 (33) pts had either progressive disease, stable disease for less than three months or were not assessable	
Motzer, et al. 2006b[85,116]	sunitinib	105	0	35 (33)	31 (30)‡	39 (37) pts had either progressive disease, stable disease for less than three months or were not assessable	

* results from blinded investigator assessment of images, † stable disease defined as stable disease for at least 28 days, ‡ stable disease defined as stable disease for three months or more

Health related quality of life

Sorafenib versus best supportive care

In the RCT of sorafenib versus placebo [113], the Functional Assessment of Cancer Treatment – General questionnaire (FACT-G) and the Functional Assessment of Cancer Therapy – Kidney Symptom Index

(FKSI) were administered to assess the impact of treatment on HRQoL (see section 2.6, page 26). Assessments were made every six weeks for the first 24 weeks and then every eight weeks. Subjects completed the questionnaires prior to seeing the physician. No further assessments were made after withdrawal from treatment. There was no significant difference between the placebo and sorafenib groups in mean FACT-G physical well-being score nor any numeric or statistical difference in mean FKSI-10 total score between groups over the first 30 weeks of treatment ($p = 0.83$ and $p = 0.98$ respectively).

However, there were statistically significant changes in some of the individual items of the FKSI-15 in patients receiving sorafenib compared with those receiving placebo in the first 30 weeks of treatment. These included less coughing ($p < 0.0001$), fewer fevers ($p = 0.0015$), a greater ability to enjoy life ($p=0.0119$) and less worry about their disease ($p=0.0004$). Fewer patients in the placebo group reported being bothered by the side effects of treatment ($p<0.0001$). There was no significant difference between groups in terms of patients' perception of fatigue, quality of sleep, pain, weight change or energy levels.

HRQoL was not assessed in the RDT.[115]

Sunitinib

EQ-5D and the Functional Assessment of Chronic Illness Therapy – Fatigue scale (FACIT-fatigue) were used to assess HRQoL in the smaller trial of sunitinib (Motzer and colleagues 2006a).[117] EQ-5D questionnaires were administered on days 1 and 28 of each cycle, and the FACIT-fatigue questionnaire was completed on day 1 and then weekly for cycles 1 to 4. Compliance with questionnaires at baseline and subsequent visits was high (at or above 90% at each visit for each instrument). Assessable baseline questionnaires were received from 60 patients and compliance with subsequent assessments was high. Mean and median health state visual analogue scale scores indicated that the study population's quality of life before treatment was similar to that of an age-matched US general population. Mean and median health state visual analogue scores were similar to baseline scores throughout the 24 weeks of treatment.

Valid baseline questionnaires for the FACIT-fatigue scale were received from 62 patients. Mean and median baseline scores for the study population were similar to scores of a population with cancer (but no anaemia) but lower than that of a general US population. Median and mean fatigue scores were similar to baseline scores throughout 24 weeks of treatment, although the authors did notice a mild and reversible effect of treatment on fatigue levels.

These results are not easy to interpret or extrapolate as there was no comparator group.

Indirect comparison of sorafenib versus sunitinib versus best supportive care as second line therapy

Although we were able to locate four trials relevant to this comparison, all of which included patients with similar baseline characteristics, because there was no common treatment arm we were unable to consider an indirect comparison of sorafenib, sunitinib and best supportive care.

Adverse events

In all trials, adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0[115,117] or version 3[113,116]. Table 61 in Appendix 5 (page 230) shows adverse events of any grade reported during the course of all four studies. In Table 33 (page 95) only those adverse events classified as grade 3 or above are included. Criteria for reporting adverse events were slightly different in the four trials. The TARGETs trial reports all adverse events of any grade occurring in at least 10% of patients, with a breakdown of grade 2 events and all adverse events of grade 3 or 4 occurring in at least 2% of patients[113] In the RDT, all adverse events occurring in at least 10% of patients in the total safety population are provided (no comparison with placebo). In the two phase II trials of sunitinib only adverse events that were considered to be treatment related occurring in 5% and 20% of patients respectively were reported together with selected laboratory abnormalities.[116,117] The data available from the latter two studies is therefore limited and reference should also be made to section 3.2.2.2 where full details of the adverse events reported in the RCT of sunitinib in first line treatment are discussed.

Table 33: Adverse events (grade 3 or 4): sorafenib and sunitinib versus best supportive care as second line therapy

Study	**Escudier, et al. 2007[113] b**		Ratain, et al. 2006[115] c	**Motzer, et al. 2006b [116] d**	**Motzer, et al. 2006a [117] e**
Intervention	**sorafenib**	**placebo**	**sorafenib**	**sunitinib**	**sunitinib**
n	**451**	**452**	**202**	**106**	**63**
Blood/bone marrow			16 (8)		
Decreased haemoglobin	12 (3)	20 (4)	14 (7)	NR	NR
Cardiovascular general			71 (35)		
Hypertension	16 (4)	2 (<1)[f]	62 (31	6 (6)	1 (2)
Ejection fraction decline	NR	NR	NR	NR	1 (2)
Dermatology / skin			34 (17)		
Hand/foot skin reaction	25 (6)	0[f]	27 (13)	NR	NR
Rash / desquamation	4(1)	1(<1)	5 (2)	NR	NR
Alopecia	1 (<1)	0	NR	NR	NR
Dermatitis	NR	NR	NR	NR	1 (2)
Pruritus	1 (<1)	0	NR	NR	NR
Constitutional symptoms			18 (9)		
Weight loss	3 (<1)	0	5 (2)	NR	NR
Fatigue	22 (5)	16 (4)	13 (6)	12 (11)	7 (11)
Other symptoms	6 (1)	6 (1)	NR	NR	NR
Gastrointestinal			28 (14)		
Anorexia	3 (<1)	5 (1)	6 (3)	1 (1)	0
Diarrhoea	11 (2)	3 (1)	8 (4)	3 (3)	2 (3)

Nausea	3 (<1)	3 (1)	0	0	2 (3)
Vomiting	4 (1)	6 (1)	0	0	2 (3)
Dyspepsia	NR	NR	NR	1 (1)	0
Stomatitis	NR	NR	0	5 (5)	1 (2)
Mucosal inflammation	NR	NR	NR	1 (1)	NR
Constipation	3 (1)	3 (1)	0	NR	0
Haemorrhage			8 (4)		
Hepatic			10 (5)		
Infection/febrile neutropenia			10 (5)		
Infection without neutropenia	NR	NR	10 (5)	NR	NR
Metabolic / laboratory			35 (17)		
Hyperglycaemia	NR	NR	6 (3)	NR	NR
Hypophosphataemia			14 (7)		
Neurology / sensory neuropathic	2 (<1)	3 (1)	12 (6)		
Pain			25 (12)		
Extremity pain	0	0	NR	1 (1)	0
Abdominal pain	7 (2)	9 (2)	0	NR	NR
Headache	1 (<1)	2 (<1)	0	NR	NR
Joint pain	7 (2)	1 (<1)	0	NR	NR
Bone pain	**3 (1)**	**15 (3)**	NR	NR	NR
Tumour pain	13 (3)	8 (2)	NR	NR	NR
Pulmonary			21 (10)		
Cough	1 (<1)	1 (<1)	0	NR	NR

Dyspnoea	16 (4)	11 (2)	18 (9)	NR	NR
Other pulmonary symptoms	NR	NR	7 (3)	NR	NR

Data presented as number (%) of patients. [b] Grade 3 or 4 adverse events that occurred in at least 2% of patients. [c] Grade 3 or 4 adverse events based on the incidence of adverse events of any grade occurring in 10% or more of patients in the total safety population. [d] Grade 3 or 4 ***treatment-related*** adverse events that occurred in at least 20% of patients. [e] Grade 3 or 4 ***selected treatment-related*** adverse events that occurred in at least 5% of patients. Figures [f]indicate a statistically significant difference between groups

Sorafenib versus best supportive care

In the TARGETs trial[113], the most common adverse events of any grade were fatigue (in 37% and 28% of patients treated with sorafenib and placebo respectively), diarrhoea (in 43% and 13% of patients), rash or desquamation (in 40% and 16%), nausea (in 23% and 19%), hand-foot skin reaction (in 30% and 7%) and alopecia (in 27% and 3%). There was a statistically significant difference between groups in the proportion of patients reporting grade 2 hypertension, weight loss, diarrhoea, hand-foot skin reaction, rash, alopecia and pruritus; these events were all more common in the sorafenib group. The difference remained significantly different for hypertension and hand-foot skin reaction when grade 3 and 4 adverse events were considered. Grade 3 or 4 bone pain was reported significantly more often by patients in the placebo group. In addition to the events described in Table 33 (page 95), cardiac ischaemia or infarction occurred in 12 patients (3%) in the sorafenib group and 2 patients in the placebo group (1%); this difference was also statistically significant ($p = 0.01$). Of these events, 11 (including two deaths in the sorafenib group and 1 death in the placebo group) were considered to be serious adverse events associated with treatment. Serious adverse events leading to hospitalisation or death were reported in 154 patients (34%) in the sorafenib group (46 deaths;10%) and in 110 patients (24%) in the placebo group (25 deaths; 6%) ($p<0.01$). The most frequent drug-related serious adverse event was hypertension (in 1% and 0% of sorafenib and placebo patients respectively).

In the RDT of sorafenib versus placebo, the most common treatment emergent adverse events were fatigue (73% of patients), rash or desquamation (66%), hand-foot skin reaction (62%), pain (58%) and diarrhoea (58%). The most common grade 3 or 4 adverse event was hypertension which was observed in 31% of patients. Nine patients discontinued drug treatment as a result of unacceptable toxicity. There were no adverse event-related deaths in the trial.

Sunitinib versus best supportive care

A similar adverse event profile is reported in both trials,[116,117] although these are described as "selected treatment related adverse events" and full information all adverse events experienced within the trials is not available. The most commonly reported adverse events were fatigue (38%), diarrhoea (24%), nausea (19%), dyspepsia (19%) and stomatitis (16%) in one trial [117] and fatigue (28%), diarrhoea (20%), dyspepsia (16%), hypertension (16%) and hand-foot syndrome (15%) in the other [116].

Decline in ejection fraction was also observed in both trials (8 patients; 4.7% [116] and 7 patients; 11% [117]), although it is unclear whether this represents incidental observation or the results of active monitoring. The decline was sufficient to warrant removal from the study in four patients.[117] One trial [116] reports a total of 31 deaths, 10 of these within 28 days of their last dose of sunitinib; one of these (myocardial infarction) was considered to be possibly related to the study medication.

Summary of safety data

From the data reported in these trials, treatment with sorafenib appears to be associated with an increased frequency of hypertension, hand-foot skin reaction and some gastrointestinal events such as diarrhoea. Although some of the events were classed as grade 3 (severe and undesirable) and grade 4 (life threatening or disabling), events of this severity occurred in a small proportion of patients (e.g. 4% and 6% for hypertension and hand-foot skin reaction in the TARGETs trial). Grade 3 hypertension is defined as needing more than one drug for treatment or more intensive treatment than used previously; hypertension with life threatening consequences (e.g. hypertensive crisis) is the definition of grade 4 hypertension.

As randomised clinical trials are not designed to collect data on rare adverse events, we briefly reviewed additional literature obtained from the results of our initial, and updated literature searches to identify any further safety concerns.

A systematic review of toxicities associated with sorafenib, sunitinib and temsirolimus in phase I, II and III clinical trials found that between 1 and 16% of patients experienced grade 3 or 4 adverse events. The most commonly reported grade 3 and 4 adverse events associated with sorafenib treatment across all trials were lymphopenia (13%), hypophosphatemia (13%), elevated lipase (12%), mucositis (6%) and hand foot syndrome (6%).[120]

In an expanded access trial of sorafenib in the US and Canada (n=2488), the following adverse events were experienced in patients receiving sorafenib as first line treatment (n=1239) at a frequency of > 2%: hand-foot skin reaction (7.7%), fatigue (4.7%), hypertension (3.8%), rash or desquamation (5.2%), dehydration (2.9%), diarrhoea (2.6%) and dyspnoea (2.6%). These data suggest an adverse event profile similar to that reported in the phase III trial.[126]

We identified a systematic review and meta-analysis of the incidence and risk of hypertension with sorafenib in patients with cancer conducted by Wu and colleagues and published in February 2008 in Lancet Oncology.[121] They identified nine studies in which 3,567 patients with RCC or other solid tumours had received sorafenib, including the TARGETs trial [113] and the RDT [115] described above. The overall incidence of all-grade hypertension amongst patients receiving sorafenib was 23.4% (95% CI 16.0 to 32.9%) with 5.7% (95% CI 2.5 to 12.6%) of patients experiencing grade 3 or 4 hypertension. The authors estimate the relative risk for all-grade hypertension in patients receiving sorafenib as 6.11 (2.44 to 15.32; $p<0.001$) using data from two RCTs (n=1089). As with all meta-analyses, this analysis is limited by the quality of the data in the contributing studies. The authors note possible areas of ambiguity in the grading of hypertension and the lack of data on baseline measurement of blood pressure, both of which may have influenced the results. Although a large proportion of the patients included in the analysis were from the expanded access programme where

measurement of hypertension in the community may not have been as precise as in laboratory conditions, the relative risk was calculated using only data allowing a comparison between events reported with and without sorafenib treatment.

A similar systematic review and meta-analysis of the incidence and risk of hand-foot skin reaction with sorafenib treatment, also published in 2008, found a 33.8% (95% CI 24.5 to 44.7) incidence of all-grade hand-foot skin reaction in patients treated with sorafenib. The relative risk of developing all-grade hand-foot skin reaction with sorafenib was 6.6 (95% CI 3.7 to 11.7; $p<0.001$).[127]

Comparison of the safety profile of sunitinib with best supportive care is not possible from the phase II trials. Sunitinib treatment was most frequently associated with fatigue, diarrhoea, nausea, hypertension and hand-foot skin reaction, although whether these events were as a result of the treatment or the disease process is unclear. Further discussion of the adverse events associated with sunitinib is provided in section 3.2.2.2 (page 51).

Subgroup analyses

Neither of our protocol-defined subgroup analyses was possible for this comparison as none of the identified trials provide relevant data.

3.2.5.3. Overall conclusion: sorafenib and sunitinib compared with best supportive care as second line therapy

From the limited clinical data available, second line therapy with sorafenib appears to have clinically relevant and statistically significant advantages over treatment with placebo (best supportive care) in terms of overall survival, progression free survival and tumour response. Median progression free survival was approximately doubled from 2.8 months with best supportive care to 5.5 months with sorafenib (HR 0.44; 95% CI 0.35 to 0.55).

Data on adverse events suggests that treatment with sorafenib is associated with an increased risk of hypertension and hand-foot skin reaction.

Both trials of sorafenib were conducted in patients with metastatic clear cell RCC, the majority of whom had undergone previous nephrectomy and were classified as having a favourable or intermediate prognosis according to MSKCC criteria. However, whether these results can be extrapolated to patients with other baseline characteristics (e.g. non clear cell RCC or features of poor prognosis) is not clear.

We were unable to identify any comparative data for sunitinib as second line therapy. The results from the two single-arm phase II trials are difficult to interpret or extrapolate. Using the placebo arm

of the sorafenib trial [113] as an informal comparator it would appear that sunitinib may be efficacious in this population. Although very limited, the safety data for patients treated with sunitinib as second line therapy do not appear to differ from that obtained in first line trials.

Formal indirect comparison of sorafenib and sunitinib was not possible in this assessment as there was no treatment arm common to all trials.

4. Assessment of Cost-Effectiveness

4.1. Aim

The aim of this section is to assess the cost-effectiveness of sunitinib, sorafenib, bevacizumab plus IFN, and temsirolimus, against relevant comparators for licensed indications. The assessment of cost-effectiveness comprises a systematic review of the literature on the cost-effectiveness of these drugs for RCC, a review of the manufacturer submissions on cost-effectiveness to NICE, and the presentation of PenTAG estimates of cost-effectiveness. An outline discussion is presented on the literature searching undertaken in the general literature on renal cancer, covering the costs associated with treatment for RCC, health-related quality-of-life (health state values) in RCC, and the modelling of disease progression in RCC.

4.2. Cost-effectiveness: Systematic review of economic evaluations

4.2.1. Methods

A systematic literature search was undertaken to identify economic evaluations of bevacizumab, sorafenib tosylate, sunitinib and temsirolimus, which met the inclusion criteria for the scope of the current report.

Appendix 1 (page 208) reports details of the search strategy used and databases searched. Manufacturer submissions to NICE were reviewed to identify additional studies. Two reviewers (CG and MH) independently examined all titles and abstracts. Full texts of any potentially relevant studies were obtained. The relevance of each paper was assessed independently (CG and MH) according to the inclusion and exclusion criteria and any discrepancies resolved by discussion.

4.2.2. Results

The literature search did not identify any published economic evaluations meeting the inclusion criteria. The search identified six abstracts meeting the inclusion criteria[104 128-132]; three reporting on sunitinib versus BSC[104,128 129], and three reporting on sorafenib versus BSC or IFN.[130-132] There is insufficient detail in the abstracts identified to undertake a critical appraisal of the methods used. However, a summary of study characteristics (Table 34), and a short summary of the literature (abstracts) is reported below.

Table 34: Summary of abstracts reporting cost-effectiveness analysis

Study / Characteristics	Gao, et al. 2006[132]	Maroto, et al. [131]	Jaszewski, et al [130]	Aiello, et al[129]	Contreras-Hernandez, et al[128]	Remák, et al[104]
Treatments	sorafenib vs. BSC	sorafenib vs. BSC	sorafenib vs. BSC	sunitinib vs. BSC, second line	sunitinib vs. BSC, second line	sunitinib vs. interferon-alpha, first- and second-line
Model type	Markov	Markov	Markov	Markov	Markov	Markov
Time Horizon	Life-time	Life-time	Life-time	Not stated	10-year	5yr & 10yr
Perspective	USA	Spain	Canada	Argentina	Mexico	USA
Effectiveness data (stated source)	Phase III RCT [113]	unnamed clinical trial	Phase III RCT [113]	unnamed clinical trial and US Medicare database	unnamed clinical trials	Phase III study [111]
Results ICER	$75,354 per life-year gained	37,667 euros per QALY	$36,046 CDN per life-year gained	cost of one progression-free month, one life-year saved, one QALY AR$9,596, AR$39,518, AR$53,445	$35,238 per QALY	First line: $7,769, $7,782 per progression-free month over 5 and 10 years. Second-line: $67,215 per life-year gained, $52,593 per QALY

4.2.3. Summary: Cost-effectiveness literature (abstracts)

The economic evaluations of sunitinib comprise two abstracts[128,129] reporting findings for second-line treatment only (versus BSC), and one study[104] reporting a model, with subsequent results, for both first-line treatment and second line treatment. The three economic evaluations on sorafenib are for first-line treatment (versus BSC), and the abstracts report a common analytical approach applied in three different country settings (USA, Canada, Spain).

All identified cost-effectiveness abstracts report the use of decision-analytic models to estimate cost-effectiveness. All use a stated Markov modelling framework. Five of the abstracts state that models are structured around the three primary health states of progression free survival, progressed disease and death. All models appear to use effectiveness data from clinical trials on difference between

progression free survival and/or overall survival between intervention and control arms, although information on source is not clear in three of the six abstracts.

Four studies[104,128,129,131]report estimates of cost per QALY, but only one study (Remak and colleagues) provides information on health state utilities.[104]

4.3. Cost-effectiveness: Review of related literature

4.3.1. Health-related quality-of-life (HRQL)

We searched the literature to inform on the health state values (utilities) for states associated with RCC and to identify studies informing on summary (preference) measures of health-related quality of life (HRQL): see search strategy in Appendix 1, page 208. No published studies were identified. Two conference abstracts were identified[97,104], but these contained limited information on which to assess methods.

Remak and colleagues[104] report a cost-effectiveness analysis for sunitinib versus IFN (see Table 34, page 103), and in material supporting their published abstract provide summary statistics for health states used in the analysis. However, there is no detail published to support the data used. Remak and colleagues refer to EQ-5D data collected in clinical trials, presumably with EQ-5D descriptions used to estimate health state values from published tariffs, but the trials/studies cited to support health state utilities used do not report EQ-5D data.

Remak and colleagues report the following health state values; utility during sunitinib treatment = 0.72, utility during 2-week rest period when on sunitinib treatment = 0.76, utility during IFN treatment = 0.71, utility on termination of first-line treatment = 0.63, utility during 2nd line treatment = 0.63, utility on termination of 2nd line treatment=0.55). These data have no published foundation (stated in one slide of conference presentation).

The abstract by Parasuraman and colleagues[97] reports health state values derived as part of an RCT of temsirolimus, in patients with a poor prognosis. The abstract (supporting materials) presents baseline 'median' EQ-5D values by treatment group; temsirolimus 0.689, IFN 0.656, temsirolimus plus IFN 0.689. Health state utility values are also reported for health states defined by the trial; baseline 0.689, relapse 0.587, toxicity 0.585, health state without symptoms or toxicity 0.689. It is assumed here that these values are median values, but given there is no supporting detail, these data should be treated with some caution, as is the case for data in the study by Remak and colleagues.[104]

4.3.2. Treatment cost / resource use

To inform on the resource use and costs associated with treatment, medical management and best supportive care in RCC, a literature search was undertaken (see search strategy in Appendix 1, page 208). There were no studies identified that reported against these issues. We note that in one of the manufacturer submissions to NICE, a reference is used to inform on cost for best supportive care in RCC. However, this reference is reporting the cost of hospital and hospice care in progressive disease for women with stage IV breast cancer in the UK[133].

4.3.3. Modelling methods for RCC

To inform on the methods available to model disease progression and cost-effectiveness in RCC, a literature search was undertaken (see search strategy in Appendix 1, page 208). There were no studies identified that reported methods for modelling treatment in RCC, or cost effectiveness analysis (other than abstracts already noted in section 4.2 - Table 34, page 103). A number of studies were identified that reported on the use of survival analysis to consider progression of disease in renal cancer (and RCC). However these were predominantly related to consideration of disease progression before and after nephrectomy, and not relevant for the current research questions.

4.4. Cost-effectiveness: Review of manufacturer submissions to NICE

4.4.1. Methods

The cost-effectiveness models reported in the manufacturer submissions were assessed against the NICE reference case,[134] and are critically appraised using the framework presented by Philips and colleagues[135], who have synthesized the literature on the evaluation of decision analytic models in a health technology assessment context to present guidelines for good practice. A summary of the reviews is presented below, with additional detail provided in Appendix 6 (page 232).

4.4.1.1. Sunitinib (manufacturer analysis/model)

Summary of industry submission

In their submission to the NICE technology appraisal process, the manufacturer of sunitinib (Pfizer) presents cost-effectiveness analyses for sunitinib compared to IFN in first-line use, and sunitinib versus BSC in second-line use, in people with advanced RCC. The submission uses a model-based approach to estimate cost-effectiveness. The modelling framework is similar in each case, but has different data inputs.[136]

Pfizer also estimate the cost-effectiveness of bevacizumab plus IFN versus IFN alone (for first-line use), and sorafenib versus BSC (for second-line use). Pfizer use these estimates for comparative purposes, and do not present head-to-head comparisons of these alternative treatments with sunitinib.

The cost-effectiveness model, written in Microsoft Excel®, comprises three health states: progression-free survival (PFS), progressive disease (PD) and death. The model uses a lifetime time horizon, and a short model cycle (first line 0.01 years [4-days] per cycle; second line variable cycle lengths, 1 – 10 weeks). Patients start in PFS in both models. Modelling uses survival analysis, employing clinical effectiveness data from a RCT (1st line) and other sources (2nd line), to model survival and disease progression over time. No subgroup analyses are presented in the submission.

In the CEA for first-line use, much of the data used is from the Phase III RCT of sunitinib versus IFN.[111] The model uses a patient population defined as in this RCT, and for baseline disease progression (IFN alone), uses Weibull survival curves, modelled from trial data.[111] To model differences between treatment (sunitinib) and controls, the analysis applies relative measures of treatment effectiveness (hazard ratios) from the RCT. In the sensitivity analysis the submission explores alternative methods for survival analysis, and the estimation of treatment effects.

In the analysis for first-line use, Pfizer assume that patients receive sunitinib or IFN until disease progression (PD state), and following progression patients receive BSC (second line drugs are not part of the analysis). The analysis uses data on health state utilities derived from EQ-5D data collected in the RCT reported by Motzer and colleagues (2007),[111] but not reported in the trial paper, with different utility values by treatment and health state (sunitinib/PFS=0.77; IFN/PFS=0.79; sunitinib/PD=0.72; IFN/PD=0.69). The resource use and cost data cover drug costs, drug administration costs, medical management, an allowance for the mean cost of differences in expected adverse events, and costs associated with ongoing BSC. Drug costs are adjusted according to RCT data on dose intensity (e.g. first line drug cost for sunitinib weighted by 86.4%).

For second line use of sunitinib (vs. BSC) the model uses clinical data from multiple sources, applying data for sunitinib and BSC from separate sources. For sunitinib, data are from Pfizer trial RTKC-0511-014, a multi-centre phase II single-arm study,[117] assessing the efficacy and safety of sunitinib in second line treatment. For BSC, the submission uses a pooled analysis of data from multiple sources. In the sunitinib treatment arm, patients take sunitinib until progression, then switch to BSC. In the BSC arm, patients receive BSC whilst alive. Survival analysis is used to model disease progression, survival and treatment effect, with Weibull survival curves used to extrapolate from different (and independent) sources of data.

Health state values for the second line analysis were taken from data collected in the phase II trial,[117] using EQ-5D (details unpublished), and are applied in a treatment-by-health state manner (e.g. sunitinib/PFS=0.803; BSC/PFS=0.758; sunitinib/PD & BSC/PD=0.683).

For both sets of analyses (first- and second-line) summary findings are presented as cost per life-year-gained (LYG) and cost per QALY. CEA estimates are presented by treatment comparison, and the submission reports sensitivity analyses, using probabilistic sensitivity analysis (PSA) to address parameter uncertainty. In all analyses the Pfizer submission applies a manufacturer pricing strategy whereby the first cycle of sunitinib treatment is free of charge to the UK NHS.

Summary of CEA results

First line use of sunitinib

The industry submission presents two levels of base case analysis, (i) using pre-planned interim analysis data, and (ii) unplanned updated analysis data. We caution that the unplanned updated analysis data includes patients who have crossed over from IFN to sunitinib, with potential for confounding in the estimates of treatment effect (hazard ratios). Therefore, this summary refers to findings presented against the pre-planned interim analysis. The base case analysis presents a cost per LYG of £21,116; an estimate of £45,736 per progression-free-year gained; and £28,546 per QALY gained; with results reported indicating that sunitinib increased OS by an additional 0.82 years, increased PFS by 0.38 years and resulted in an additional 0.60 QALYs when compared to IFN.

One-way sensitivity analyses are reported against a range of scenarios. The most important factors affecting the ICER are the health state utilities (values) assigned to the PFS and PD states, and the shapes of the OS and PFS curves (extrapolation method). The probabilistic sensitivity analysis (PSA) reported that at a willingness to pay threshold of £30,000 per QALY, sunitinib has a 54% probability of being cost-effective compared to IFN.

In the comparison of bevacizumab plus IFN versus IFN, the manufacturer (Pfizer) submission estimates a cost per LYG and cost per QALY at £81,754 and £107,357 respectively.

Second line use of sunitinib

For second line use of sunitinib compared to BSC, the submission estimates (base case assumptions) costs per LYG and per QALY of £29,061 and £37,519 respectively; with results reported indicating sunitinib increased OS by 0.77 years, PFS by 0.54 years and resulted in an additional 0.60 QALYs when compared to BSC.

Sensitivity analyses reported in the submission indicate that the most important factors affecting the ICER are the health state utilities (values) assigned to the PFS and PD states, and the shapes of the OS

and PFS curves (and data source). The PSA reported that at a willingness to pay threshold of £30,000 per QALY, sunitinib has a 36% probability of being cost-effective compared to BSC.

In the comparison of sorafenib versus BSC, the sunitinib manufacturer (Pfizer) submission estimates a cost per LYG and cost per QALY at £54,750 and £73,078 respectively.

Review of industry submission

Appendix 6 (page 232) presents a summary review of the sunitinib manufacturer submissions against the main items in the NICE reference case requirements, and against criteria set out by Philips and colleagues[135].

1st-line use of sunitinib

Structure: The submission uses a simple model of disease progression, considering PFS, PD and death. This seems appropriate given the decision problem and the data available. The time horizon and model cycle length employed are both appropriate. The model assumes that patients receive sunitinib or IFN until disease progression. Following progression, patients receive BSC. Patients cannot switch from sunitinib to IFN or visa versa, in line with the protocol of the Phase III RCT.

The model uses survival analysis to consider disease progression and treatment effect, based on data from the RCT reported by Motzer and colleagues in 2007.[111] For baseline disease progression, Weibull curves were fitted separately to Kaplan-Meier data (from RCT) for progression free survival (PFS) and overall survival (OS) for interferon treatment. In the base case, treatment effectiveness is modelled using the relative measures of treatment effectiveness (hazard ratios for OS and PFS) from the RCT, to adjust the OS and PFS baseline progression. As data are available for only PFS and overall survival, the model calculates the proportion of patients in the progressive disease (PD) health state over time as the proportion alive minus the proportion of patients in the PFS health state.

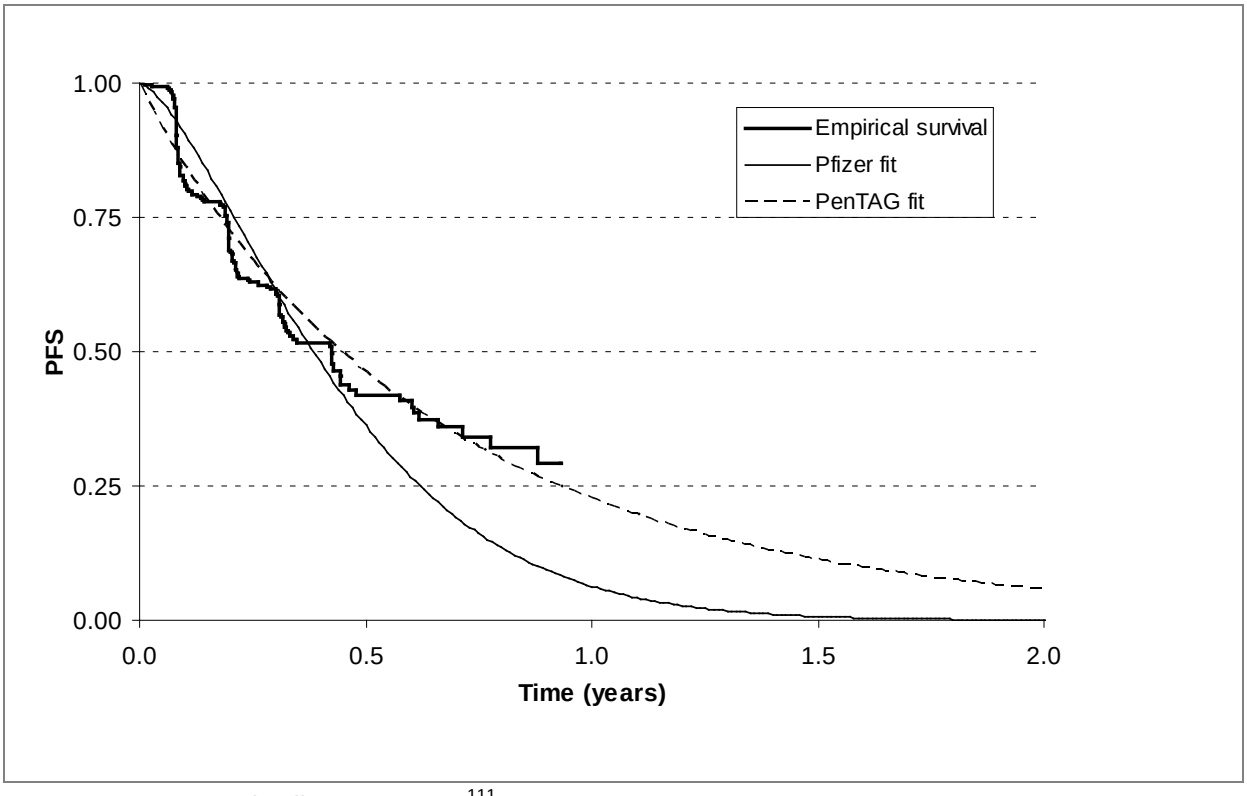
In sensitivity analyses, structural assumptions on modelling disease progression are tested, with OS and PFS curves for sunitinib fitted separately to trial data, instead of using hazard ratios to adjust baseline disease progression. Also in the sensitivity analysis, baseline disease progression (IFN) was estimated by fitting Weibull curves to OS survival data from three independent trials, with trial hazard ratios used to model treatment effect, as in the base case analysis.

We have some concerns with the model used to estimate the cost-effectiveness of sunitinib for 1st line use. First, and a major concern, is that the Weibull curve fitted to trial data[111] on progression free survival (PFS) for IFN is a poor fit to the empirical survival data. Figure 6 (page 109) shows that the Weibull curve fits the empirical data well up to about 0.5 years, but that thereafter the model predicts a much shorter tail (more rapid disease progression) than is shown by the actual PFS survival data. The

manufacturer submission acknowledges that the curve "does not fit the latter proportion of the Kaplan-Meier data, and therefore the PFS benefit of IFN-α could be underestimated" (p58 of the industry submission[135]). We suggest that the consequences of this poor fit are important, and in addition to the suggested underestimated benefit, the modelling creates an underestimate of the cost per QALY (due to incremental costs and effects associated with PFS).

We have noted that the Pfizer survival analysis for PFS is heavily influenced by the first few data points in the Kaplan-Meier trial data. The submission has the curve fitted to multiple data points each month (and the transformation of the Weibull survival function S(t) for regression, ln(-ln(S(t)) is very large and negative when S(t) is just below 1, i.e. for small time t). PenTAG suggest that the first few data points are outliers in the regression. When we fit a Weibull curve to fewer data points, in this case one data point per month, the fit to the actual data is much improved, because there are then no outliers in the regression, see Figure 6, page 109.

Figure 6: Pfizer and PenTAG Weibull curve fits to empirical progression-free survival data for interferon.



Source: Motzer and colleagues, 2007[111]

Using the PenTAG (improved) Weibull fit in the industry model submitted (all else equal), the base case ICER increases greatly, from £28,500 to £48,100 per QALY. Furthermore, most of the ICERs in

the sensitivity analyses increase substantially, see Table 35, page 111. The ICERs increase mostly because time in the PFS health state increases, and therefore the duration of treatment increases. Both IFN and sunitinib treatment costs increase, but due to the much lower cost for IFN per cycle the mean incremental total cost for sunitinib (compared to IFN) increases and consequently the cost per QALY estimate is higher.

Table 35: Comparison of manufacturer CEA and PenTAG adjusted CEA (sensitivity analysis) for sunitinib vs. IFN using Pfizer's model, with PenTAG adjustment (modelled fit to PFS survival data for IFN).

Analysis	Base-case value	New value	Sunitinib vs. IFN ICER Pfizer model	Sunitinib vs. IFN ICER Pfizer model adjusted by PenTAG
Base Case Results			£28,546	£48,052
Varying source of IFN-α OS extrapolation	Trial data	Flanigan et al[47]	£26,244	£43,334
		Mickisch et al[137]	£27,709	£46,367
		Bevacizumab plus IFN RCT[106]	£30,965	£52,798
Extrapolation method	Weibull with hazard ratio	Independent Weibull	£40,536	£41,096
Restricting time horizon	Lifetime (10 years)	5 years	£34,223	£59,739
Alternative utility values	Varied by treatment and health state using EQ-5D	EQ-5D by treatment only	£29,766	£51,640
		EQ-VAS by treatment only	£25,908	£44,946
		EQ-VAS by treatment and health state	£29,207	£44,866
		EQ-5D values taken from sunitinib 2nd line trial	£30,828	£47,511
		Utility when progressed 0.5	£36,284	£48,689
		Utility when progressed 0.7	£31,207	£51,013
Discount rates	Costs and benefits discounted to 3.5%	No discounting	£27,508	£46,364
Relative dose intensity calculation	Includes dose interruptions and reductions Sunitinib – 86.4% IFN-α – 83.08%	Includes dose interruptions only Sunitinib – 97.20% IFN-α– 95.90%	£31,410	£53,936
	No dose reduction	All treatments 100%	£32,154	£55,484
IFN-α price	Price based upon Roferon	Price based upon IntronA (£4.32 per MU)	£29,145	£48,923

Our second concern is also about Pfizer's assumption for PFS with IFN, but is related to sensitivity analysis undertaken using separate sources of data to predict baseline (IFN) disease progression (PFS data from the trial of sunitinib versus IFN by Motzer and colleagues [111], but OS data from the trial of bevacizumab plus IFN versus IFN by Escudier and colleagues[106]). The consideration of this sensitivity analysis is important because, as highlighted in the manufacturer submission, the most important source of uncertainty in the analysis is the extrapolation of overall survival data. The OS curves are immature; 65% of interferon patients and 67% of sunitinib patients are alive at the time of the interim analysis. This is the most complete unconfounded overall survival data available as patients were permitted to crossover to active treatment after this analysis. Where Pfizer apply OS data from Escudier and colleagues,[106] the cost per QALY increases from the base case of £28,500 to £30,965 per QALY (£52,800 in PenTAG adjusted analysis). However, we feel that using different data sources for OS and PFS in the model has the consequence/potential to distort the modelled disease progression due to the fact that the number of people in the progressive disease (PD) health state over time is calculated from (is a function of) related data on PFS and OS. We would suggest that where different OS data are used (due to possible limitations in the sunitinib trial data) that baseline (IFN) disease progression for PFS should also come from that same data source, in this case the trial of bevacizumab plus IFN versus IFN reported by Escudier and colleagues in 2007. This is the method used in the PenTAG analysis (Section 4.5.4.3), and acknowledged by Pfizer as a valid approach (p67 of the manufacturer submission).[135] When Weibull curves are fitted (by PenTAG) to the manufacturer model using IFN PFS and OS curves from the RCT of bevacizumab plus IFN vs. IFN,[106] the cost per QALY increases from £28,500 (Pfizer base case) to £56,000 per QALY. This increase is mostly due to the adjustment in the fit of progression free survival data for IFN.

In summary, we suggest that the manufacturer estimate of cost effectiveness presents a cost per QALY that is underestimated. Where we adjust the manufacturer model to address both highlighted structural concerns (albeit one is in sensitivity analysis), the base case ICER moves from £28,500 to between £48,100 and £56,000 per QALY.

Data: See Appendix 6, page 232 for more detailed comments on data inputs. In summary, the submission uses data from clinical trials to inform the patient population considered within the economic model of first line treatment.[111] The above discussion considers the effectiveness data used from clinical sources to inform modelling of disease progression and treatment effect (and our main concerns). Drug costs are estimated using list prices, recommended dose data, and dose intensities from clinical sources. Pfizer assume that the first cycle of sunitinib is free to the NHS (this is not consistent with the NICE reference case requirements). Whilst the use of dose intensity data to adjust the drug costs in the model (i.e. in an ITT manner; sunitinib at 86.4%; IFN at 83.1%) is open to some debate, it seems reasonable to consider this where it is expected that some patients in the cohort will

have periods 'off therapy'. The manufacturer model assumes that people receive sunitinib or IFN until disease progression. However, we believe, based on the views of the expert advisory group, that IFN will generally be prescribed for a maximum period of 12 months, as in the RCT of bevacizumab plus IFN vs. IFN[106] Therefore, the model may overestimate the costs and effects associated with IFN treatment (i.e. underestimate the incremental cost for sunitinib).

When estimating drug administration costs the submission assumes that IFN is administered from a titrated pen syringe subcutaneously three times a week at home (by self, carer, or occasionally district nurse). The submission estimates that 50% of patients self-inject, and that the remainder have injections given by a district nurse at home, at a cost of £21 per visit. Whilst this assumption may be reasonable, we suggest a higher proportion may self administer; therefore the submission probably slightly overestimates the cost of IFN. Furthermore, the submission assumes that patients receiving IFN make more frequent outpatient visits for clinical assessment of efficacy and toxicity than patients on sunitinib; a maximum of eight outpatients visits in the first six months. These issues are expected to have only a small impact on estimates of cost per QALY.

Health state utilities/values are reported to be estimated from the resuls of the EQ-5D questionnaires administered in the Phase III RCT of sunitinib versus IFN,[111] and values are derived from UK population data. Utility estimates were treatment and state specific: sunitinib/PFS = 0.77 (s.d.=0.22), sunitinib/PD = 0.72 (0.25), IFN/PFS = 0.79 (s.d.=0.20), IFN/PD = 0.69 (0.29). We are concerned that these values are unpublished. There is one published abstract reporting utility data derived from the paper by Motzer and colleagues 2004[138] and the RCT of sunitinib vs. IFN,[111] and this abstract is not consistent with the data used in the manufacturer submission. However, we acknowledge that there is no other published data on health state utilities for RCC.

The model assumes a monthly cost of £600 for hospital and hospice care following disease progression, based upon a study of stage IV breast cancer in the UK.[133] There is an absence of reported data (in the literature) to inform this model input, and whilst we suggest that the costs for BSC may be lower (on average) with care delivered from a primary care setting, the approach taken in the Pfizer model may be seen as reasonable.

Uncertainty/Inconsistency: In survival analysis, we note that for each fitted Weibull curve, the two parameters (lambda and gamma) were drawn from a multivariate normal distribution. However, these don't appear to have been used in the probabilistic sensitivity analysis (PSA), and instead the progression free survival (PFS) and overall survival (OS) hazard ratios were assumed to follow independent univariate lognormal distributions. In the probabilistic analysis the hazard ratios for OS and PFS are not correlated for either sunitinib or bevacizumab plus IFN. In practice, these quantities

are most probably correlated. However, if such correlations are not known, the approach may be seen as reasonable.

The health state utilities used in the model followed univariate normal distributions. Various costs data were varied stochastically. We suggest that the approaches used in the PSA may underestimate the variability of the ICER.

In survival analysis, and modelling of effectiveness, the manufacturer submission quotes the appropriate standard errors of the hazard ratios (HR) for sunitinib and bevacizumab plus IFN, compared to IFN, for PFS and OS data. However, in the Pfizer model there is a potential mix-up, as the standard errors of the HRs for OS are used for PFS and vice versa (for both sunitinib vs. IFN and bevacizumab plus IFN vs. IFN). This confusion in the assignment of data will affect the results of the PSA. Specifically, the standard error of the log-transformed HR between sunitinib and IFN for OS is assumed to be 0.10, but should be 0.19, the standard error of the log-transformed HR between sunitinib and IFN for PFS is assumed to be 0.19, but should be 0.10, the standard error of the log-transformed HR between bevacizumab plus IFN and IFN for OS is assumed to be 0.10, but should be 0.13, and the standard error of the log-transformed HR between bevacizumab plus IFN and IFN for PFS is assumed to be 0.13, but should be 0.10.

In the sensitivity analysis, Pfizer state that £259.20 represents the cost of 50MU of IntronA (interferon alpha), whereas this is the cost of 75MU (50MU/ml, 1.5ml). Using the corrected value, the ICER (sensitivity analysis in submission) changes slightly (from £29,145 to £29,880 per QALY).

We have highlighted that the submission includes an analysis based on the unplanned updated trial analysis data. We caution that this data includes patients who have crossed over from IFN to sunitinib, and thus will confound the HR estimates to some extent. However, we assume that the manufacturer has analysed this data because it is more mature than the pre-planned interim analysis data.

Bevacizumab plus IFN versus IFN

Pfizer do not perform an indirect comparison between sunitinib and bevacizumab plus IFN, even though they state that the patient populations in the sunitinib vs. IFN and bevacizumab plus IFN vs. IFN RCTs are similar. Nonetheless, they do present a comparison of the cost-effectiveness of bevacizumab plus IFN versus IFN.

2nd line use of sunitinib

Structure: The model structure has been outlined above. The cycle-length and time horizon are appropriate. We have concerns about the effectiveness data used to model disease progression. The

submission uses effectiveness data from trial RTKC-0511-014, a multi-centre phase II, single-arm study assessing the efficacy and safety of sunitinib in second line treatment.[117] In the absence of a BSC arm in this trial, the submission modelled BSC survival based on pooled analysis and an analysis of SEER-Medicare data. The pooled analysis[138] is a review describing the survival of previously treated metastatic RCC patients who were candidates for clinical trial agents as second-line therapy. It pools survival analyses involving 251 patients with advanced RCC treated in 29 trials between 1975 and 2002. However the population included in the review does not correspond to the trial population of RTKC-0511-014 in terms of previous first-line therapy received and response to previous therapy. Only 50% of patients received prior first-line cytokine immunotherapy in the review, compared to all patients in trial RTKC-0511-014.[117] In addition, the review considered clinical trials of second-line experimental treatment programs for mRCC which included cytokines. The submission does suggest that this could have had an impact on survival; suggesting the use of this data alone to estimate survival in BSC patients could lead to an overestimation of survival.

One of our concerns with the submission's methods is the use of the SEER Medicare data. We acknowledge that Pfizer caution that these data have important limitations. First, differences in patient characteristics and in underlying health status and projected course of RCC at baseline may call into question the comparability of the pooled analysis[138] and the SEER-Medicare populations. Second, the definition of cytokine failure used in the pooled analysis relies on clinical signs and symptoms, while the definition used in the SEER-Medicare analysis relies on observed health care resource utilisation. Because of the gap between the time of clinical progression and the need for health care services, the starting point for the survival analysis among the SEER-Medicare patients may be somewhat later than that for the patients in the pooled analysis. This lag is expected, everything being equal, to lead to shorter observed survival post-diagnosis for the SEER-Medicare patients (lead-time bias). Moreover, close monitoring for cytokine failure is likely to be the norm once sunitinib or other effective second-line therapies become available, since there will be an incentive to detect cytokine failure.

We have serious concerns about the approach used to model sunitinib for 2nd-line use. First, and most importantly, the OS and PFS curves for sunitinib are taken from one trial[117] and the corresponding curves for BSC are taken from a different trial.[138] We believe that this approach is invalid, since randomization has been broken. Second, as the submission acknowledges, the two data sources for BSC survival have important limitations, as discussed above.

Finally, we highlight that the single arm trial of sunitinib was very small, with only 63 patients. Furthermore, OS for sunitinib from the single-arm trial is not mature. Approximately 40% of patients were still alive at data cut-off. Therefore, cost-effectiveness estimates are sensitive to extrapolation of OS beyond data cut-off. The submission does not state why the manufacturer did not model PFS and OS for sunitinib from the other single-arm trial of sunitinib, trial A6181006.[116]

Data: The cost of sunitinib was estimated using list prices and the recommended dose. Pfizer estimated the dose intensity of sunitinib as 80.8% from the single-arm trial. The cost of sunitinib was reduced by this dose intensity.

Costs associated with BSC are the same in both arms of the model. BSC is defined as treatment to control, prevent and relieve complications and side effects and to improve comfort and quality of life. Within the BSC arm, costs for diagnostic tests, acquisition and administration are set to zero as they are included in the BSC costs. For the Pfizer comparison of sorafenib and BSC, resource use for sorafenib was assumed equal to that for sunitinib.

As in the first line model, utility values were assigned by treatment and health state. The submission states that EQ-5D scores were derived from data taken from the single-arm trial,[117] and are: sunitinib/PFS = 0.803 (s.d.=0.25), sunitinib/PD = 0.683 (0.29). BSC patients in PFS were assigned the same utility as the baseline in the single-arm sunitinib trial (0.758, s.d.=0.227). BSC patients in PD were assigned the same utility as sunitinib 0.683 (s.d.=0.29). There is some weighting of utility values, based on values whilst on treatment, or whilst in the rest period. However, in general we are concerned that these data are unpublished, and there is insufficient detail to consider the methods used. We also note again that the number of people in the trial is low.[117]

Uncertainty/inconsistency: In the PSA, parameter uncertainty was modelled in a similar fashion as in the 1st-line model. For each fitted Weibull curve, the two parameters lambda and gamma were drawn from a multivariate normal distribution (see comment under first line use). The utilities followed univariate normal distributions, and various costs were modelled by gamma distributions.

4.4.1.2. Bevacizumab plus IFN (manufacturer analysis/model)

Summary of industry submission

In their submission to NICE the manufacturer of bevacizumab (Roche) present a cost-effectiveness analysis of bevacizumab plus IFN versus IFN alone as first-line therapy in patients with advanced RCC.

The submission uses a model-based approach to estimate cost-effectiveness. The cost effectiveness model, written in Microsoft Excel®, comprises three health states: progression free survival (PFS), progressed diseases (PD) and death. The model uses a lifetime time horizon, and a model cycle of 1 month. The model uses survival analysis, employing clinical effectiveness data from the RCT reported by Escudier and colleagues,[106] to model survival and disease progression over time. As in the RCT, all patients in the cohort model start in PFS in the analysis. No subgroup analyses are presented.

The model uses a patient population defined as in the Escudier and colleagues RCT[106], and for baseline disease progression (IFN alone), uses Weibull survival curves, modelled from the same trial.[106] To model differences between bevacizumab plus IFN and IFN, the analysis considers PFS by applying a Weibull survival curve for bevgacizumab plus IFN, modelled from trial data.[106] For overall survival, modelling applies a relative measure of treatment effectiveness (hazard ratios) from the RCT to the baseline survival analysis. The submission explores alternative mathematical survival curves in sensitivity analyses.

The modelling assumes that patients receive bevacizumab until disease progression, and IFN until disease progression, although IFN use is limited to 1 year, consistent with the RCT.[106] Following disease progression (PD health state) patients receive BSC, and are assumed to use second line drugs. The health state utilities used are taken from EQ-5D data collected in the sunitinib versus IFN RCT. The trial was reported by Motzer and colleagues in 2007,[111] but EQ-5D data are not reported in the trial paper. The Roche model uses a utility of 0.78 in PFS, and 0.705 in PD health, both applied independent of treatment (values are derived by averaging over the treatment specific data reported from the sunitinib vs. IFN RCT[111]). The resource use data covers costs for drug acquisition, drug administration, medical management, adverse events, and costs associated with BSC in progressive disease. The costs of drug acquisition and administration are reduced according to the dose intensity data reported in the RCT.[106]

Summary findings are presented as cost per life-year-gained and cost per QALY. Sensitivity analyses, using probabilistic sensitivity analysis (PSA) to address parameter uncertainty, are presented. All cost-effectiveness analyses presented in the submission are based on a scenario where a manufacturer pricing strategy is used to cap the cost of bevacizumab (this is not consistent with the NICE reference case requirements); whereby bevacizumab is free to the UK NHS once 10,000mg has been purchased in an individual patient within a year of treatment initiation. (Roche describe this as European-wide 'dose-cap' scheme).

Summary of CEA results

The submission reports a base case cost per life-year gained of £58,712, and cost per QALY at £75,000; bevacizumab plus IFN increases overall survival by 0.34 years, increases PFS by 0.36 years, and results in an additional 0.27 QALYs when compared to IFN. The incremental costs for bevacizumab were around £20,000 (almost entirely made up of drug and drug administration costs). The probabilistic sensitivity analysis reported shows that at a willingness to pay threshold of £30,000 / QALY, bevacizumab plus IFN has a 0% probability of being cost-effective compared to IFN.

Review of industry submission

Appendix 6 (page 232) presents a summary review of the manufacturer submission against the main items in the NICE reference case requirements, and against the criteria proposed by Philips and colleagues[135].

Structure: The model considers the cost-effectiveness of bevacizumab plus IFN versus IFN in first-line use, and the submission provides a rationale for not comparing bevacizumab plus IFN versus temsirolimus for poor prognosis patients.[118]

Whilst the model structure is simple, considering PFS, PD and death, this seems appropriate given the decision problem and the data available. The time horizon and model cycle length are appropriate. In the model, PFS is estimated separately for IFN and for bevacizumab plus IFN based on extrapolation of the Kaplan-Meier data from the RCT.[106] The overall survival (OS) data are modelled differently, given that it is still immature for bevacizumab plus IFN (RCT reported data). In the model, the RCT data on OS for IFN alone is used (as OS data in the IFN arm is more mature) to extrapolate and estimate the OS for IFN over time.[106] To model OS for bevacizumab plus IFN the baseline progression (IFN alone) is used in conjunction with the relative measure of effectiveness (hazard ratio) reported in the RCT[106]. The submission, reports that several mathematical survival curves were fitted to the Kaplan-Meier data, and that the Gompertz function is used in the model on the basis that it gave the best fit to both the PFS and OS data.

Data: Drug costs are estimated using list prices, and recommended dose data. Roche use the average body weight of 76.5 kg from the RCT by Escudier and the colleagues[106] to estimate average dose, and hence the cost of bevacizumab. Patients in the bevacizumab plus IFN arm received 10mg/kg of bevacizumab every 2 weeks, and IFN three times per week at a dose of 9MU. As noted above the analysis assumes a European-wide 'dose cap' scheme (where costs for bevacizumab are much reduced i.e. by a mean of £8,900 in base case analysis). Modelling assumes that IFN is administered by patients, with no additional resource use/cost. The model assumes one outpatient visit for every intravenous administration of bevacizumab (2-weekly), at a cost of £233 per visit.[139] For bevacizumab this administration cost is assumed to capture all other monitoring costs. In patients taking IFN alone, one outpatient appointment each month is assumed. The drug-related cost of bevacizumab administration (unit cost) was calculated as a weighted average of chemotherapy administration costs from NHS reference costs data. Costs for adverse events are included in the analyses.

The manufacturer analysis assumes that patients in the PD health state will be offered 2nd-line drug treatments, such as sunitinib or sorafenib. They assume a cost of £405.50 per month in the bevacizumab plus IFN arm and £495.95 in the IFN arm. These figures are based on data from the RCT by Escudier and colleagues[106] which details 2nd-line treatments. A larger proportion of patients

in the IFN arm received 2nd-line treatment than in the bevacizumab plus IFN arm; with differences attributed to the relative lack of effectiveness of IFN. Specifically, the monthly costs of the 2nd-line drug were estimated based on 2nd-line drug use for 8.3 months, the duration of 2nd-line PFS according to the 2nd-line sunitinib trial for RCC patients.[116] The total expected drug cost in PD was thus calculated and then the monthly cost in PD was estimated by spreading this total cost over the time spent in PD in the model (12.7 months). In addition, Roche assume that all patients in PD had one outpatient appointment per month for monitoring.

As noted above, the health state utilities (for PFS and PD health states) are taken from the sunitinib versus IFN RCT,[111] which used the EQ-5D measure. As noted in the PenTAG review of the sunitinib model (manufacturer submission) these utility data are not published, and we are unable to consider them in much detail.

Uncertainty/Inconsistency: The submission presents findings from probabilistic modelling to address parameter uncertainty in cost per QALY estimates, but other sensitivity analyses are performed only on model structure, reporting against the choice of mathematical function of the survival curves (see below). PenTAG note that the absence of sensitivity analysis is a weakness in the reporting of the cost-effectiveness analysis, and suggest that the submission could have performed/reported additional sensitivity analysis, to help assess the uncertainty in results.

We have a number of concerns with the model and analysis presented in the Roche submission to NICE.

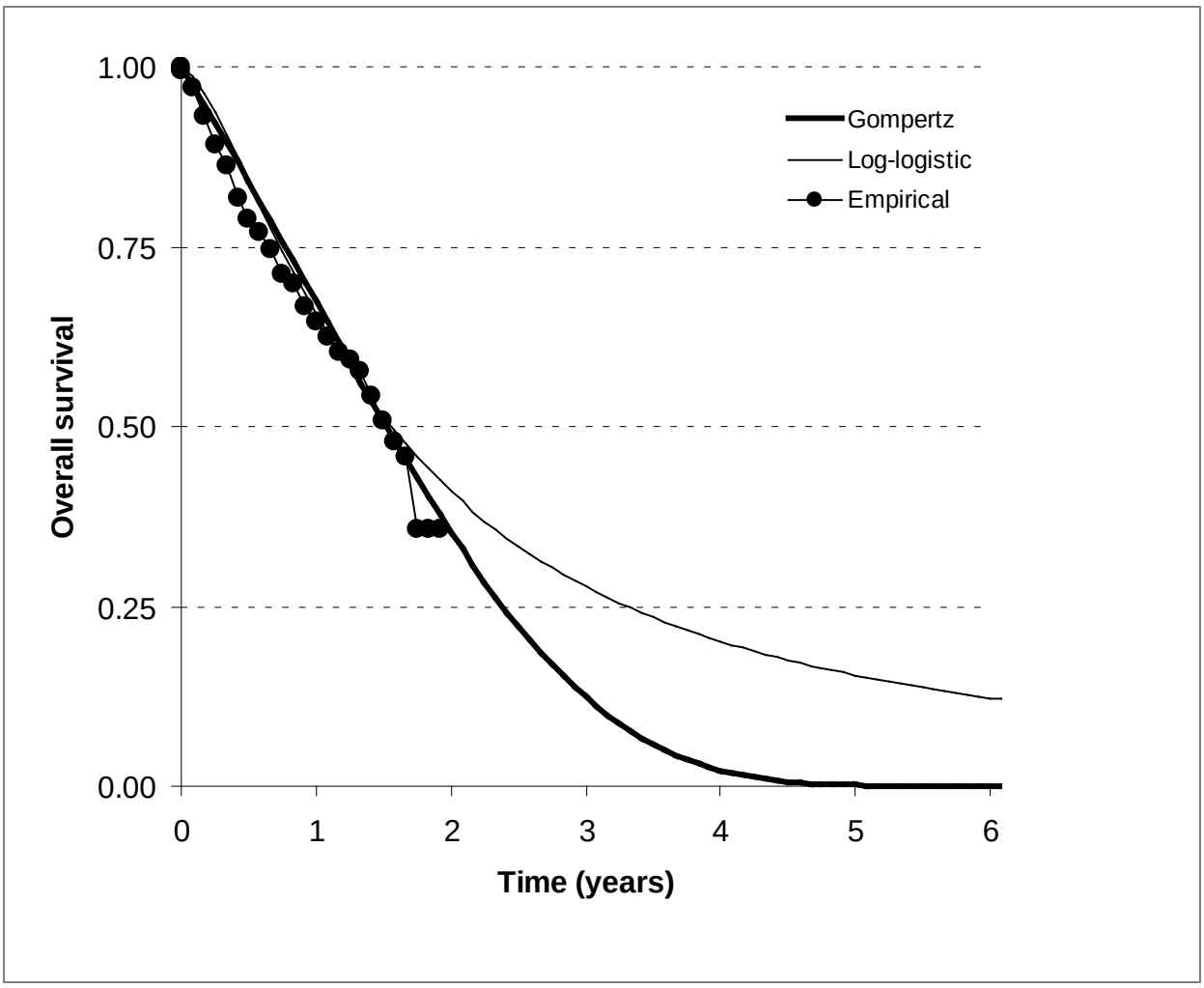
First, we highlight a concern over the assumptions and data used to estimate dose intensity which is used to adjust drug and drug-related costs. The manufacturer analysis multiplies the costs of drug acquisition and drug administration using dose intensity data (unpublished data from the bevacizumab plus IFN RCT[106]). In the model, dose intensity data for bevacizumab is estimated using the average time taking the drug in the trial divided by the average time patients spend in PFS in the model. Similarly for IFN, the estimation is the average time actually taking the drug in the trial divided by the average time patients spend in PFS up to 1 year in the model. In this way, the dose intensities are calculated as 62% for bevacizumab, 80% for IFN when used with bevacizumab, and 63% for IFN alone (monotherapy). Although these data are not reported in the written submission they are used in the model. This data, applied to adjust costs, is different to that reported in the RCT[106], and different to the data quoted in the Roche submission (their Table 13). Dose intensity data used in the model are generally much lower than the *mean* dose intensities reported in the RCT (88% for bevacizumab, 83% for IFN in bevacizumab plus IFN arm, and 89% IFN alone arm) [106], and lower than the *median* dose intensities quoted in the manufacturer submission. Where PenTAG have used the dose intensity data

reported in the published RCT[106] in the manufacturer model, the base case ICER increases substantially, from £75,000 to £117,000 per QALY.

Second, we highlight a concern over the clinical effectiveness data (HRs) used in the manufacturer analysis for overall survival (OS) and progression free survival (PFS). The analysis uses the HR for OS from unpublished data on what is classed a 'safety population' (not the RCT data), using the OS HR of 0.709. This differs from the OS HR of 0.75 from the RCT reported by Escudier and colleagues (2007)[106]. Where PenTAG have used the manufacturer model and applied the RCT data of 0.75 (HR for OS), the ICER increases from £75,000 to £87,400 per QALY. It is not clear why the manufacturer analysis uses data from the safety population (compared to RCT data). Again, with PFS we note that the model uses a HR of 0.609 (CI 0.508, 0.728) for PFS and that this is from a 'safety population' (stratified, by risk group) rather than the data reported in the RCT. The RCT[106] reports a HR of 0.63 (95% CI 0.52, 0.75) in unstratified analysis. However in their model, a PFS HR is not explicitly applied, because PFS for both treatment arms is fitted to empirical trial data independently (we assume that this HR is implicit in the Kaplan-Meier data).

Also, in sensitivity analysis the submission reports findings where cost-effectiveness has been assessed using a log-logistic model (instead of the Gompertz methods in the base case analysis), and PenTAG would question the appropriateness and prominence of this sensitivity analysis. In this case, the ICER falls greatly, from £75,000 to £40,000 per QALY, and at a willingness to pay threshold of £30,000 / QALY, bevacizumab plus IFN has a 9% probability of being cost-effective compared to IFN. However, Roche acknowledge that this ICER may be unrealistic because the log-logistic model results in an expected lifetime which may be unrealistically long (see Figure 7). We do not see the log-logistic method as a credible approach, i.e. we agree with Roche that it is unreasonable to use the log-logistic distribution to model PFS and OS in the sensitivity analysis because the tail of the distribution is too long.

Figure 7: Comparison of the fit to OS data for IFN, using Gompertz and log-logistic curves (as manufacturer sensitivity analysis).



Source: Escudier and colleagues, 2007 [106]

4.4.1.3. Temsirolimus (manufacturer analysis/model)

Summary of industry submission

In their submission to NICE[125], the manufacturer of temsirolimus (Wyeth) present a cost-effectiveness analysis of temsirolimus versus IFN in first-line use in patients with poor prognosis. Wyeth also present an indirect comparison of temsirolimus versus best supportive care (BSC) using data from a RCT of IFN versus BSC.

The submission uses a model-based approach to estimate cost-effectiveness. The cost-effectiveness model, written in Microsoft Excel®, comprises three primary health states: progression free survival (PFS), post-progression and death. However, the PFS health state is sub-divided into 3 categories (sub-states), of complete/partial response, stable disease, and progressive disease (PD). The model uses a time horizon of three years, and a model cycle of 1 month. The model uses survival analysis,

employing clinical effectiveness data from a single RCT[112] to model survival and disease progression over time. The approach uses Weibull regression models, applied to PFS and OS data, to calculate the time dependent transition probabilities used to model disease progression, and cost-effectiveness.

The cohort starting the model are distributed across health states based on the RCT data.[112] Modelling assumes that patients receive temsirolimus and IFN until disease progression, consistent with the RCT.[112] In the post-progression health state patients receive BSC and 2nd-line drugs. Health state utilities were derived from the EQ-5D questionnaire collected during the RCT,[112] although this data is not reported in the trial publication. Resource use data covers costs for drug acquisition, drug administration, medical management, adverse events, and BSC and 2nd-line drugs in the post progression health state. The costs of temsirolimus and IFN and the cost of administration of temsirolimus are reduced according to dose intensity data from the temsirolimus RCT.[112] The administration of IFN is not adjusted by dose intensity data.

Summary findings are presented as cost per life-year-gained and cost per QALY. Sensitivity analyses, using probabilistic sensitivity analysis (PSA) to address parameter uncertainty, are presented. In addition to the base case analysis which uses data from all the patients in the RCT, Wyeth present subgroup analyses for clear cell RCC, non-clear cell RCC, patients with prior nephrectomy and for those with no prior nephrectomy.

Summary of CEA results

The base case analysis estimates a cost per LYG of £35,577, and a cost per QALY of £55,814. The incremental LYG and QALYs were 0.21 and 0.13 respectively, and the incremental costs were £7,493. The major components of the incremental cost were linked to additional drug cost for temsirolimus (£10,348) and a suggested cost saving (-£3,347) in the cost for drug administration (temsirolimus compared to IFN). The results are given in more detail in Appendix 6 (page 232). In manufacturer sensitivity analysis the cost effectiveness was sensitive to changes in drug-related treatment costs/assumptions. Probabilistic sensitivity analysis reports a 0% chance that temsirolimus is cost-effective compared to IFN at willingness to pay of £20,000/QALY or £30,000/QALY.

In subgroup analyses, the ICER for the clear-cell patient subgroup was £57,731 per QALY, for the non-clear-cell subgroup £51,159 per QALY; for patients with prior nephrectomy £60,575 and for patients without prior nephrectomy £49,690 per QALY. For the indirect comparison of temsirolimus versus BSC, the ICER was £81,201 per QALY and cost per LYG £43,746 (see Appendix 6, page 232).

Review of industry submission

Appendix 6 (page 232) presents a review of the manufacturer submission against the main items in the NICE reference case requirements, and against the criteria set out by Philips and colleagues[135]. Summary detail is presented below.

Structure: The model uses a simple structure with three primary health states (PFS, post-progression, and death) which is similar to the other models presented for RCC. However, PFS is divided into sub-states (based on response, stable disease, and progressive disease), and the post-progression health state is the state analogous to the progressed/progressive disease (PD) health state/s used in other models for RCC. The model structure appears appropriate given the decision problem and data available. The time horizon is short, at 3-years, but appears to capture the main impacts of disease and treatment, although it has not been tested in sensitivity analysis. The cycle length is appropriate. The model is based on a set of time dependent transit probabilities, derived from individual patient level data (not available to PenTAG) from the RCT by Hudes and colleagues (2007).[112] We are unable to consider the derivation of these probabilities in any detail. Transit probabilities cover PFS to death, and PFS to post-progression. Thereafter the model makes assumptions over other transition probabilities. An assumption is made that the probability of transition from post-progression to death is equal to that for PFS to death. An assumption is made that the probability of transition from post-progression to post-progression (i.e. remaining in that state) is equal to that for PFS to post-progression. The rationale / support for these assumptions is/are not presented. The probability for remaining in the PFS state is derived from the other possible transitions.

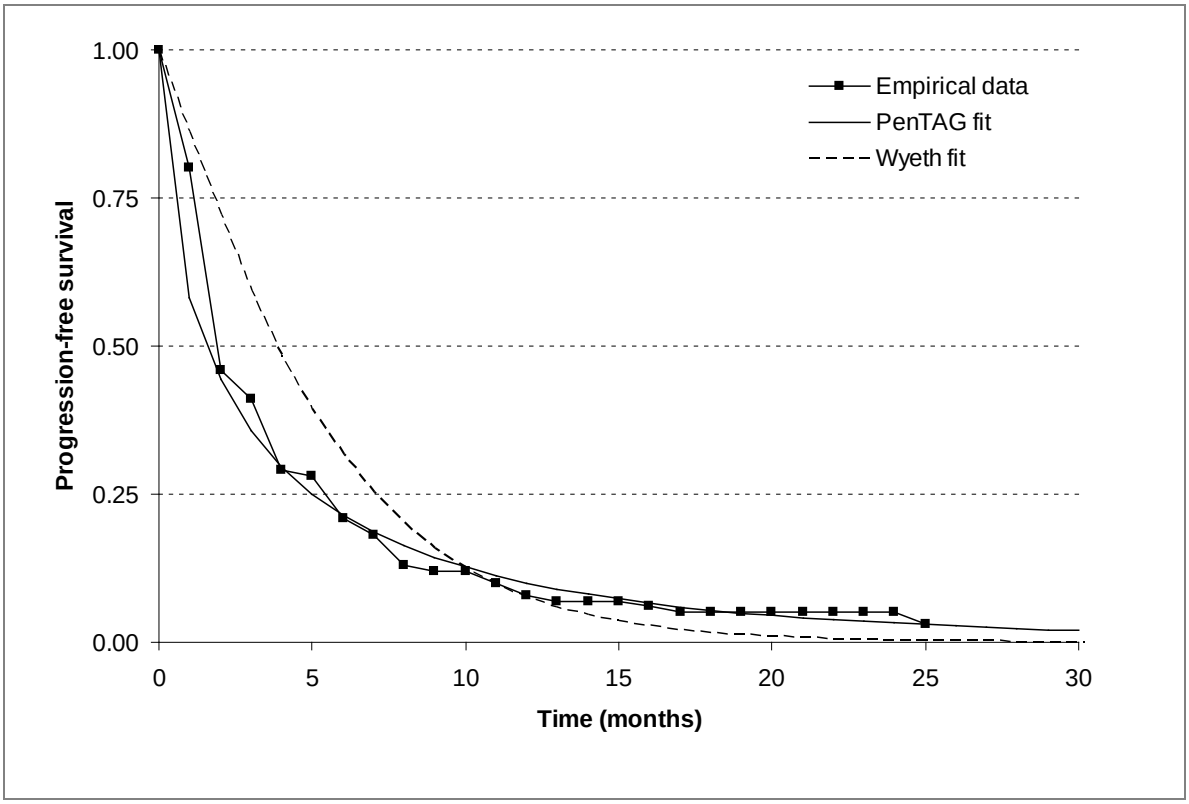
In the model, patients start in a PFS health state. The model assumes that patients starting in a PFS state are treated with IFN or temsirolimus, and stop treatment when they enter a post-progression health state. After disease progression (post-progression), patients take 2nd line drugs (sunitinib, sorafenib, bevacizumab) or receive BSC only.

For each treatment, Weibull regression models are used to derive transition probabilities, with Weibull data fitted for transition from PFS to death, and from transition from PFS to post-progression. For subgroup analysis, the PFS and OS Weibull curves are unique for each patient subgroup: clear cell, non-clear cell, nephrectomy, non-nephrectomy. See Section 3, page 35 for discussion on effectiveness data available to model subgroups.

We note/assume that when calculating disease progression (transition probabilities) the model uses effectiveness data from all patients in the RCT reported by Hudes et al[112]. It is important to remember that the definition of poor prognosis used in this trial differs from the MSKCC prognosis scale. Using this scale, only 75% of patients in this trial would be considered to have poor prognosis. The remaining 25% of patients had intermediate prognosis.

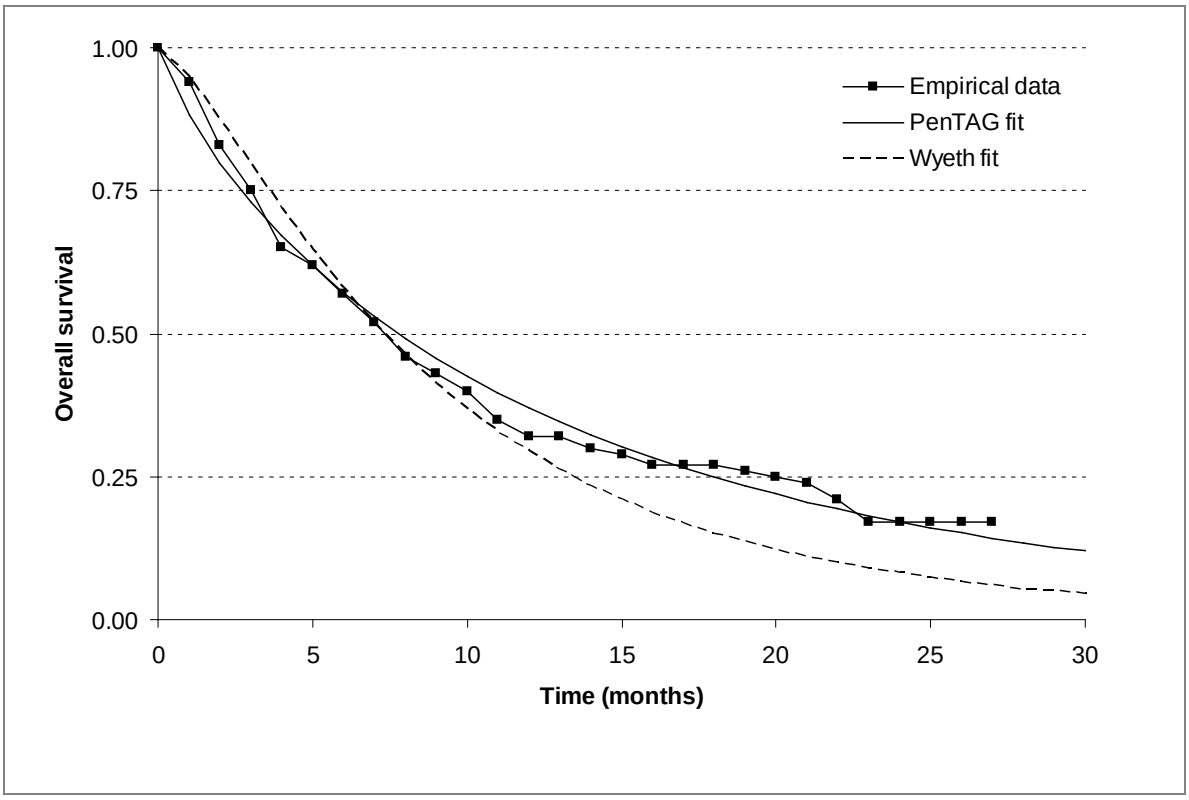
We have a major concern over the structure of the temsirolimus model. In the analysis undertaken (survival analysis / transition probabilities), whilst the base case median PFS and OS data for IFN and temsirolimus calculated are similar to the values given in the temsirolimus RCT,[112] the shapes of the PFS and OS curves calculated (from transition probabilities) are noticeably different to the empirical Kaplan-Meier curves reported in the RCT,[112] see Figure 8 and Figure 9 (pages 124 and 125) for an illustration of this in the IFN group.

Figure 8: Fit to empirical PFS for IFN by Wyeth and PenTAG



Source: Hudes and colleagues, 2007 [112]

Figure 9: Fit to empirical OS for IFN by Wyeth and PenTAG



Source: Hudes and colleagues, 2007[112]

Given the expectation that the cost-effectiveness estimates are sensitive to the shape of the PFS and OS survival curves, this is an important discrepancy, and is explored further below.

Although we have been unable to explore the calculation of transition probabilities (data not available), it is possible to consider, from the disease progression profiles presented in the submission (reading from hard copy predicted progression), estimates of the hazard ratios (relative differences) between temsirolimus and IFN profiles (albeit implicitly), and compare these to those reported in the Hudes and colleagues RCT.[112] The RCT hazard ratio is 0.74 for PFS, whereas we estimate that the time dependent hazard ratios in the manufacturer model vary between 0.61 and 0.70 (generally lower than the reported RCT data). The RCT hazard ratio for OS is 0.73, whereas we estimate that the time dependent hazard ratios in the manufacturer model vary between 0.45 (at month 1) and 1.17 (at the 36th month).

Data: As well as concerns over issues linked to effectiveness data (outlined above), we have some concerns over a number of the assumptions in the model over resource use and cost. We summarise our main concerns below, covering costs associated with administration of IFN, use of dose intensity data, and assumptions used to estimate drug costs. See Appendix 6 (page 232) for more detailed comments on data inputs.

The costs associated with the administration of IFN, and the cost differences between IFN administration and temsirolimus administration, are an important component in the cost-effectiveness estimates. The manufacturer model assumes all IFN is administered in the hospital outpatient setting, costing £127.80 per visit. With IFN administered 3 times per week this leads to a high cost associated with IFN treatment. Based on information on current practice from the expert advisory group we do not believe this is an accurate reflection of current practice. Based on the clinical opinions received, we would expect that in most cases IFN injections would be administered in the patient's home either by themselves or by friends, relatives or carers. It may be that in some cases a district nurse, community or practice nurse would give injections (in the patient's home). Where we assume resource use based on the clinical opinion received (i.e. we assume typically 25% of patients have IFN administered by a district nurse, at a cost of £25 per visit, and the remaining 75% self-inject, at no cost (Table 40, section 4.5.4.5, page 148), the base case ICER (using the manufacturer model) increases substantially from £55,814 per QALY to £102,000 per QALY. In subgroup analyses, this pattern is also noted: the cost per QALY for the clear-cell subgroup increases from £57,731 to £121,300, for the non-clear-cell subgroup from £51,159 to £63,100, for patients with prior nephrectomy from £60,575 to £117,000 and for patients without prior nephrectomy from £49,690 to £84,000.

A further concern is that the Wyeth submission assumes that the drug administration costs for temsirolimus should be adjusted using dose intensity data from the RCT [112] i.e. costs are reduced. However, Wyeth do not apply this same assumption to costs associated with IFN.
Drug costs are estimated using list prices (expected list prices) and recommended dose data. Patients receive IFN three times per week at a recommended dose of 18MU. In the Wyeth analysis the cost of temsirolimus is based on the 25mg per dose, one dose per week, at £20.60 per mg, giving £515 per dose. The analysis acknowledges that due to vial size, at 30mg each, there will be waste/overfill of 5mg, although the cost for this is not addressed. There is some outline discussion on potential for vial sharing schemes (and sensitivity analysis), but no detail is provided. We suggest that for each dose of temsirolimus the real cost will be 30mg (unit cost for each infusion, with product waste). In the view of the expert advisory group it is not likely that vial sharing schemes would be feasible across the UK. Using one 30mg vial per infusion, would result in a cost per dose of £618, and applying this cost in the manufacturer model increases the ICER of temsirolimus versus IFN from £55,800 to £74,819 per QALY.

The temsirolimus model uses health state utilities of 0.60 for the baseline entry health state of stable disease (analogous to PFS), and 0.446 for the health states of progressive disease and post progression. The model also includes an incremental gain in utility in patients where a response (positive) to initial treatment is reported, with a value of 0.658. The progressive disease and 'response' states (utility

values) do not play a major part in the cost-effectiveness analyses, so we do not dwell on them here; focussing on the more generic states of stable/PFS and post progression. The submission reports that utilities were modelled under the Q-TWiST structure, according to whether patients were in the TOX state (suffering Grade 3 or 4 AEs), PD, or TWiST state (Time Without Symptoms of progression or Toxicity). The submission states that utility values were derived from EQ-5D data collected during the temsirolimus RCT,[112] although limited details are available on this. We have some concerns over the lack of transparency in the data used to derive health state utilities (section 4.5.4.4).

Uncertainty/Inconsistency: The submission presents one-way sensitivity analyses. However, we are concerned that they have performed no sensitivity analyses on the PFS and OS survival curves, especially since these are major drivers of the ICER. However, in the probabilistic analysis the submission does incorporate some variation in these curves.

Indirect comparison: temsirolimus vs. BSC

For the comparison between temsirolimus and BSC, the submission uses data from the MRCRCC RCT,[140] and we have concerns over the use of this data. The data is based on patients with a range of prognoses, not just those with poor prognosis. Therefore, we suggest that the results of the indirect comparison should be treated as suggestive only.

4.4.1.4. Sorafenib (manufacturer analysis/model)

Summary of industry submission

In their submission to NICE the manufacturer of sorafenib (Bayer), present a cost-effectiveness analysis of sorafenib versus BSC in patients with advanced RCC. Analysis is presented for the following patient groups; (i) patients on 2nd-line therapy, (ii) patients unsuitable for cytokines (IFN and IL-2), and (iii) combined treatment group with both 2nd-line therapy and patients unsuitable for treatment with cytokines. In addition, cost-effectiveness analyses are presented for further subgroups. The submission also estimates the cost-effectiveness of sorafenib versus sunitinib for 2nd-line treatment.

The cost-effectiveness model of sorafenib versus BSC, written in Microsoft Excel®, comprises three health states: progression free survival (PFS), progressed disease (PD) and death. The model uses a 10-year time horizon, and a 1 month model cycle. The model uses survival analysis, applying data from the RCT reported by Escudier and colleagues,[113] to model survival and disease progression over time. Data from the RCT are classed as mature for the PFS survival analysis, but immature (short follow-up) for the data on overall survival of patients. Therefore, whilst trial data (Kaplan Meier) was used for PFS in both sorafenib and BSC, for the OS data trial data were extrapolated (using an

exponential function) over time. The analysis uses survival data (empirical, or projected) for both sorafenib and BSC (to derive time dependent transition probabilities), and the model does not use relative measures of treatment effect (hazard ratios) to predict differences between treatment arms. In subgroup analyses, different methods were employed to model progression and treatment effect, adjusting baseline survival analysis using different data on median PFS and OS.

Modelling assumes patients receive sorafenib until disease progression, and that all patients start in the PFS state (consistent with RCT methods[113]). Following disease progression, patients receive BSC. The health state utilities used are 0.737 for PFS and 0.548 for the PD health state, both being independent of treatment group. These data are taken from an unpublished survey of physicians. Resource use data cover costs of drug acquisition, medical management, adverse events, and BSC costs in the PD health state. There are no drug administration costs. Modelling assumes a dose intensity of 100% for sorafenib, i.e. there is no reduction in the costs/price for sorafenib to reflect time off treatment.

Summary findings are presented as cost per life-year-gained and cost per QALY. Sensitivity analyses, including probabilistic sensitivity analysis (PSA) to address parameter uncertainty, are presented.

Summary of CEA results

For the comparison of sorafenib and BSC, the ICER for the combined patient group (both 2nd line therapy, and those unsuitable for cytokines) was £90,630 per QALY. For 2nd-line patients (only) the cost per QALY was [redacted], and the ICER for patients unsuitable for cytokines was [redacted] per QALY. Further detail on cost-effectiveness results are given in Appendix 6 (page 232). The probabilistic sensitivity analysis reports that there is a 0% probability of sorafenib being cost-effective (compared to BSC) at a willingness to pay of £30,000 per QALY [redacted]. The submission considers the indirect comparison of sunitinib vs. sorafenib, reporting an ICER of [redacted] per QALY, [redacted]. This indirect comparison is stated as being for descriptive purposes only, due to the fact that the comparative data are not good quality and therefore largely uncertain.

The submission acknowledges that there are no good data available for subgroup analysis, but a series of subgroup analyses are still reported. The submission considers the following subgroups; patients with prior nephrectomy, ECOG (performance status) 0, ECOG 1, diagnosis of RCC greater than 18 months, no lung metastasis at treatment commencement, liver metastasis at treatment commencement.[141] See Appendix 6 (page 232) for a summary.

Review of industry submission

Appendix 6 (page 232) presents a summary review of the manufacturer submission against the main items in the NICE reference case requirements and against the criteria by Philips and colleagues[135]. Here we present a short summary of the main issues.

Structure: Although the model of disease progression is simple, considering PFS, PD and death, we regard this as appropriate given the decision problem and data available. The time horizon and model cycle length are also regarded as appropriate. As above, the model uses trial data to model disease progression, PFS and OS, in the main analysis (combined patient groups). Using PFS and OS data, the time patients spend in the PD state is calculated from estimated time alive minus time in PFS. As acknowledged by the manufacturer in the submission, data available to model subgroups is not good quality, and the modelling is undertaken using an adjustment of the baseline disease progression against data on PFS and OS in the subgroups, with a ratio of median PFS in the subgroup to the median PFS in all patients analysis used for the adjustment. Whilst the method is clear, there is some uncertainty over data available on subgroups (PFS and OS), and these data are largely unpublished. Therefore, we are unable to comment further.

Data: Drug costs are estimated using list prices, and recommended dose data. In the model patients are on sorafenib treatment whilst in the PFS health state, and were assumed to receive 400mg sorafenib twice daily (costing £2,721 per month). Although approximately 6% of patients receiving sorafenib in the RCT by Escudier and colleagues (2007)[113] had dose reductions, it was conservatively assumed that all patients would receive 400mg sorafenib.

Resource use within the model was estimated via two internet-based surveys of 6 and 31 UK clinicians. Four clinicians with experience of sorafenib estimated resource use in the PFS state for sorafenib-treated patients, while clinicians who had not used sorafenib estimated resource use in patients receiving BSC in the PFS state. Resource use estimates were weighted by performance status (ECOG score), with an assumption of 35% ECOG 0, and 65% ECOG 1. There are no published data on resource use for RCC, and there are limited alternatives to estimate resource use. Whilst we consider the estimates used to be high (i.e. higher than the estimated costs in the PenTAG analysis) in some cases, for example the manufacturer estimate of £673 per month for patients treated with BSC in the PFS health state, it is acknowledged that this is an area where judgments may differ. We urge caution when using data from such surveys in small samples, and such caution also applies to the estimates used in the PenTAG analysis. See Appendix 6 (page 232) for more detailed comments on cost data inputs.

Health state utility data were collected from a survey of 31 UK clinicians working in the field of RCC using the EQ-5D questionnaire. EQ-5D values for patients on sorafenib were based on views elicited from only five physicians. We have significant concerns over the methods used here, and note that physician valuations (descriptions) are not methodologically robust, and are inconsistent with the NICE reference case requirements. Utilities were higher in PFS than in PD and higher for ECOG 0 than ECOG 1: PFS ECOG 0: 0.903 (0.858, 0.948), PFS ECOG 1: 0.648 (0.582, 0.714), OS ECOG 0: 0.692 (0.606, 0.778), OS ECOG 1: 0.471 (0.389, 0.553). The analysis combining both ECOG values (all patient subgroups combined) used the average utility across both ECOG groups weighted by the proportion of patients in ECOG 0 and ECOG 1. These treatment-independent averages were 0.737 for PFS and 0.548 for PD, for both sorafenib and BSC.

Uncertainty/Inconsistency: The submission presents one-way sensitivity analysis, and probabilistic sensitivity analysis. There is no statement of model checking for consistency and/or accuracy, although there is a reference to an accurate prediction median PFS in the TARGET trial (Escudier and colleagues[113]).

Further detail is provided in Appendix 6; we have no other major concerns with the modelling presented in this submission.

4.4.1.5. Summary

The above reviews on the four manufacturer submissions (CEA and modelling methods), although summary in nature cover much ground. They are presented to introduce the reader to the submissions, research questions, methods used, data inputs, summary results, and importantly, to highlight our concerns. They are complemented by material presented in appendices, but we stress that the review of industry models has still been outline in nature, and does not represent a thorough investigation of methods, data, and model workings (i.e. not a "cell by cell" audit of model implementation). In the next section, we present the PenTAG cost-effectiveness analysis (methods, results, limitations, discussion). Unlike the individual manufacturer submissions, which have an emphasis on specific products and data sources (i.e. trial/effectiveness data), the PenTAG analysis has attempted to apply common methods across the assessment of the cost effectiveness of all drugs included in the scope for treatment of RCC.

In a later section (section 4.6) we present a discussion and comparison of the cost-effectiveness analysis presented by PenTAG and that presented in the manufacturer submissions to NICE which presents more detail, in a comparative context, on the implications of many of the assumptions used by drug manufacturers in assessing cost-effectiveness.

4.5. PenTAG cost-effectiveness analysis

4.5.1. Statement of problem and perspective of CEA

The cost-effectiveness analysis presented here addresses the research questions set out in section 2.9 on page 31. The analysis takes the perspective of the NHS and Personal Social Services in the UK.

4.5.2. Strategies/Comparators

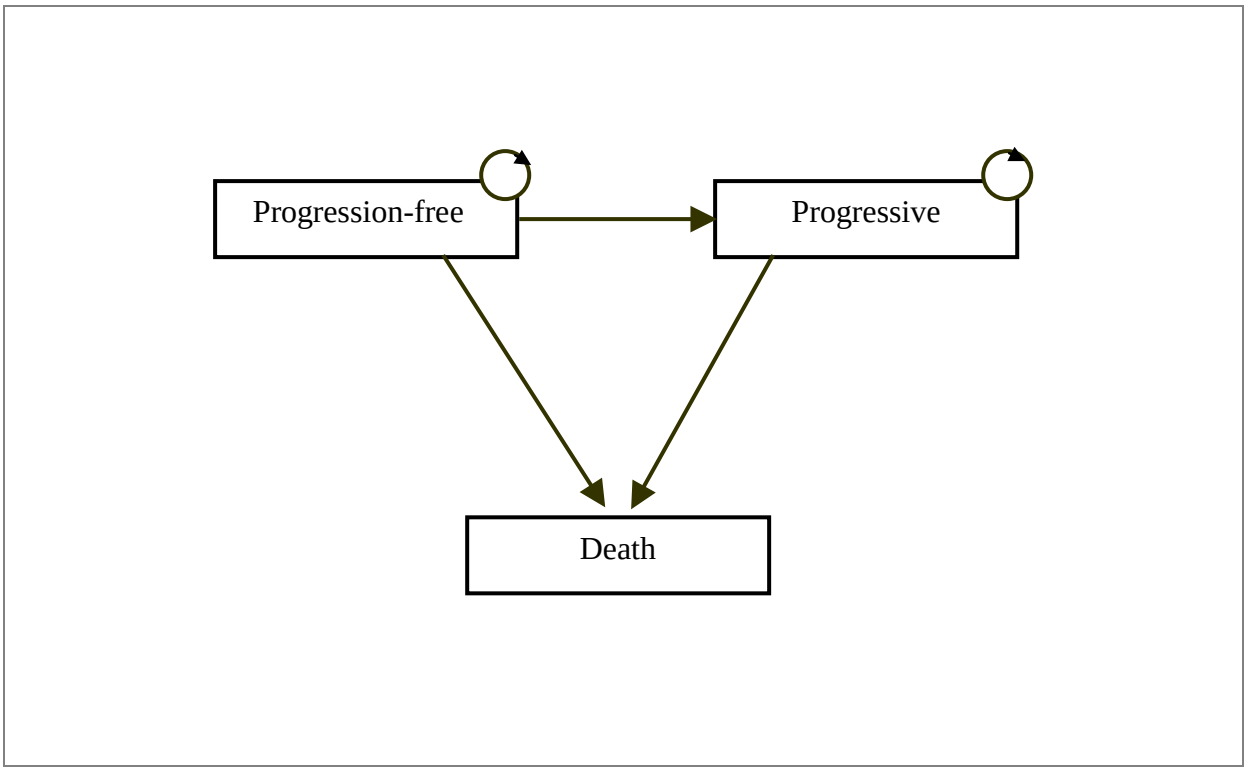
The analysis estimates the cost effectiveness of sunitinib, sorafenib, bevacizumab plus IFN and temsirolimus against relevant comparators for licensed indications (as detailed in 2.7 on page 26), where data allows. The modelling of cost effectiveness considers 1st line treatment, 2nd line treatment, and treatment of RCC patients with a poor prognosis (1st line), separately, using a similar model structure, but employing different data to inform the model parameters.

4.5.3. Model Structure / Rationale

We developed a decision-analytic model to simulate disease progression in RCC, and to estimate the cost-effectiveness of the drugs under consideration. The model uses survival analysis to consider progression of RCC in a cohort of patients over time. The model was written in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA). The structure was informed by a review of the available literature, clinical guidelines for treatment of RCC, and expert opinion on the clinical progression of the disease.

The model uses three distinct health states: progression-free survival (PFS), progressive disease (PD) and death (Figure 10). The model uses estimates of effectiveness, costs and health state values against these health states to model progression of disease and cost-effectiveness over time. The model uses a 10-year time horizon, and a 6-week model cycle. This structure is regarded as appropriate for capturing the health effects, and complexities of natural history / disease progression in RCC. Future costs and benefits are discounted at 3.5% per annum.[134]

Figure 10: Influence diagram for PenTAG RCC cost-effectiveness model



In Figure 10, boxes represent health states and arrows represent transitions between states. At any moment, a patient is assumed to be in one of the states. Patients move between states once during each cycle. This means that if a patient is in PFS, for example, then during the next cycle they can either die, move to PD or stay in PFS. The health states of a cohort of patients are modelled at each discrete model cycle. All patients enter the model in PFS, having been diagnosed with advanced/metastatic RCC. Patients remain in PFS until they either die or until the disease progresses. Once patients enter the PD state, they remain there until death.

In the survival analysis used to structure the model, for each baseline strategy/treatment a Weibull curve is derived to describe the number of patients alive over time (overall survival data) and another Weibull curve describes the number of patients in PFS over time. Weibull survival curves were fitted separately, corresponding to a chosen baseline treatment (i.e. IFN or BSC), to the PFS and OS Kaplan-Meier curves from the RCT judged most appropriate. For each treatment being compared to the baseline disease progression (e.g. sunitinib vs. IFN) the model uses relative measures of treatment effectiveness (hazard ratios) to estimate the expected disease progression compared to baseline. For each treatment (baseline and comparator), the number of patients in the PD health state at any time is calculated as the number alive minus the number in PFS health state, at that time. This is analogous to the methods used in previous Health Technology Assessments of treatment for metastatic colorectal

cancer[142] and ovarian cancer,[143] where the mean duration patients were in the progressive health state was calculated as the duration in the overall survival state minus the duration in PFS. Appendix 7 (page 254) presents details of the methods used for the survival analysis used to structure the model.

The model uses the survival analysis approach to structure a Markov-type model, which estimates the costs and effects across a cohort of patients over time, estimating the costs and effects for each health state at each model cycle (to estimate a cost for each cohort at each cycle). A half-cycle correction is applied in the modelling.

In modelling cost-effectiveness, the approach includes additional costs associated with each of the treatment strategies (drugs), covering drug administration costs (where required), and medical management costs when in the PFS health state (outpatient monitoring, scans, tests, treatment of adverse events). The model makes assumptions over expected resource use to estimate the costs associated with BSC, and the expected additional resources and costs associated with serious (Grade 3 & 4) adverse events. When estimating drug costs, the modelling applies data on dose intensities (from RCTs), to adjust the costs of interventions. This complements ITT effectiveness data (with drug cost being a primary cost driver in analysis).

Where manufacturers have advised of drug pricing strategies in submissions to NICE[118,136] these are not included in the modelling of the base case cost-effectiveness of treatment, based on advice from NICE and the inconsistency of the pricing strategies with the NICE reference case requirements. However, such pricing strategies have been included in sensitivity analyses.

4.5.4. Data

The modelling framework synthesises data from a number of different sources, including data for baseline disease progression, measures of clinical effectiveness from RCTs (section 3), health state utility data (for PFS and PD health states), resource use and cost data associated with drug treatment and non-drug related resource use and costs. These are outlined below.

4.5.4.1. Patient cohort characteristics

All patients in the model were assumed to have advanced / metastatic renal cell carcinoma, and all patients were assumed to start in PFS.

4.5.4.2. Model structure

In the approach employed (i.e. survival analysis), the baseline progression of disease is modelled in each CEA question using data from clinical trials, with treatment effect modelled using measures of

relative treatment effect (as reported in relevant RCTs). These data are discussed in more detail below.

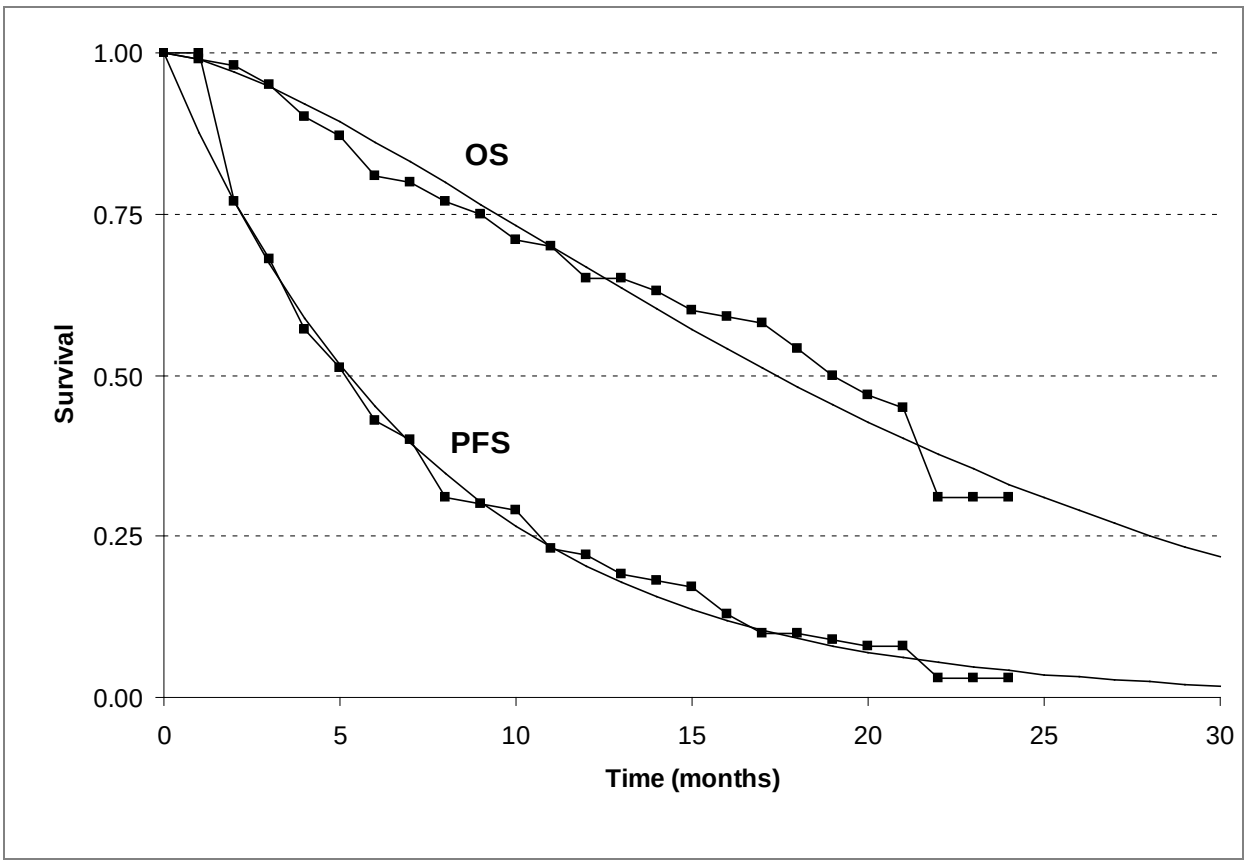
4.5.4.3. Effectiveness data

The details of the survival analysis for each of the cost-effectiveness (policy) questions is outlined below.

Question 1 - Modelling survival data: In those who are suitable for treatment with immunotherapy, what is the cost effectiveness of (i) bevacizumab plus IFN, (ii) sunitinib, compared to IFN as first line therapy?

To estimate baseline disease progression, i.e. when patients are on IFN alone, data are taken from the RCT reported by Escudier and colleagues[106], which compares bevacizumab plus IFN to IFN alone. For the IFN alone patient group, the overall survival and progression free survival (PFS) data (Kaplan Meier survival data) are used to model disease progression over time. PFS and OS data for IFN were read directly from the published Kaplan-Meier survival curves in the bevacizumab plus IFN RCT,[106] and Weibull curves were than fitted to the data for use in the PenTAG model. The fit of the Weibull curves to the empirical Kaplan Meier data is shown in Figure 11. Appendix 7 (page 254) reports further detail on the methods used to model survival data.

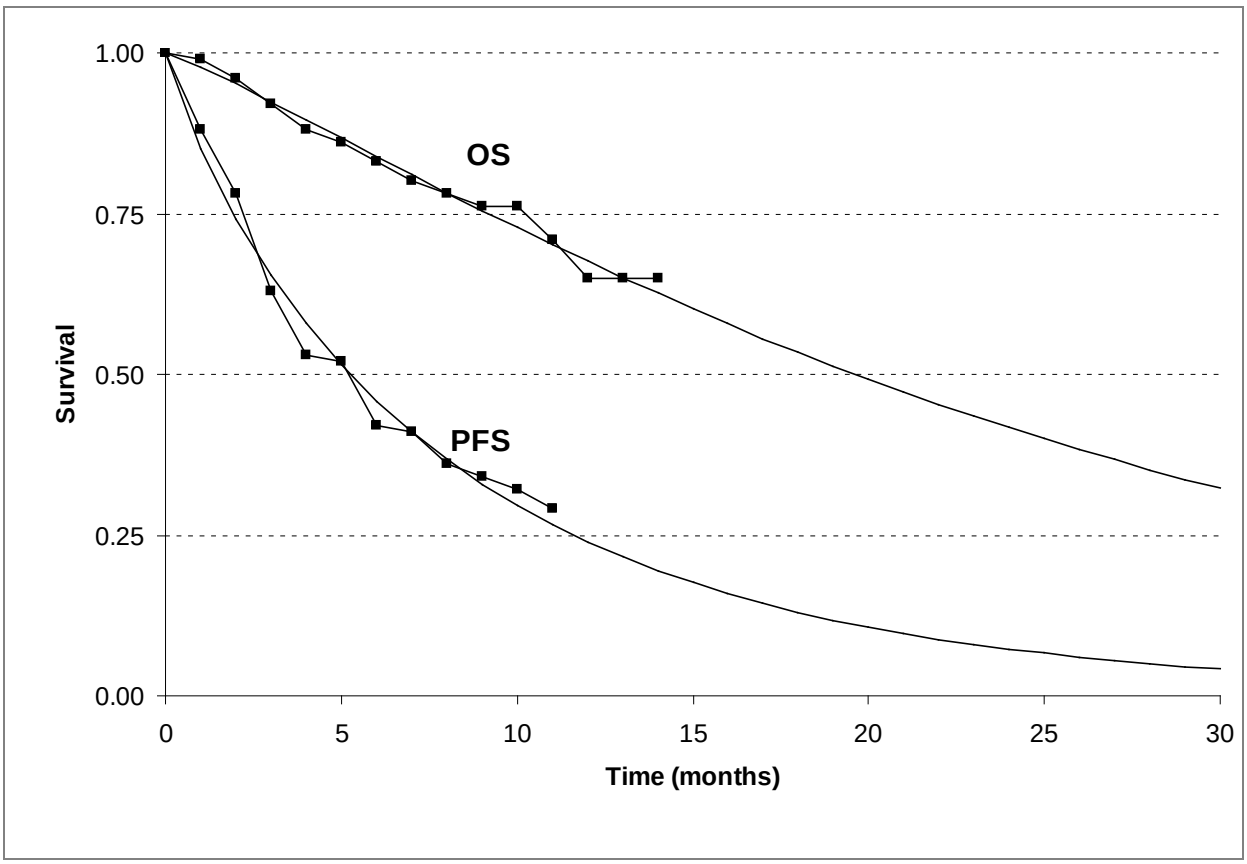
Figure 11. Survival analysis for base case: Weibull curves fitted to IFN PFS and OS Kaplan-Meier data



Source: Escudier and colleagues, 2007[106]

We chose data from the bevacizumab trial[106] to model baseline data based on our judgment that it is the most appropriate option from the two potential sources of data available. Alternatively, data from the trial of sunitinib versus IFN reported by Motzer and colleagues[111]could have been used. However, the Kaplan-Meier data for overall survival in this RCT has not been published, and secondly, the data are immature (see Figure 12, page 136). Given the use of a multiple comparison approach for IFN, bevacizumab plus IFN and sunitinib, one baseline data source had to be chosen from the options available. However, this structural assumption is considered in the sensitivity analysis by using disease progression data from the RCT of sunitinib vs. IFN.[111] PFS was taken from the published paper and OS from the Pfizer submission to NICE{1076). See Figure 12 for the fit of the Weibull curves to the empirical survival data used in sensitivity analysis (note the shorter duration of empirical data).

Figure 12. Survival data for sensitivity analysis: Weibull curves fitted to IFN PFS and OS Kaplan-Meier data.



Source: Motzer and colleagues, 2007 [111] and Pfizer industry submission[136]

Using the baseline (IFN alone) disease progression data, the disease progression for bevacizumab plus IFN and for sunitinib were estimated using the relative measures of treatment effect reported in section 3.2.2.2. For bevacizumab plus IFN the hazard ratios for PFS and OS were 0.63 (95% CI: 0.52-0.75) and 0.75 (95% CI: 0.58-0.97) respectively. For sunitinib the hazard ratios for PFS and OS were 0.42 (95% CI: 0.33-0.52) and 0.60(95% CI: 0.45-0.94) respectively.

For this policy question, we performed a multiple comparison of bevacizumab plus IFN, sunitinib, and IFN alone. An indirect comparison of bevacizumab plus IFN vs. sunitinib was possible due to the judged exchangeability of the RCTs reported. The patient characteristics (e.g. % nephrectomy, % clear-cell, MSKCC severity scale, dose of interferon) are very similar in the RCTs of bevacizumab plus IFN vs. interferon and sunitinib vs. interferon (section 3.2.2.2). However, the two RCTs differ in two ways relevant to the indirect comparison. First, in the RCT of sunitinib vs. IFN patients took IFN whilst in the PFS category (with no constraint on time period), whereas in the RCT of bevacizumab plus IFN vs. IFN (in both treatment arms), patients were able to stay on IFN up to a maximum of one year. In the base case analysis undertaken we assumed the latter, i.e. IFN is taken whilst in PFS up to

a maximum of one year (this assumption was tested in sensitivity analysis). Secondly, the dose intensities (see discussion below) of IFN monotherapy differed slightly in the two RCTs: 83% in the sunitinib RCT and 89% in the bevacizumab plus IFN RCT.[106] For the indirect comparison, we chose the average of these values, i.e. 86% for IFN monotherapy. All other dose intensities were set equal to the values from the relevant RCT.

Question 2 - Modelling survival data: In those who are not suitable for treatment with immunotherapy, what is the cost effectiveness of sorafenib and sunitinib compared to best supportive care?

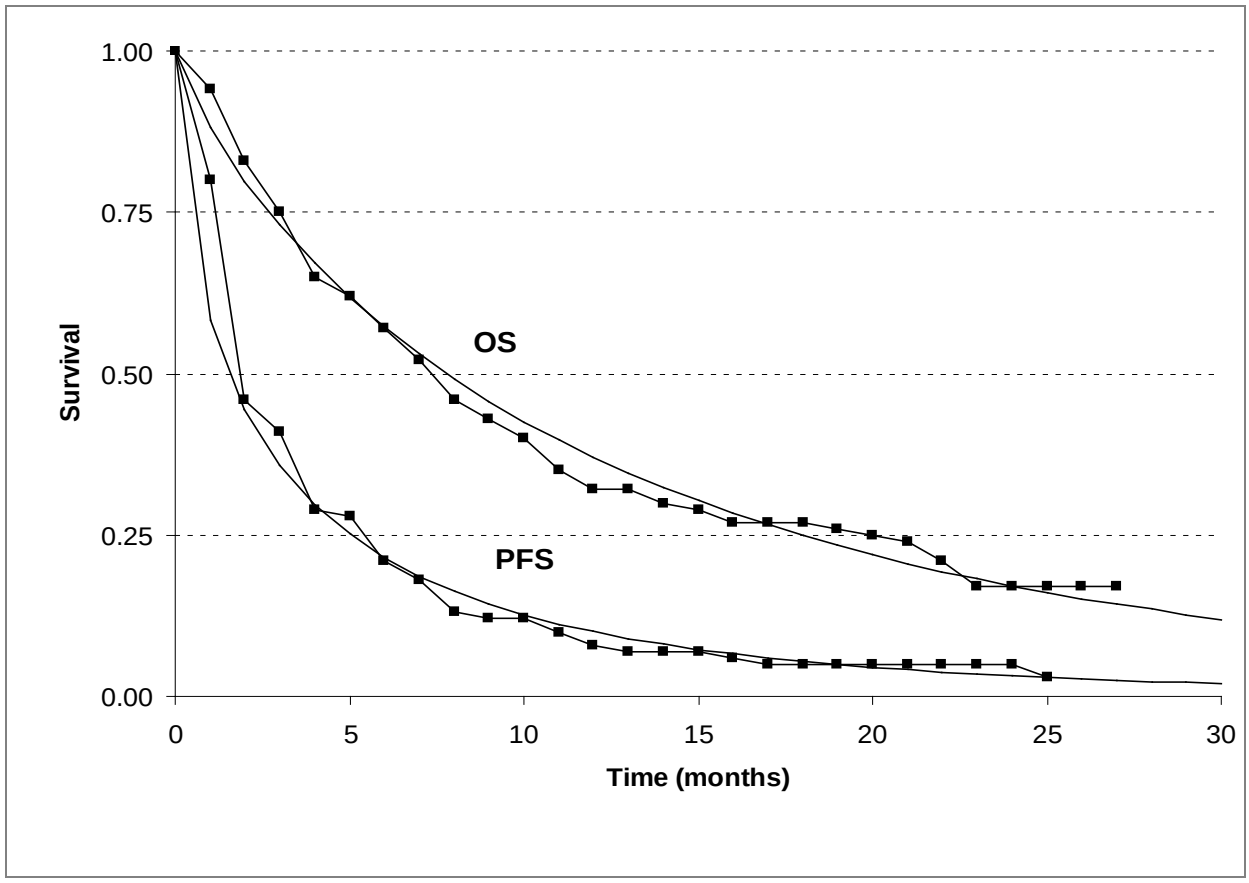
There is an absence of clinical effectiveness data for this comparison, therefore no analysis has been undertaken.

Question 3 - Modelling survival data: In those with three or more of six poor prognostic factors what is the cost effectiveness of bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and best supportive care compared to IFN?

Against this question, the only data identified to enable the modelling of the cost-effectiveness of treatment was for the comparison of temsirolimus versus IFN (see section 3.2.4.1, page 65). Therefore analyses for the other comparators are not undertaken. In particular, we report that we were unable to use data from the RCT of sorafenib[113] to help answer this question, as there were no poor prognosis patients in this trial (see section 3.2.5.1, page 82). We have not modelled the cost-effectiveness of sunitinib for poor prognosis patients for two reasons. Firstly the clinical effectiveness data for overall survival (OS) in poor prognosis patients included in the RCT of sunitinib vs. IFN,[111] has not been reported. Secondly, only 48 patients in this RCT were reported as poor prognosis (see section 3.2.2.1, page 44). We note that we have not modelled the cost-effectiveness of bevacizumab plus IFN for poor prognosis patients because there were only 52 poor prognosis patients in the RCT of bevacizumab plus IFN vs. IFN.[106] More importantly, whilst noting the sparsity of data, we felt unable to consider any form of indirect comparison of bevacizumab plus IFN versus temsirolimus for poor prognosis patients, given: (1) the definitions of poor prognosis in the bevacizumab plus IFN vs. IFN and temsirolimus vs. IFN RCTs differed, and (2) the doses of IFN in these two RCTs differed: 9MU and 18MU respectively (see section 3.2.4.1, page 65).

To model temsirolimus versus IFN we used Kaplan Meier survival data from the RCT reported by Hudes and colleagues[112] In the base case analysis we used data from the RCT reported by Hudes and colleagues for all patients in the trial, and Weibull curves were fitted to empirical Kaplan Meier data on PFS and OS for the patient group on IFN, see Figure 13 below. To model progression of disease in those treated with temsirolimus we applied relative measures of clinical effectiveness (hazard ratios) for PFS (0.74, 95% CI: 0.60 – 0.91) and OS (0.73 95% CI: 0.58 – 0.92), from Hudes and colleagues, see section 3.2.4.2 (page 70).

Figure 13. Survival analysis for base case: Weibull curves fitted to IFN PFS and OS Kaplan-Meier data



Source: Hudes and colleagues, 2007 [112]

We note that due to difference in the definition of poor prognosis used in the RCT of temsirolimus versus IFN, only 75% of included patients were described as having poor prognosis according to the MSKCC prognostic score; the remainder had intermediate prognosis. Due to the absence of survival data (Kaplan-Meier curves) for only those patients with poor prognosis (MSKCC score) the 'all patients' data has been used in the base case analysis.

In the comparison of temsirolimus versus IFN we were able to consider subgroup analyses, as data are available for five subgroups. However, the data available is on relative measures of clinical effectiveness (hazard ratios for OS and PFS), see Table 36 (page 139), and there is no data on baseline disease progression for the subgroups. In subgroup analysis for patients with an MSKCC poor prognosis score we adjusted the baseline IFN PFS and OS curves to model only those 75% of patients who are poor prognosis according to this scale. Specifically, we forced the median PFS and OS modelled times to equal the median PFS and OS times for the poor prognosis patients from the

temsirolimus vs. IFN RCT.[112] This was achieved by appropriately varying the parameter λ (lambda) of the Weibull distribution separately in the PFS and OS curves. For other subgroup analyses (clear-cell, non-clear-cell, prior nephrectomy, no prior nephrectomy) we assumed the same baseline IFN PFS and OS curves as for all patients from the temsirolimus vs. IFN RCT,[112] using the reported hazard ratios for these subgroups (Table 36).

Table 36: Survival data: subgroup clinical effectiveness. Hazard ratios of temsirolimus vs. IFN

Subgroup	Survival	Number of patients	Hazard ratio (95% CI)	Data source
All data †	PFS	416	0.74 (0.60 – 0.91)	Wyeth submission p16[125]
	OS	416	0.73 (0.58 – 0.92)	Hudes et al [112]
Motzer poor prognosis¶	PFS	301	0.69 (0.54 – 0.87)	Dutcher et al [94]
	OS	301	0.70 (0.55 – 0.89)	Dutcher et al [94]
Clear-cell / not clear-cell †	PFS	Clear cell = 339, Not-clear cell = 73	Clear cell = 0.84 (0.67-1.05), Not-clear cell = 0.36 (0.22-1.59)	Dutcher et al [94]
	OS	Clear cell = 339, Not-clear cell = 73	Clear = 0.85 (0.64-1.06), Not-clear cell = 0.55 (0.33-0.90)	Dutcher et al [94]
Prior nephrectomy (Y/N) †	PFS	Yes = 278, no = 138	Yes 0.74 (0.58-0.95), no 0.63 (0.44-0.91) ‡	Wyeth submission p22[125]
	OS	Yes = 278, no = 138	Yes 0.84 (0.63-1.11), no 0.61 (0.41-0.91)	Wyeth submission p22[125]

† Includes the 25% of patients at intermediate Motzer score

¶ Baseline IFN PFS and OS curves adjusted, see text

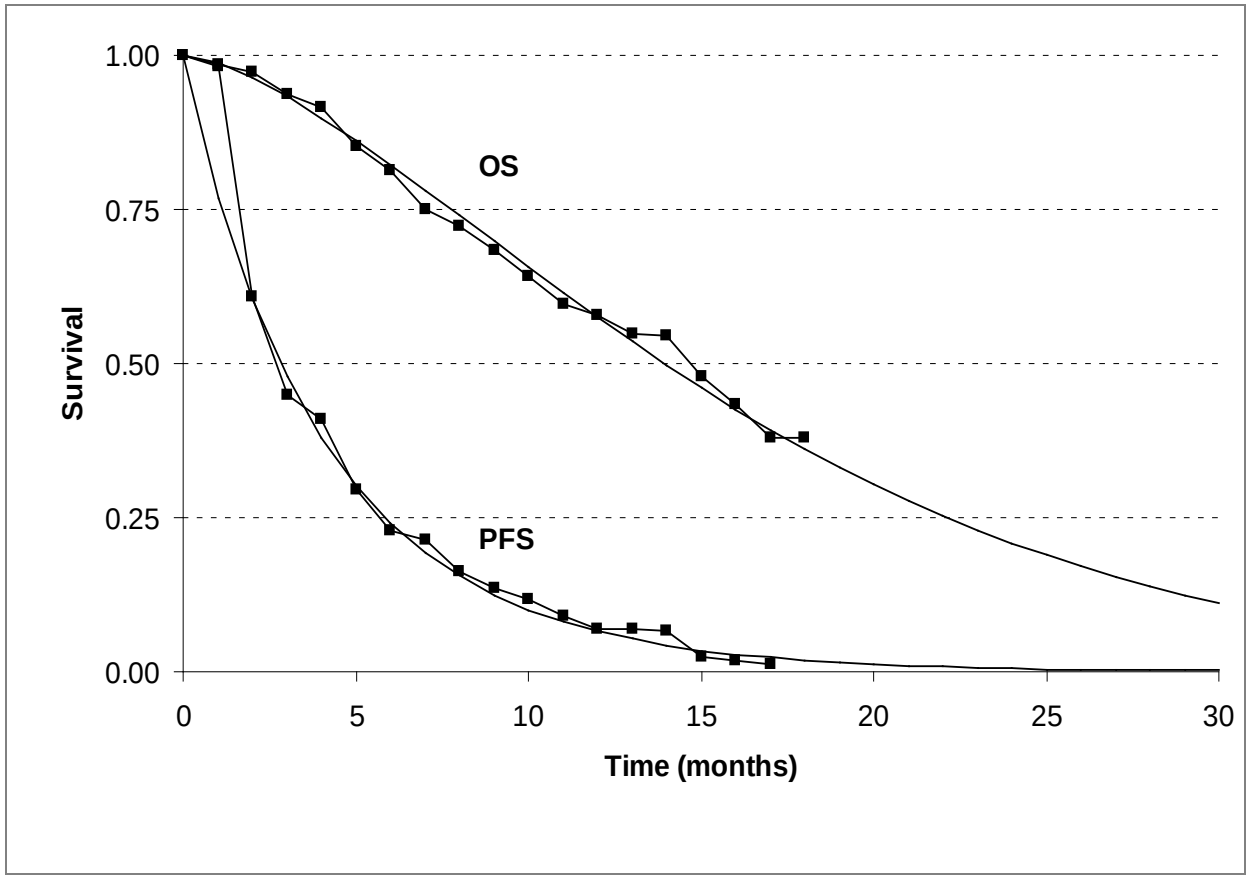
‡ Investigator assessment

Question 4 - Modelling survival data: In those who have failed treatment with cytokine based immunotherapy what is the cost effectiveness of sorafenib tosylate and sunitinib as second line therapy compared to best supportive care?

For this question we identified data on sorafenib versus best supportive care (BSC) only. Whilst data were identified on sunitinib versus BSC in second line therapy it comes from two single-arm trials.[116,117]. We did not use this data to model cost effectiveness due to methodological concerns.[144]

We modelled disease progression and cost effectiveness for sorafenib compared to BSC using data from the RCT reported by Escudier and colleagues[113]. We used data from this RCT for all patients in the trial, although we note that only 82% had been previously treated with immunotherapy. The manufacturer submission (Wyeth)[141] reports that the remaining patients in the trial (18%) were unsuitable for immunotherapy.

Figure 14. Survival analysis for base case: Weibull curves fitted to BSC PFS and OS Kaplan-Meier data



Source: Escudier and colleagues, 2007[113]

Data from the BSC arm of the RCT (Kaplan-Meier curves for PFS and OS) were used to model baseline disease progression.[113] Weibull curves were fitted to the empirical data, detailed in Appendix

7 (page 254). Figure 14 (page 140) reports the fit of the Weibull curves to the data. In modelling disease progression for people on sorafenib we used the hazard ratios for PFS and OS reported by Escudier and colleagues; for PFS the (investigator-assessed) HR was 0.51 (95% CI: 0.43 – 0.60),[113] and for OS the HR was 0.72 (95% CI: 0.54 – 0.94). [113]

4.5.4.4. Health state utilities

Table 37 (page 143) presents the health state values used in the PenTAG base case analysis. We found no published data on health state values for RCC, across all of the patient groups, and we are unable to draw on the published literature (section 4.3.1) to inform the choice of health state values in the PenTAG model. Manufacturer submissions to NICE did contain further information as model inputs (see section 4.4, page 105), but uncertainties remain surrounding the collection and presentation of available data. We believe that all available sources of health state value data for RCC have limitations, and some judgment is required to select parameters for the base case scenarios in the PenTAG analysis.

In the base case analysis, we use the data presented in the sunitinib submission to NICE (Pfizer)[136] for health state values for 1st and 2nd line treatment. The health state values in the submission are derived from trial data (stated source: RCT by Motzer and colleagues (2007) (1st line),[111] and Motzer and colleagues (2006) [117] (2nd line)), and UK EQ-5D tariffs, although published reports of these trials do not include the EQ-5D data used to estimate health state values. In the absence of supporting material for these reported health state values, we are unable to comment further on methods used. The manufacturer submission reports, and applies, treatment-specific health state values, however, we do not support the use of treatment (drug) specific health state values. We assume at baseline in the trials that patients are similar, and do not see support in the evidence for differential utilities by treatment.

In the PenTAG analysis, we use the same estimates of health state value for the health states of PFS and PD for both treatment and control arms in the model. For analysis of 1st line treatment we use the health state values presented 'by disease progression' in the manufacturer submission (Pfizer)[136], and for 2nd line we apply the values reported against 'baseline' and 'progression', as per the same submission.

Data for health state values in the poor prognosis treatment group are taken from the temsirolimus industry submission[125], which are derived from EQ-5D data collected in the trial reported by Hudes and colleagues (2007).[112] The EQ-5D data are not reported in the publication of the trial, although some brief detail is presented in a published abstract.[97] These values place PFS and PD for poor prognosis at a different point, compared to the other indications, on the 0-1 health utility scale, which may be legitimate, given the poor prognosis for the patients in the temsirolimus RCT.[112] However, we

feel that differences are significant and are potentially inconsistent with the data used for health state values in analysis of 1st line and 2nd line treatment. For patients with poor prognosis, we note, from data describing patient characteristics in clinical trials, that these patients are reported at a worse/poorer level against measures of performance status. The majority of patients in the sunitinib RCT[111] had an ECOG performance status of 0 (approx 60%), whilst 80% of patients in the temsirolimus RCT[112] had a Karnofsky performance score of 60 or 70,[112] which has been shown to be approximately equivalent to an ECOG performance status of 2 (where 2 is a worse status that 0 and 1).[4,27] However, we believe that the difference in utility values obtained from the two trials may not be adequately explained by differences in performance status, and by using data from different sources we may be introducing a lack of continuity in modelling the policy questions.

However, in the absence of other data, the estimates derived from the temsirolimus RCT[112] are used in the base case for the temsirolimus CEA, with further scenarios explored in sensitivity analyses. We do not use data from the manufacturer submission which assumes an increment for the health state value (PFS) according to a measure of 'response' to treatment.

We note that where the multiple data sources are applied (as set out above) within a common modelling framework for 1st line, 2nd line, and poor prognosis patient groups, there may be a lack of intuition over the disease pathway, and perceived continuum of health state values. We note that assumptions made give a utility difference between PFS and PD of 0.08 for 1st line, 0.075 for 2nd line, and 0.15 for poor prognosis. We note that patients starting in both 1st line and 2nd line treatment have similar starting values, whilst patients with poor prognosis are assumed to have a much lower starting health state value. We recognize that where patients fail 1st line treatment (often against measurable criteria e.g. tumour growth rather than impacts against HRQL), patients are then eligible for 2nd line treatment, and start 2nd line treatment as PFS (with a similar health state value to that in 1st line, due to a recognised new starting point for PFS/PD).

We acknowledge limitations in the utility data available to populate the model, and we explore the impact of assumptions on health state values in sensitivity analyses.

Table 37: Health state utilities used in PenTAG model

Policy question	Treatments	Health state	Base case (s.e.) *	Source / Justification
1st-line (not poor prognosis)	IFN, sunitinib, bevacizumab plus IFN	PFS	0.78 (0.01)	Pfizer submission[136]
		PD	0.70 (0.02)	
1st-line (poor prognosis)	IFN, temsirolimus	PFS	0.60 (0.06**)	Wyeth submission[125]
		PD	0.45 (0.04**)	
2nd-line & unsuitable IFN	Sorafenib, BSC	PFS	0.76 (0.03)	Pfizer submission[136]
		PD	0.68 (0.04)	

* s.e. derived from s.d. and number of patients from RCTs, reported in industry submissions.
** s.e. estimated as 10% of mean.

4.5.4.5. Resource Use / Cost data inputs

Resource use, and associated costs, are estimated from a range of sources and refer to the baseline costs of managing RCC and additional costs associated with different treatment options. The cost components include, drug cost, related drug administration costs, costs for treatment of serious adverse events, costs associated with treatment-related monitoring when in the PFS health state, and the costs associated with BSC when in the PD health state. As discussed in section 4.3.2 there is an absence of published data to inform on the costs associated with treatment of RCC, and assumptions have been made against a number of the cost components used in the modelling. Assumptions have been based on guidelines outlining current practice and the information provided by clinicians in the expert advisory group. BNF current list prices are used for drug pricing, and all other costs are inflated to 2007/8 values.[145]

Drug Costs

Table 38 presents the drug prices used to inform the analysis, and the estimated cost for each of the drugs for the 6-week cycle used in the model. Drug prices have been taken from the British National Formulary (No.55),[70] with the exception of the temsirolimus price which is not listed at the time of

writing. The pricing information for temsirolimus is based on advice to NICE by the manufacturer (Wyeth).

Table 38: Drug costs in the PenTAG model

Drug	Brand	Dose and frequency	Cost *	Cost per 6-week cycle
interferon-alpha (18MU)	Roferon-A	18MU† 3 times per week	£90.39 per 18MU ††	£1,265 first model cycle, £1,627 future cycles
interferon-alpha (9MU)	Roferon-A	9MU††† 3 times per week	£45.19 per 9MU ††	£678 first model cycle, £813 future cycles
bevacizumab	Avastin	10mg/kg given once every 2 weeks	£924.40 per 400mg	£5,304‡
bevacizumab + interferon alpha (9MU)	Avastin + Roferon-A	Combination of above		£5,982 first model cycle, £6,117 future cycles
sorafenib	Nexavar	400 mg twice daily	£2,504.60 per 200mg 112-tablet pack	£3,767
sunitinib	Sutent	50 mg daily for 4 weeks, followed by 2-week rest period	£3,363 per 30-capsule 50mg pack	£3,139
temsirolimus	Torisel	25mg once per week	£618 per dose‡‡	£3,708‡‡

* All cost data taken from British National Formulary (BNF) No. 55,[70] except that of temsirolimus, which was provided by Wyeth.[125]

† 3 million units / mL (MU) per dose in 1st week, 9MU per dose in 2nd week, 18MU per dose thereafter.

†† 3MU dose costs £15.07, 6MU dose costs £30.12, 9MU per dose costs £45.19, 18MU dose costs £90.39.

††† 3 MU per dose in 1st week, 6MU per dose in 2nd week, 9MU per dose thereafter.

‡ Assuming average weight of patients from the RCT of bevacizumab plus IFN vs. IFN[106] of 76.5kg. Base case figure assumes no wastage of bevacizumab. Allowing for wastage by assuming 800mg taken per patient every 2 weeks, increases cost per 6 weeks to £5,546.

¶ In the sensitivity analysis, we assume that the first 6-week treatment cycle is free to NHS.

‡‡ £20.60 per mg (Wyeth). Assumes some wastage of temsirolimus given that all 30mg in a vial is used. In a sensitivity analysis, we assumed no wastage, i.e. £515 per 25mg dose, £3,090 per 6-weeks.

Where drug pricing strategies have been presented by manufacturers, these have not been used in the current base case cost-effectiveness analysis. The manufacturer of sunitinib (Pfizer) has advised that for the UK NHS the first cycle of sunitinib will be supplied free of charge.[136] The manufacturer of bevacizumab (Roche) has advised that for the UK NHS (also a European wide scheme) there is a 'dose cap' pricing strategy, where there are no charges for bevacizumab once, an individual has had 10,000mg within one year of treatment initiation.[118] When introducing these pricing strategies into sensitivity analysis, we estimate that under the bevacizumab 'dose cap' scheme, there will be no cost beyond thirty weeks of treatment (assuming a bevacizumab dose intensity of 88% mean patient weight of 76.5kg, and 765mg dose every two weeks).

As noted in the footnote to Table 38 (page 144), in the base case cost-effectiveness analysis for temsirolimus we have assumed that there will be one 30mg vial used per dose, which, given the licensed 25mg dose, includes 5mg waste in the cost effectiveness analysis.

Drug Cost: Dose intensity

For all drugs in the cost-effectiveness analysis, with the exception of sorafenib, the clinical trials, and/or the manufacturer submissions to NICE, report data on dose intensity i.e. the mean dose of drug that is expected in a cohort of patients. The dose intensity of a drug is defined as the amount of drug administered in a clinical trial as a proportion of the amount that should have been administered if there had been no patient withdrawals or dose reductions. Reported dose intensities are presented in Table 39.

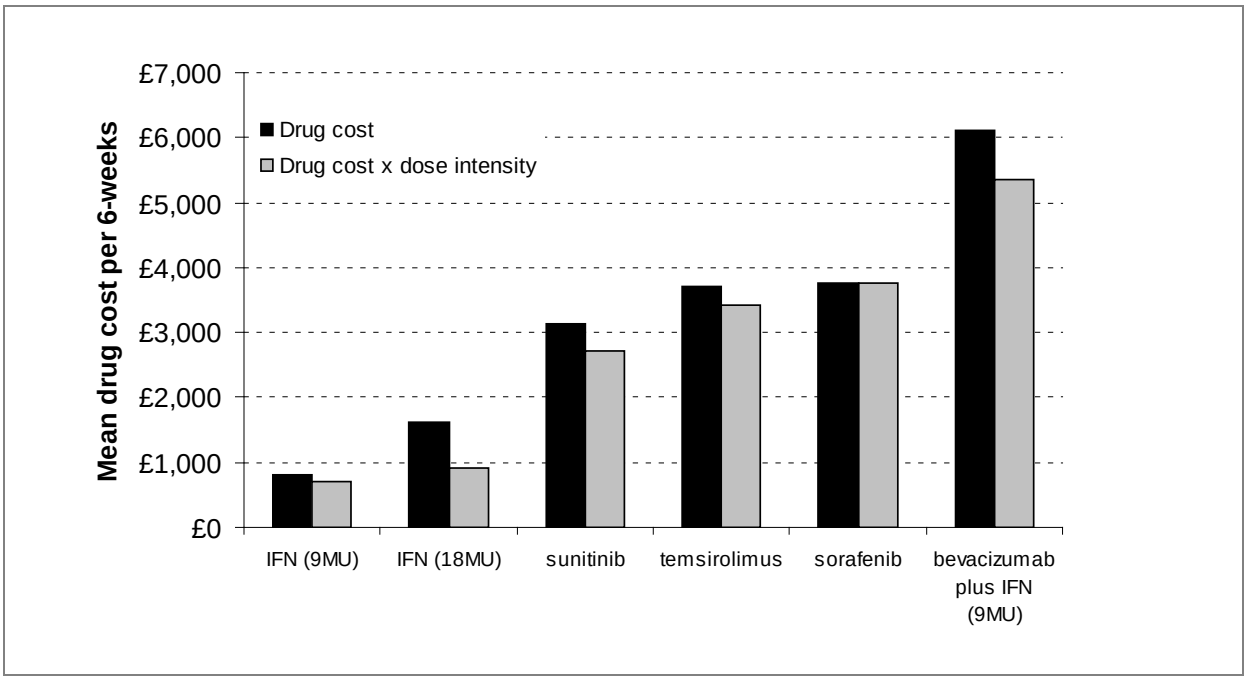
Table 39: Dose intensities applied to drug costs in the PenTAG model.

Treatment	Drug dose intensity	Source
IFN (18MU), 2nd-line	56%	RCT of temsirolimus vs. IFN[112]. Measured in first 8 weeks of treatment.
Temsirolimus	92%	RCT of temsirolimus vs. IFN[112]. Measured in first 8 weeks of treatment.
Sorafenib	100%§	Bayer submission [141]
Sunitinib	86%	Value quoted by Pfizer from RCT of sunitinib vs. IFN[111], but not published.
Bevacizumab	88%	RCT of bevacizumab+IFN vs. IFN[106]
IFN (9MU, with bevacizumab) 1st-line	83%	RCT of bevacizumab+IFN vs. IFN[106]
IFN monotherapy (9MU) 1st-line	86%	Average of IFN monotherapy values from Motzer et al (2007)[111] (value quoted by Pfizer 83.1% from RCT of sunitinib vs. IFN[111]), but not published) and Escudier et al (2007)[106] (89%)

§ Approx. 6% of patients receiving sorafenib in the pivotal sorafenib RCT[113] had dose reductions[141]

In the base case cost-effectiveness analysis these dose intensity data are used in the modelling framework to adjust the cost of the drug (see data in Figure 15, page 147). This assumption is based on an acceptance that the clinical effectiveness data are from RCTs reporting intention-to-treat analysis (ITT), and the use of the reported dose intensity data makes some allowance in treatment cost (especially given the finding highlighted in the results section that drug cost is the major component of total cost) for an ITT analysis. This assumption is tested in sensitivity analyses.

Figure 15: Drug costs and mean drug cost adjusted for dose intensity



Drug-related costs: Administration of drugs

There is a drug-related administration cost for three of the drug treatment strategies; IFN, bevacizumab plus IFN, and temsirolimus. There is no administration cost for BSC, sunitinib (oral) or sorafenib (oral). Cost estimates are presented in Table 40.

IFN (monotherapy) is administered by injection 3 times per week. The assumption in the current analysis is that the administration of IFN is at home on all occasions, and by patients or carers in 75% of cases, with 25% of cases (injections) being administered by a district nurse. These assumptions are based on information provided by the clinical community on current practice (five members of our expert advisory group). The estimated cost per 6-week cycle for the administration of IFN is £112.

Both temsirolimus and bevacizumab are administered in a hospital setting, temsirolimus once per week and bevacizumab once every two weeks. We have assumed a cost per administration based on an HRG (SB/5Z) from the NHS Reference Costs database, covering 'chemotherapy outpatient' episode for delivery of chemotherapy. For each 6-week cycle we estimate drug administration costs of £590 for bevacizumab and £1,179 for temsirolimus. These costs represent significant additional drug-related costs, compared to IFN alone.

Table 40: Estimated cost for administration of IFN, bevacizumab and temsirolimus.

	IFN monotherapy	Bevacizumab	Temsirolimus
Dose frequency	3 per week	1 per 2 weeks	1 per week
Resource use	75% self-administered 25% district nurse administered	Outpatient attendance (chemotherapy)	Outpatient attendance (chemotherapy)
Unit cost for resource use	£25 per district nurse administration §	£197 per administration †	£197 per administration
Mean estimated 6-week cost for administration (s.e.)	£112 (£7)	£590 (£52)	£1,179 (£105)

§ Schema 9.1 Community nurse (includes district nursing sister, district nurse).[146]

† "Chemotherapy Outpatients". HRG code = SB15Z. "Deliver subsequent elements of a chemotherapy cycle".[145]

When estimating the costs associated with administration of drugs we do not adjust the cost for administration using the dose intensity data (reported above). This assumption is based on information from the clinical members of the expert advisory group who indicated that doses of IFN would be reduced, rather than omitted/missed completely, suggesting that dose intensities should not be applied to reduce the cost of administration of IFN. We make this assumption (for consistency) across all three drugs with an administration cost. The assumption is tested in sensitivity analyses.

Medical management costs

When patients are in the health state of PFS, and on drug treatment, there is a resource use / cost associated with outpatient monitoring, scans and tests. We found no specific published literature to inform on such resource use, and assumptions have been made on the resource use and subsequent costs associated with monitoring, as part of the medical management of people with RCC.

Table 41 presents cost estimates per 6-week cycle for medical management. When patients are on drug treatment (in PFS) there is an assumption that they will all have one outpatient appointment every month, one CT scan every 3-months and standard blood tests once every month (with outpatient appointment). When patients are not on active treatment with bevacizumab plus IFN, sunitinib, sorafenib, temsirolimus or IFN we assume that they will have a GP visit every month and a CT scan every 6-months.

When patients are in the progressive disease (PD) health state (both first- and second-line therapy) we assume that they will be managed in primary care (EAG advice), and that they will have mean NHS resource use comprising one GP visit per month, 1.5 community nurse visits per month, and pain medications throughout the month. This resource use over a 6-week cycle gives a mean cost estimate of £435, (see Table 41 below). Sensitivity analysis tests the sensitivity of the cost-effectiveness analysis to this cost assumption, using an estimate from the literature on costs associated with BSC in breast cancer.[133]

The industry submissions to NICE include a cost associated with death. We have not included this item in our base case cost effectiveness analysis but carry out a sensitivity analysis where a cost for death is included, based on an estimate from the literature (Coyle et al, 1999[133]).

Table 41: Cost parameters in the PenTAG cost-effectiveness model

	Progression-free survival (PFS) medical management		**Progressive Disease (PD) medical management**
	BSC	**All drug treatments**	**All treatments (drugs & BSC)**
Consultations per month	1 GP	1 consultant outpatient	1 GP, 1.5 community nurse
Tests	1 CT scan per 6 months, blood tests monthly	1 CT scan per 3 months, blood tests monthly	None
Other‡	None	None	Pain medication (morphine sulphate) daily¶
Cost per 6-week model cycle (s.e.)	£81 (£3)	£223 (£9)	£435 (£22) #

Unit costs (inflated to 2007/8):

Consultant, outpatient visit: £107 per visit[145], £111 inflated to 2007/8 (Specialty code 370).

GP Visit: £34 per visit[146] , £35 inflated to 2007/8.

Community Nurse visit: £83 per visit[145], £86 inflated to 2007/8.Band 2 - Palliative / Respite Care : Adult : Face to Face Total Contacts NHS

CT Scan: £135 per scan[139], £140 inflated to 2007/8 (Specialty code RBD1. "Band D1 – CT".)

Haematology, blood tests [Excluding Anti-Coagulant Services]: £3 per test[145], £3 inflated to 2007/8.

¶ Morphine Sulphate £5 per pack, 1 dose per day. (Non-proprietary); 1 mg/mL, net price 50-mL vial prefilled syringe £5.00 per pack.[70]

Notes:

As a sensitivity analysis, we assumed a cost of £937 per month for treatment in PD for hospital and hospice care, based on a study of costs of managing women with stage IV breast cancer in the UK[133]. Mostly medication, scans, tests, hospitalization, outpatient visits.

‡ In the base case, we assumed no cost of death. As a sensitivity analysis, we assumed a cost of £3,923, taken from Coyle et al (1999),[147] averaged over hospital and hospice stays = £2,701, revalued to 2007/8.

Costs associated with Adverse Events

The review of clinical effectiveness (Section 3) reports adverse events for each of the treatment strategies. In the cost-effectiveness analysis the mean cost for treatment of adverse events (AEs) is

included. At a cohort level these costs are very small, given the relatively rare incidence of events regarded as serious and associated with NHS resource use. Only costs associated with Grade 3 or 4 adverse events (AEs) are included, since these are expected to be those that incur additional NHS costs. Table 42 (page 152) reports the basis for costing the AEs included in the model.

For the comparison of sunitinib, bevacizumab plus IFN and IFN, we considered only those AEs with a meaningful difference in incidence between treatments, based on data from the two pivotal RCTs, Motzer and colleagues [111] and Escudier and colleagues[106]. In this multiple comparison it was not possible to use statistical significance as a guide, therefore there was an element of judgement, informed by clinical opinion. In the absence of data on statistically significant differences in AEs, the same approach was taken for the comparison of temsirolimus vs. IFN, using incidence of AE from the RCT of Hudes and colleagues 2007[112]. For the comparison of sorafenib vs. BSC, we considered only those AEs whose incidence differed with statistical significance between treatment according to the trial by Escudier and colleagues (2007).[113]

The adverse events that required cost estimates were vomiting, diarrhea, and hypertension. In the absence of reported cost estimates for these events we made assumptions on NHS resource use. For vomiting and diarrhea we assumed that these events would involve (on average) an inpatient stay of 2 days, at a cost per event of £489 (at £244.50 per day[146]). For ongoing hypertension treatment, we assumed two GP visits per year (cost per visit = £35[146]), two district nurse visits per year (cost per visit = £25[146]), and medication for hypertension (cost per year = £246[148]), with a total cost estimate of £367 per year. For the comparison of temsirolimus vs. IFN, we do not expect to see differential resource use / cost for AEs (based on clinical effectiveness data and current practice). For the comparison between sorafenib and BSC, we expect differential costs for AEs to include only the ongoing treatment of hypertension (as cost estimate above), (see Table 42, page152 for detail).

When integrating costs for AEs into the model, we assumed that patients would have at most one episode of any AE during their treatment, except for hypertension, which we assumed would continue for the duration of PFS. The approach to costing AEs in the model is a simple one, and we acknowledge that it is a limitation. However, given the clinical profiles for AEs, and the relatively small mean costs for treatment (and the fact that many AEs have no treatment options, or are reported as lab abnormalities with no/limited impact on HRQL), we see the approach as parsimonious.

Table 42: Base case mean cost estimates for adverse events when on treatment for RCC

Treatment	AEs modelled	Cost	AE incidence (% patients)	Base case total cost per patient
IFN monotherapy (9MU)	vomiting	£489 per event	0.5%	£3
	hypertension	£367 per year	0.5%	
bevacizumab + IFN	diarrhea	£489 per event	2%	£21
	hypertension	£367 per year	3%	
sunitinib	diarrhea	£489 per event	5%	£88
	vomiting	£489 per event	4%	
	hypertension	£367 per year	8%	
IFN monotherapy (18MU)	none			£0
temsirolimus	none			£0
BSC	none			£0
sorafenib	hypertension	£367 per year	4%	£11

Summary Data Inputs:

The estimates of resource use / cost identified above have been used to populate the PenTAG cost-effectiveness model. We acknowledge that data on costs and health state utilities is sparse and that assumptions have been made over data inputs to the cost-effectiveness analyses. However, these assumptions have been tested in sensitivity analyses.

4.5.5. Presentation of results

Table 43 presents a summary of the research/policy questions that are the focus of the current assessment, highlighting the instances where it has been possible to present cost-effectiveness analyses (✓), and those where it has not (see also section 3, page 35).

Table 43: Presentation of PenTAG cost-effectiveness estimates against research/policy questions

Questions	Q1: 1st line therapy vs. immunotherapy	Q2: 1st line therapy vs. BSC	Q3: 1st line therapy in poor prognosis vs. IFN	Q4: 2nd line therapy vs. BSC
sunitinib	✓	X	X	X
bevacizumab plus IFN	✓	N/A	X	N/A
temsirolimus	N/A	N/A	✓	N/A
sorafenib	N/A	X	X	✓

Note: See section 2.9 (page 31) for detail on research/policy questions. N/A indicates not applicable / not licensed indication; ✓ indicates cost-effectiveness undertaken; x indicates cost-effectiveness not undertaken.

Where cost-effectiveness estimates are presented, findings are presented against summary measures of cost-effectiveness (cost per life year, cost per QALY), using incremental cost-effectiveness ratios (ICERs), together with disaggregated data on mean incremental costs and benefits. All future costs and benefits are discounted (unless stated). Where ICERs are presented (base case and sensitivity analysis) they are based on the use of deterministic modelling, applying mean parameter values for model inputs.

4.5.6. Assessment of uncertainty

Sensitivity analysis has been undertaken to address uncertainty in the cost-effectiveness analyses. Methodological and structural uncertainty has been considered in a number of cases in sensitivity analysis (e.g. time horizon, data for baseline disease progression, drug pricing strategies). Parameter uncertainty has been considered through one-way and multi-way sensitivity analysis, using deterministic modelling, and through probabilistic sensitivity analysis (PSA) where uncertainty across a range of parameter inputs is propagated in the model simultaneously. Probabilistic analyses were based on 1,000 simulations of a cohort of patients (1,000 patient cohort) with outputs presented as cost effectiveness acceptability curves (CEACs). Appendix 8 (page 256) and Appendix 10 (page 259) also supplement the material presented in the main report, presenting cost-effectiveness planes, from simulation analysis, and the predicted profile (location) of the cohorts of patients over time.

A series of accuracy and consistency checks have been undertaken by PenTAG. The team members responsible for model development have undertaken checks to audit the model (for accuracy, structural wiring, data inputs). Model checking has also been undertaken by a PenTAG modeller not associated with this report/project/model. Further information is available from PenTAG.

4.5.7. PenTAG CEA Results

4.5.7.1. Research/Policy Question 1 - Cost effectiveness of bevacizumab plus IFN and sunitinib compared to IFN as first-line therapy

Table 44 presents the mean estimates of costs and benefits for IFN, sunitinib, and bevacizumab plus IFN, and the incremental benefits associated with sunitinib and bevacizumab compared to IFN, in the patient group suitable for treatment with immunotherapy as first line therapy.

Table 44: PenTAG base case cost-effectiveness analysis: mean costs and effects for bevacizumab plus IFN, sunitinib and IFN as first line therapy

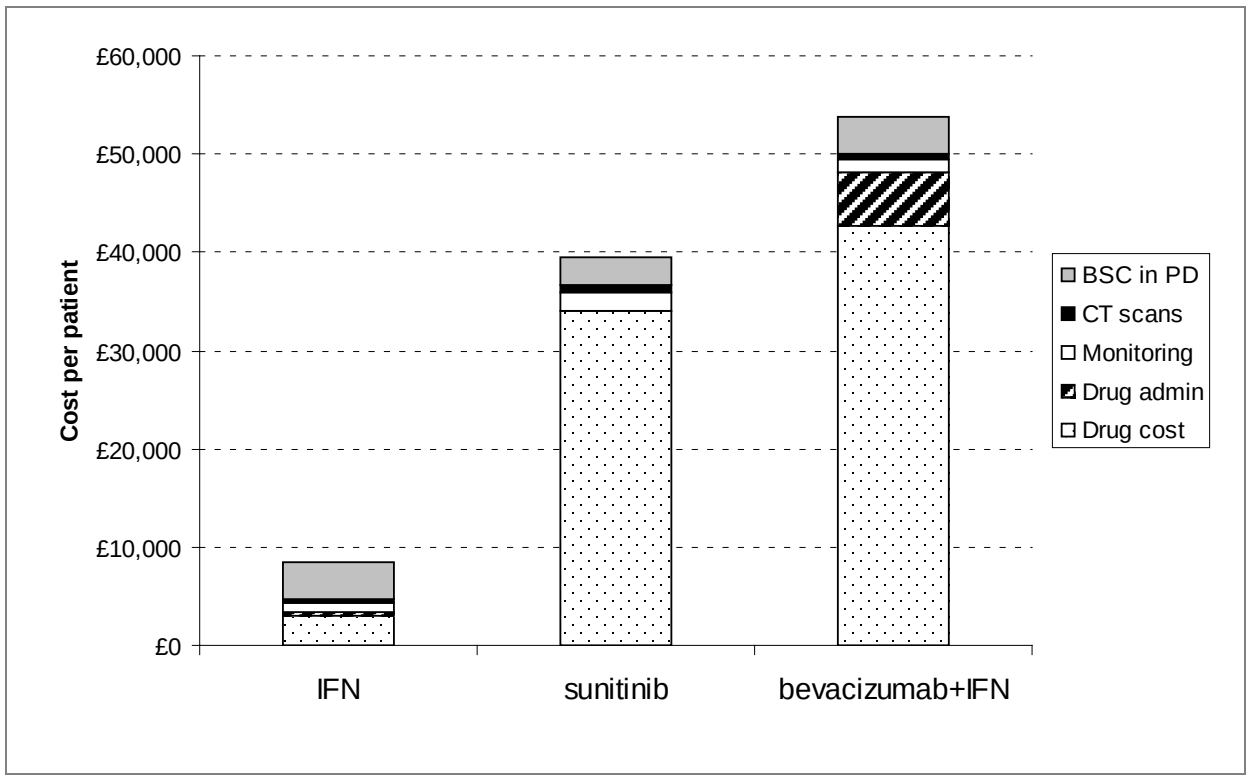
	IFN monotherapy	sunitinib	bevacizumab plus IFN	sunitinib vs. IFN	bevacizumab plus IFN vs. IFN
Life Years	1.63	2.16	1.96	0.53	0.34
QALYs	1.19	1.62	1.45	0.44	0.27
Time on treatment (months)	6.0	17.9	12.0	11.9	6.0
Drug cost	£2,952	£34,012	£42,667	£31,060	£39,715
Drug admin	£491	£0	£5,554	-£491	£5,063
Medical management #	£1,198	£2,832	£1,887	£1,635	£689
BSC in PD	£3,798	£2,779	£3,766	-£1,019	-£31
Total costs	£8,438	£39,623	£53,873	£31,185	£45,435
ICERs					
Cost / LYG				£58,647	£133,952
Cost/QALY				**£71,462**	**£171,301**

refers to monitoring, blood tests, CT scans and AEs combined.

The mean life-years (LYG) varies between 1.63 years and 2.16 years, with sunitinib and bevacizumab having greater survival and greater mean QALY benefits compared with IFN alone. Compared with IFN alone, sunitinib and bevacizumab plus IFN are associated with increased total costs of £31,185 and £45,435 respectively. Table 44 (page 154) and Figure 16 (page 156) show the main components of the total cost estimates. For both sunitinib and bevacizumab plus IFN, drug costs are the main component of total cost, and for bevacizumab there is also a related drug cost for the administration of bevacizumab. Time on treatment (in the PFS health state) is greater for both sunitinib and bevacizumab plus IFN, compared to IFN alone (IFN treatment was constrained in the model to 12-months maximum), with sunitinib at 17.9-months and bevacizumab at 12-months treatment duration (PFS).

When compared to IFN, sunitinib has an ICER of £58,647 per LYG, and £71,462 per QALY gained. When compared to IFN alone, bevacizumab plus IFN has an ICER of £133,952 per LYG and £171,301 per QALY gained. In the comparison of sunitinib versus bevacizumab plus IFN, sunitinib presents with additional benefits at lower cost, dominating bevacizumab plus IFN.

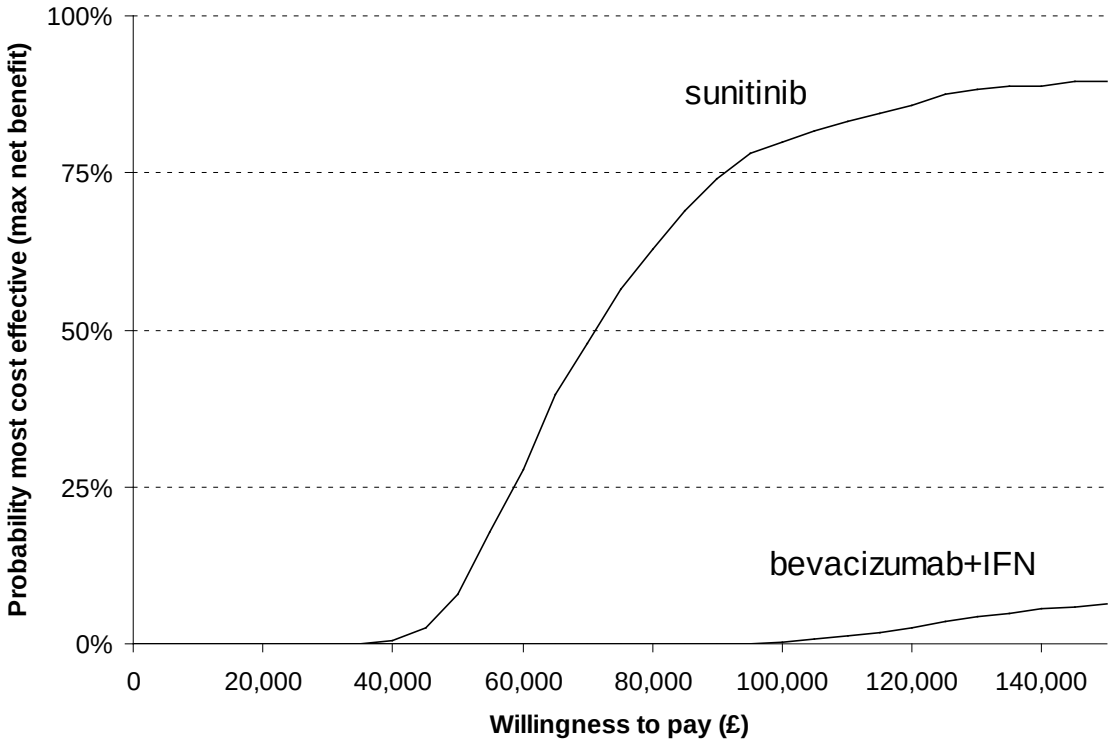
Figure 16: Breakdown of the estimated mean total costs: bevacizumab plus IFN, sunitinib and IFN as first line therapy.



Probabilistic sensitivity analysis

Figure 18 (page 157) presents a measure of uncertainty around the base case estimates of cost-effectiveness (cost per QALY), using CEACs derived using the net-benefit statistic against a range of potential values representing the willingness of the NHS to pay per QALY gained. See Appendix 9 (page 259) for detail on the probabilistic analysis undertaken. The figure shows that where the NHS are willing to pay £30,000 per QALY the probability that sunitinib is cost-effective compared to IFN is 0% and the probability that bevacizumab plus IFN is cost-effective compared to IFN is also 0% (see cost-effectiveness planes presented in Appendix 8, page 256). Sunitinib is likely to be cost-effective compared to bevacizumab plus IFN and IFN only above a willingness to pay of approximately £75,000 / QALY. Bevacizumab plus IFN is not cost-effective compared to sunitinib and IFN for any reasonable willingness to pay.

Figure 17: Cost-effectiveness acceptability curves for sunitinib vs. bevacizumab plus IFN vs. IFN



Deterministic sensitivity analysis

One-way and multi-way sensitivity analyses are reported in Table 45 (page 159), Table 46 (page 162), Figure 18 (page 161) and Figure 19 (page 164). The cost-effectiveness of sunitinib and bevacizumab plus IFN, compared to IFN alone, are particularly sensitive to variations in the estimates of treatment effectiveness, drug pricing (including dose intensity data), and health state utility input parameters. The ICERs are insensitive to a number of assumptions and data estimates, in particular, discounting, time horizon, limiting IFN administration to 1 year, non-drug costs, inclusion of estimates associated with costs of death, and estimates of adverse event costs.

The ICERs for both drugs are particularly sensitive to variations in the estimate of the hazard ratio (HR) for overall survival (OS) from the clinical effectiveness review. This is a particularly uncertain parameter in the modelling of disease progression and cost-effectiveness, with wide confidence intervals. The ICERs are less sensitive to changes in the estimates of clinical effectiveness against PFS, and are also seen to change in a counter intuitive manner. As would be reasonably expected, when the HR for OS is reduced (greater benefit), the ICER decreases. However, when the HR for PFS is reduced (greater benefit), the ICER *increases*. As shown in the tables and figures this is the case for both sunitinib and bevacizumab plus IFN. This result is due to the fact that the change in effect size (HR) retains a greater proportion of patients in PFS, which has a relatively high incremental cost (drug

and drug administration costs). The incremental costs in PFS outweigh the survival and QALY gains when in PFS. Sensitivity analysis against cost per life-year gained also shows the same finding when estimates of PFS effectiveness are varied, and the same effect can be seen in manufacturer models for sunitinib and sorafenib. We were unable to replicate the effect in the models of temsirolimus and bevacizumab plus IFN due to differences in methodology used.

The importance of the balance between costs and benefits in the PFS and PD states is also demonstrated when considering one-way sensitivity analysis of health state utility inputs. Sensitivity analysis indicates that the ICER is much more sensitive to the difference in the health state utility used for the PD health state than it is to differences in the incremental difference between health state values for PFS and PD (see discussion, section 5.2.6). This indicates, as above, that the effectiveness data for overall survival, and the difference between death (0) and the PD health state utility (base case of 0.70) are the factors driving the ICER estimate (sensitivity of ICER). This is discussed further in section 5.2.6.

The ICERs for sunitinib and bevacizumab plus IFN are also sensitive to the structural assumption in the model over the prediction of baseline disease progression for the IFN alone strategy. The base case uses data from the RCT reported by Escudier et al 2007[106], with the rationale for this base case assumption supported/presented in section 4.5.4.3. However, when data from Motzer et al 2007[111] are used the ICER for sunitinib decreases by approx. £10,000 to £61,868, and the ICER for bevacizumab plus IFN decreases by approx. £33,000 to £138,745 per QALY.

Table 45: Sensitivity analyses: sunitinib vs. IFN as first line therapy

	Base case	Sensitivity analysis	ICER sunitinib vs. IFN
Base case	n/a	n/a	**£71,462**
General			
Time horizon	10 years	5 years	£75,766
Discounting	3.5% p.a. costs and benefits	0% p.a. costs and benefits	£68,627
Effectiveness `			
Baseline progression data: RCT for fitting IFN OS and PFS	Bevacizumab (Escudier et al 2007)[106]	Sunitinib (Motzer et al 2007)[111]	£61,868
Effectiveness: HR PFS	0.42	0.33 (lower 95% CI)	£82,546
		0.52 (upper 95% CI)	£61,487
Effectiveness: HR OS	0.65	0.45 (lower 95% CI)	£39,759
		0.94 (upper 95% CI)	£263,363
Costs			
Drug pricing strategy: 1st cycle sunitinib free?	No	Yes	£65,362
Cost associated with death	£0	£3,923	£71,294
Cost estimate for BSC in PD health state (per 6-weeks)	£435	£1,297*	£66,830
Cost IFN administration	£112	£0	£72,587
(a) assumption on cost (per 6-weeks) for administration		£224	£70,337
Cost IFN administration (b) assumption on numbers treated (admin) at hospital	None	30% admin in hospital setting	£64,601
Cost monitoring, outpatient costs. (per 6-weeks)	£154	£0	£69,008
		£308	£73,914
Cost CT scan (per 6-weeks)	£65	£0	£70,430
		£130	£72,500
AE cost	£4 IFN, £88 sunitinib	£0 both treatments	£71,269

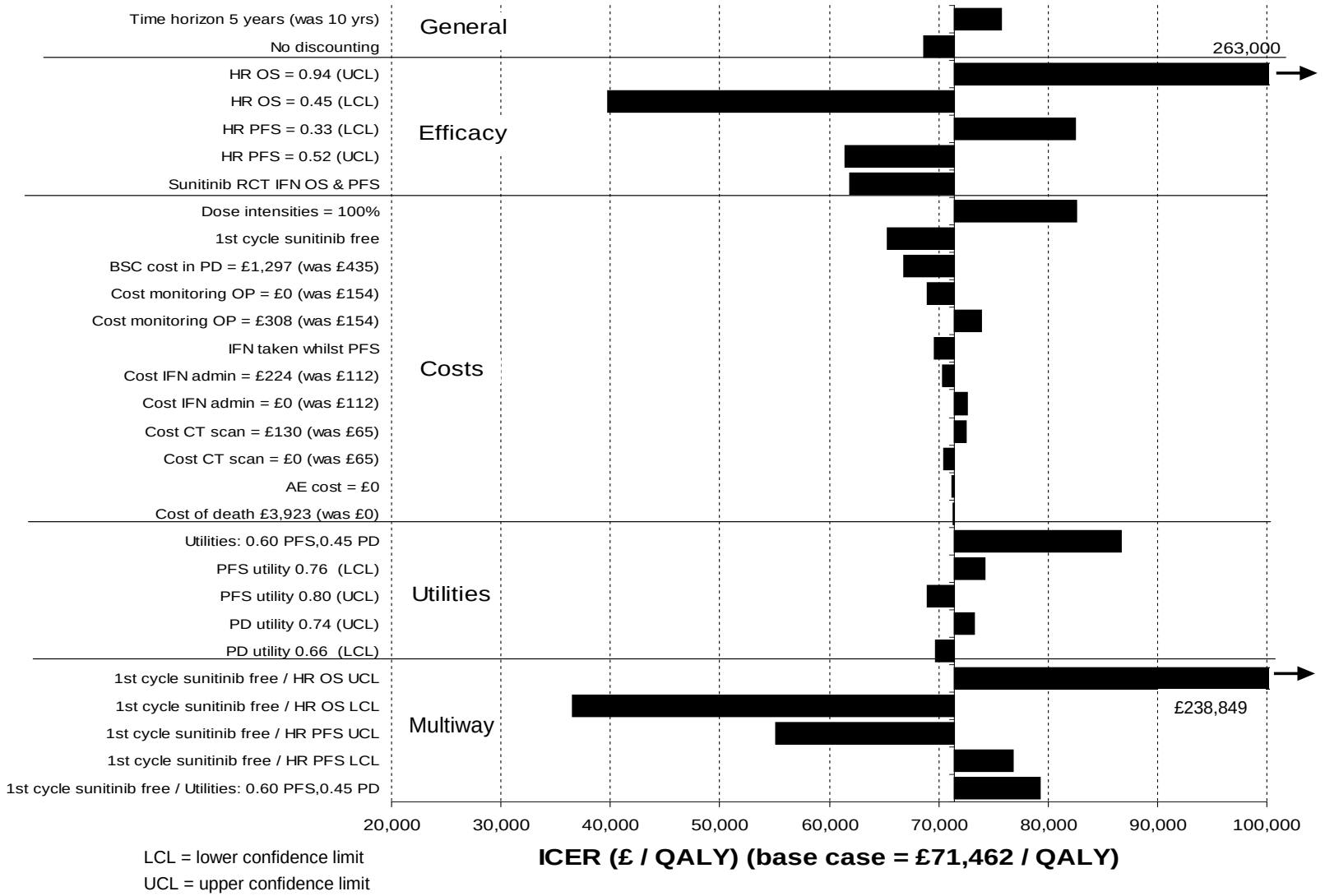
Dose intensity data	86% IFN monotherapy, 86% sunitinib	100% both treatments	£82,634
Duration IFN taken	PFS, max 12 months	PFS, no limit	£69,633
Health state utilities			
Utility estimates (by health states)	0.78 PFS 0.70 PD	0.60 PFS, 0.45 PD**	£86,722
		PFS utility 0.76 (lower 95% CI)	£74,189
		PFS utility 0.80 (upper 95% CI)	£68,928
		PD utility 0.66 (lower 95% CI)	£69,734
		PD utility 0.74 (upper 95% CI)	£73,278
		0.70 PFS, 0.62 PD***	£79,181
Multi-way			
1st cycle sunitinib, HR PFS	Not free, HR = 0.42	Free, HR = 0.33 (lower 95% CI)	£76,763
		Free, HR = 0.52 (upper 95% CI)	£55,109
1st cycle sunitinib, HR OS	Not free, HR = 0.65	Free, HR = 0.45 (lower 95% CI)	£36,587
		Free, HR = 0.94 (upper 95% CI)	£238,849
1st cycle sunitinib, utilities	Not free, utilities 0.78 PFS, 0.70 PD	Free, 0.60 PFS, 0.45 PD**	£79,320

* Based on Remak & Brazil (2004) [133].

** Taken from Hudes et al (2007) RCT [112].

*** PenTAG assumptions

Figure 18: Sensitivity analyses for sunitinib vs. IFN.



LCL = lower confidence limit

UCL = upper confidence limit

Table 46: Sensitivity analyses: bevacizumab plus IFN vs. IFN as first line therapy.

	Base case	Sensitivity analysis	ICER bevacizumab + IFN vs. IFN
Base case	n/a	n/a	**£171,301**
General			
Time horizon	10 years	5 years	£182,490
Discounting	3.5% p.a. costs and benefits	0% p.a. costs and benefits	£161,955
Effectiveness			
Baseline progression data: RCT for fitting IFN OS and PFS	Bevacizumab (Escudier et al 2007)[106]	Sunitinib (Motzer et al 2007)[111]	£138,745
Effectiveness: HR PFS	0.63	0.52 (lower 95% CI)	£193,343
		0.75 (upper 95% CI)	£152,296
Effectiveness: HR OS	0.75	0.58 (lower 95% CI)	£90,693
		0.97 (upper 95% CI)	£868,881
Costs			
Drug pricing strategy: bevacizumab dose cap / manufacturer pricing strategy	No	Yes	£90,584
Cost associated with death	£0	£3,923	£171,127
Cost estimate for BSC in PD health state (per 6-weeks)	£435	£1,297*	£171,066
Cost IFN administration	£112	£0	£170,810
(a) assumption on cost (per 6-weeks) for administration		£224	£171,792
Cost IFN administration (b) assumption on numbers treated (admin) at hospital	None	30% admin in hospital setting	£174,298
Cost bevacizumab admin (per 6-weeks)	£590	£0	£152,705
		£1,180	£189,897
Cost monitoring,	£154	£0	£169,551

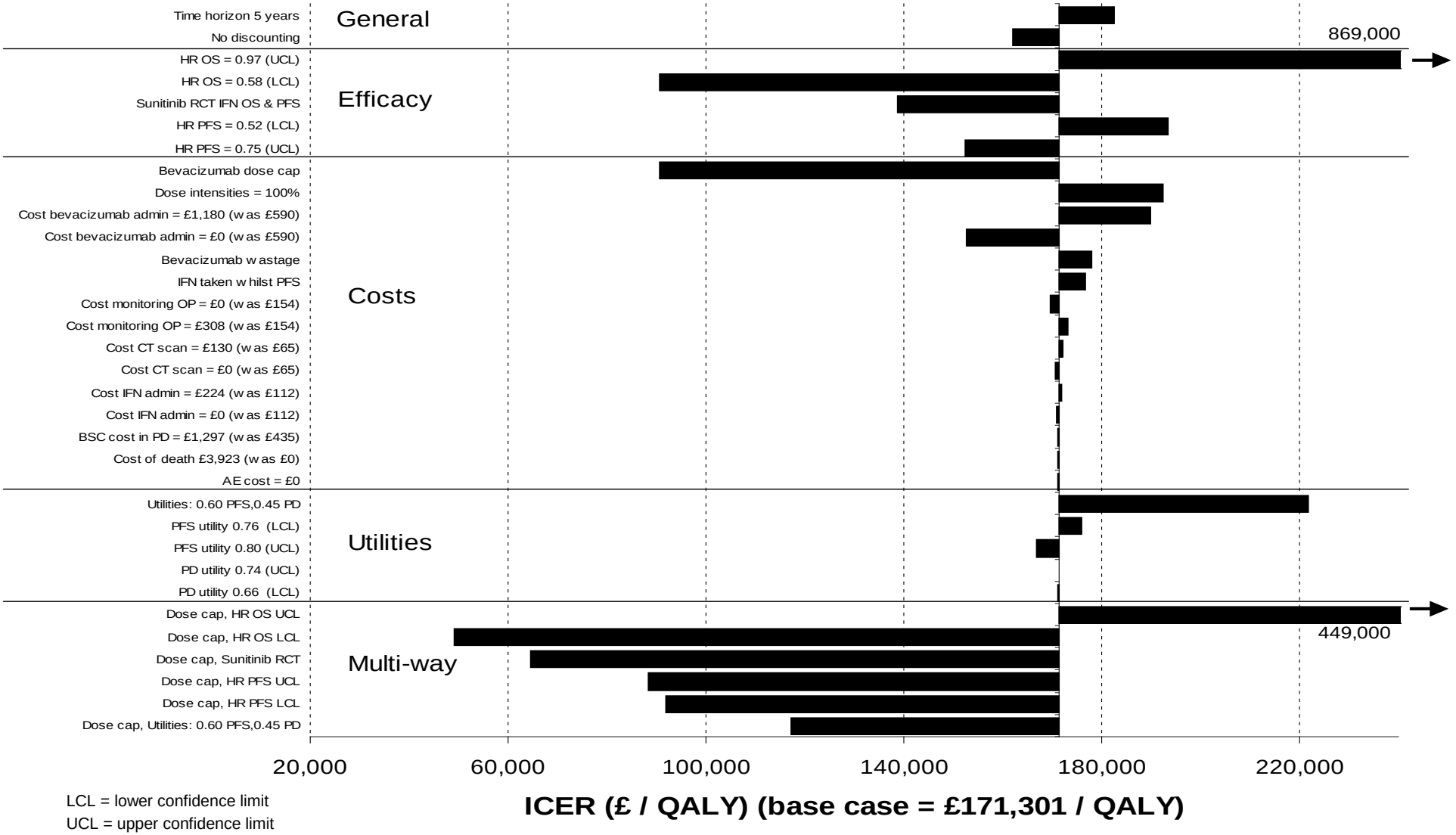
outpatient costs (per 6-weeks)		£308	£173,051
Cost CT scan (per 6-weeks)	£65	£0	£170,565
		£130	£172,037
AE cost	£4 IFN, £21 bevacizumab+IFN	£0 both treatments	£171,237
Dose intensity	86% IFN monotherapy, 88% bevacizumab, 83% IFN (with bevacizumab)	100% all drugs	£192,369
Duration IFN taken	PFS, max 12 months	PFS, no limit	£176,707
Bevacizumab wastage	No	Yes	£178,035
Health state utilities			
Utilities	0.78 PFS, 0.70 PD	0.60 PFS, 0.45 PD**	£221,888
		PFS utility 0.76 (lower 95% CI)	£175,911
		PFS utility 0.80 (upper 95% CI)	£166,927
		PD utility 0.66 (lower 95% CI)	£171,086
		PD utility 0.74 (upper 95% CI)	£171,517
		0.70 PFS, 0.62 PD***	£190,824
Multi-way			
Bevacizumab dose cap, & assumptions over baseline data (RCT for fitting IFN OS and PFS)	Dose cap no, bevacizumab (Escudier et al 2007)[106]	Dose cap yes, sunitinib (Motzer et al 2007)[111]	£64,487
Bevacizumab dose cap, & utilities	No, utilities = 0.78 PFS, 0.70 PD	Yes, utilities = 0.60 PFS, 0.45 PD**	£117,334
Bevacizumab dose cap, & effectiveness estimate for HR PFS	No, HR = 0.63	Yes, HR = 0.52 (lower 95% CI)	£91,973
		Yes, HR = 0.75 (upper 95% CI)	£88,308
Bevacizumab dose cap, & effectiveness estimate for HR OS	No, HR = 0.75	Yes, HR = 0.58 (lower 95% CI)	£49,190
		Yes, HR = 0.97 (upper 95% CI)	£448,811

* Based on Remak & Brazil (2004) [133].

** Taken from Hudes et al (2007) RCT [112].

*** PenTAG assumptions

Figure 19: Sensitivity analysis for bevacizumab plus IFN vs. IFN.



LCL = lower confidence limit
UCL = upper confidence limit

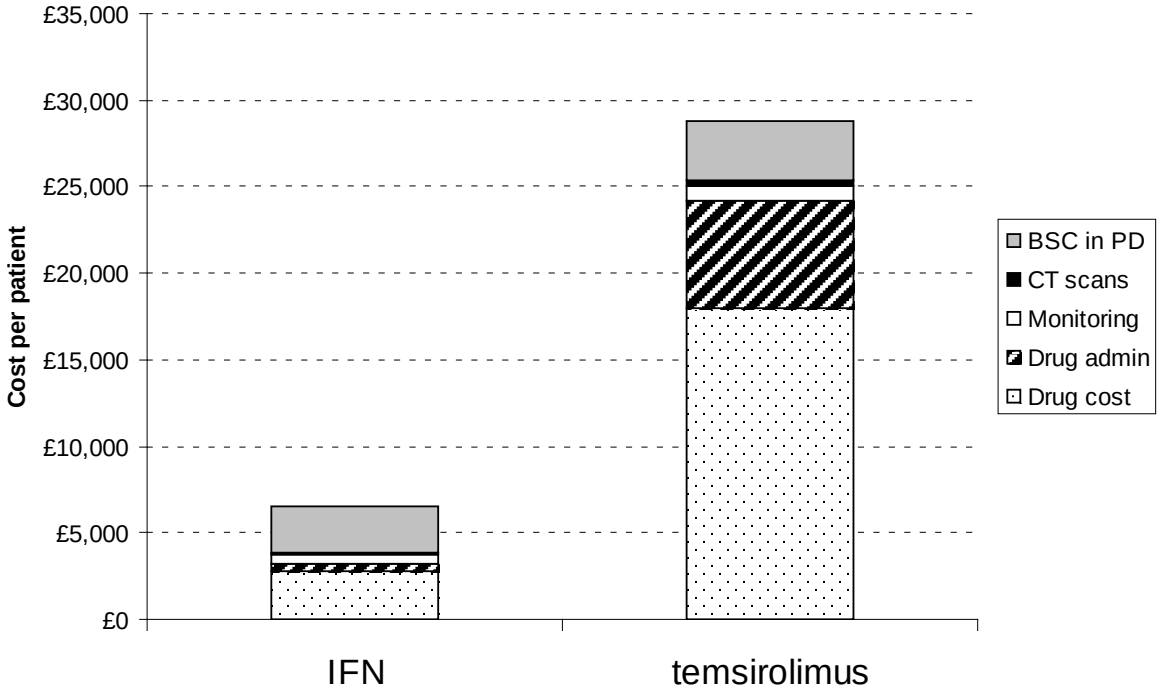
4.5.7.2. Research/Policy Question 3 - Cost effectiveness of temsirolimus compared to IFN as first line therapy

Table 47 presents the mean estimates of costs and benefits for temsirolimus and IFN, and the incremental benefits associated with temsirolimus compared to IFN, in the patient group with three or more of six prognostic factors. For temsirolimus compared to IFN, the incremental life years and QALYs gained are 0.45 and 0.24 respectively, and the incremental cost is £22,272. Table 47 below and Figure 20 (page 166) report the breakdown of the main components of the total cost estimates, with drug costs and the related costs for administration of temsirolimus reflecting the majority of the reported difference in costs. Time on treatment (in the PFS health state) is greater for temsirolimus, at 7.6 months compared to 4.6 months for IFN. When compared to IFN temsirolimus has an ICER of £49,571 per LYG and £94,385 per QALY gained.

Table 47: PenTAG base case cost-effectiveness analysis: mean costs and effects for temsirolimus vs. IFN as first line therapy in patients with poor prognosis

	IFN	Temsirolimus	Temsirolimus vs. IFN
Life Years	1.07	1.52	0.45
QALYs	0.53	0.77	0.24
Time on treatment (months)	4.6	7.6	3.0
Drug cost	£2,823	£17,978	£15,155
Drug admin cost	£367	£6,215	£5,848
Medical management	£729	£1,176	£447
BSC cost in PD	£2,599	£3,422	£822
Total costs	£6,519	£28,791	£22,272
ICERs			
Cost / LYG			£49,571
Cost/QALY			**£94,385**

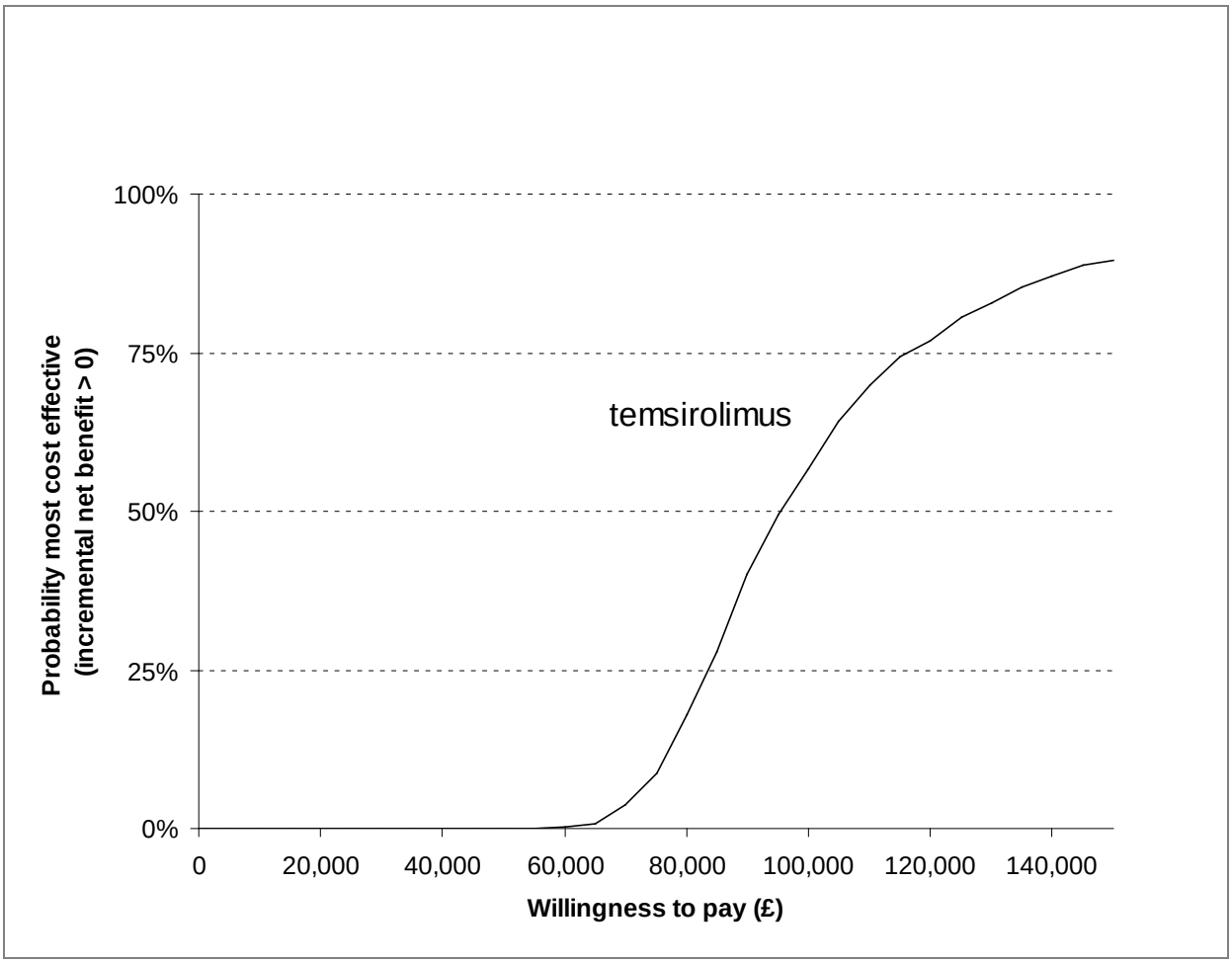
Figure 20: Breakdown of the estimated mean total costs: temsirolimus vs. IFN as first line therapy in patients with poor prognosis.



Probabilistic sensitivity analysis

Figure 21 (page **Error! Bookmark not defined.**) explores the parameter of uncertainty around the base case estimates of cost-effectiveness (cost per QALY), using a CEAC derived using the net-benefit statistic against a range of potential values representing the willingness of the NHS to pay for a QALY gained. See Appendix 9 (page 259) for detail on the probabilistic analysis undertaken. The figure shows that where the NHS is willing to pay £30,000 per QALY the probability that temsirolimus is cost-effective compared to IFN is 0% - this also being the case for all subgroup analyses (see cost-effectiveness plane presented in Appendix 8, page 256). Temsirolimus is likely to be cost-effective compared to IFN only above a willingness to pay of approximately £95,000 / QALY.

Figure 21: Cost-effectiveness acceptability curve for all patients for temsirolimus vs. IFN



Sub-group cost-effectiveness analysis

Table 48 (page 169) presents subgroup analysis for temsirolimus versus IFN by nephrectomy status, Motzer severity score, and by type of RCC (clear cell, non-clear cell). The estimated ICERs are higher in those patients with a poor Motzer score (compared to base case; similar benefits with higher costs), by type of RCC and in the group with prior nephrectomy. Note that these sub-group analyses are undertaken using the baseline disease progression applied in the base case analysis (i.e. baseline disease progression on IFN from the RCT by Hudes et al [112]). The ICER for the group with non-clear cell RCC is relatively close to the base case cost per QALY, at £102,457 (with higher benefits, but at greater cost). The ICER estimated for the subgroup with no prior nephrectomy is lower than the base case, at £74,184 per QALY. CEACs for sub-group cost-effectiveness analysis are presented in Appendix 11 (page 268).

In the subgroup ICERs for the non-clear cell patients the incremental costs are very large, outweighing the increased effectiveness reported. The effect size for PFS in this subgroup is large, although not

statistically significant (HR for PFS of 0.36; with CI:0.22-1.59). Given that the HR used retains a large proportion of patients in the PFS state for a longer period of time (compared to IFN) there is a very high cost associated with a mean treatment duration of 22-months.

Subgroups

Table 48: PenTAG subgroup cost-effectiveness analysis: mean costs and effects for temsirolimus vs. IFN as first line therapy in patients with poor prognosis

Sub-group:	Motzer poor			Clear cell			Non-clear cell		
	IFN	temsirolimus	temsirolimus vs. IFN	IFN	temsirolimus	temsirolimus vs. IFN	IFN	temsirolimus	temsirolimus vs. IFN
Life Years	0.83	1.25	0.42	1.07	1.28	0.21	1.07	2.04	0.97
QALYs	0.46	0.70	0.25	0.53	0.65	0.11	0.53	1.17	0.64
Time on treatment (months)	6.8	12.0	5.2	4.6	6.2	1.6	4.6	22	17.4
Drug cost	£4,132	£28,069	£23,938	£2,823	£14,706	£11,882	£2,823	£49,888	£47,065
Drug admin	£529	£9,704	£9,175	£367	£5,084	£4,717	£367	£17,247	£16,880
Medical management	£1,051	£1,836	£784	£729	£962	£233	£729	£3,262	£2,534
BSC in PD	£1,092	£1,140	£48	£2,599	£2,955	£356	£2,599	£1,334	-£1,265
Total costs	£6,804	£40,749	£33,945	£6,519	£23,707	£17,188	£6,519	£71,732	£65,214
ICERs									
Cost / LYG			£81,114			£80,008			£66,909
Cost/QALY			**£136,260**			**£150,305**			**£102,457**

Sub-group:	Nephrectomy			No nephrectomy		
	IFN	temsirolimus	temsirolimus vs. IFN	IFN	temsirolimus	temsirolimus vs. IFN
Life Years	1.07	1.30	0.23	1.07	1.84	0.77
QALYs	0.53	0.67	0.14	0.53	0.94	0.41
Time on treatment (months)	4.6	7.6	3.0	4.6	9.9	5.3
Drug cost	£2,823	£17,978	£15,155	£2,823	£23,118	£20,295
Drug admin	£367	£6,215	£5,848	£367	£7,992	£7,625
Medical management	£729	£1,176	£447	£729	£1,512	£783
BSC in PD	£2,599	£2,602	£3	£2,599	£3,972	£1,373
Total costs	£6,519	£27,972	£21,453	£6,519	£36,594	£30,076
Cost / LYG			£92,518			£39,101
ICER			**£154,334**			**£74,184**

Deterministic sensitivity analysis

One-way sensitivity analysis is presented in Table 49 (page 172) and Figure 22 (page 174). The cost-effectiveness of temsirolimus versus IFN is sensitive to variations in estimates of treatment effectiveness, cost of temsirolimus (wastage assumption), the choice of health state utility parameters, and the costs associated with the administration of temsirolimus. The ICER is only marginally influenced by the other parameters, including discounting, time horizon, dose intensity, non-drug costs and AE costs.

As discussed for sunitinib/bevacizumab plus IFN (sensitivity analysis) the ICER is particularly sensitive to the estimate of the hazard ratio (HR) for overall survival (OS). From the clinical effectiveness review this is an uncertain parameter with wide confidence interval. The ICER is sensitive to the HR for PFS, and as discussed under sunitinib/bevacizumab, the effect of the PFS HR on the ICER is counter-intuitive, with increased effectiveness (lower HR) resulting in a higher ICER, and a reduced effectiveness (higher HR) resulting in a lower ICER.

The ICER is sensitive to the assumption around drug costs, related to an assumption made in the base case over waste when administering temsirolimus (30mg vial per administration). Where the assumption is no wastage (potential vial sharing scheme; although difficult to envisage successful introduction of such) the ICER reduces to £81,687 per QALY.

The ICER for temsirolimus is also sensitive to the choice of utilities, and as seen in sensitivity analysis for sunitinib/bevacizumab, where the increment in utility between PFS and PD states is varied there is little impact on the ICER, but where the health state value for the PD state is higher (with a greater difference between death i.e. zero, and PD health state value) the ICER is reduced considerably (£66,885/QALY), even though the difference in utility between the two health states is reduced by circa. 50%.

Table 49: Sensitivity analysis: temsirolimus vs. IFN as first line therapy in patients with poor prognosis

	Base case	Sensitivity analysis	ICER Temsirolimus vs. IFN
Base case (cost/QALY)	n/a	n/a	**£94,385**
General			
Time horizon	10 years	5 years	£105,519
Discounting	3.5% p.a. costs and benefits	0% p.a. costs and benefits	£89,839
Effectiveness			
HR PFS	0.74	0.60 (lower 95% CI)	£114,582
		0.91 (upper 95% CI)	£75,391
HR OS	0.73	0.58 (lower 95% CI)	£56,452
		0.92 (upper 95% CI)	£253,443
Costs			
Costs associated with death	£0	£3,923	£94,055
Cost for BSC in PD (per 6-weeks)	£435	£1,297*	£101,299
Cost for IFN administration (per 6-weeks)	£112	£0	£95,940
		£224	£92,830
Cost for temsirolimus administration (a) assumption on cost (per 6-weeks) for administration	£1,179	£0	£68,046
		£2,359	£120,724
Cost IFN administration (b) assumption on numbers treated (admin) at hospital	None	30% admin in hospital setting	£84,898
Cost monitoring, outpatient costs (per 6-weeks)	£154	£0	£93,077
		£308	£95,693
Cost CT scan (per 6-weeks)	£65	£0	£93,835
		£130	£94,935

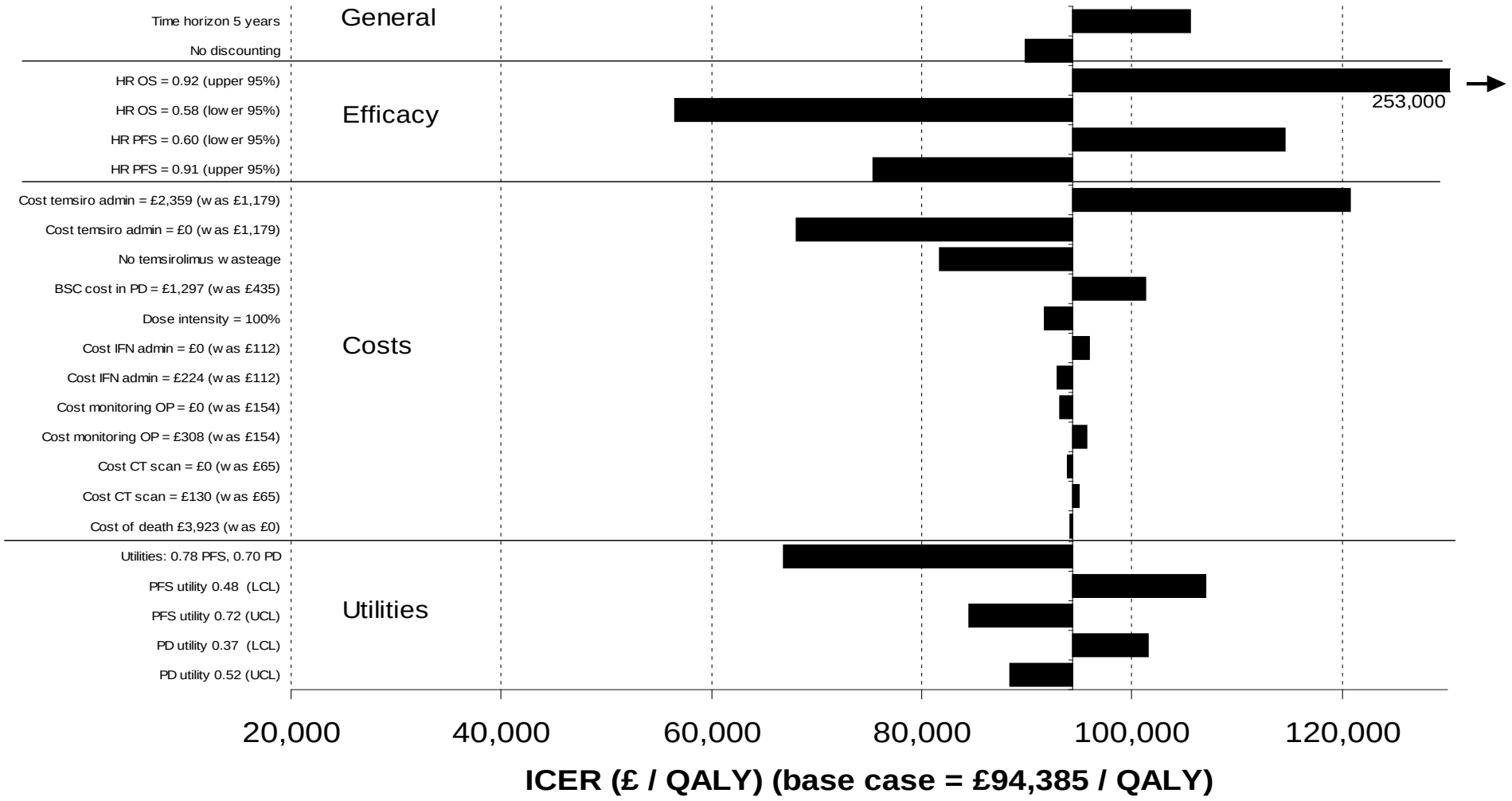
Dose intensity	92% temsirolimus, 56% IFN	100% both treatments	£91,610
Temsirolimus wastage (assumption)	Yes	No	£81,687
Health state utilities			
Utilities	0.60 PFS, 0.45 PD	0.78 PFS, 0.70 PD**	£66,885
		PFS utility 0.48 (lower 95% CI)	£106,953
		PFS utility 0.72 (upper 95% CI)	£84,460
		PD utility 0.37 (lower 95% CI)	£101,520
		PD utility 0.52 (upper 95% CI)	£88,340
		0.65 PFS, 0.54 PD***	£83,093

* Based on Remak & Brazil (2004).[133]

** Taken from Motzer et al (2007) RCT.[111]

*** PenTAG assumptions

Figure 22: Sensitivity analysis for temsirolimus vs. IFN as first line therapy in patients with poor prognosis.



LCL = lower confidence limit
UCL = upper confidence limit

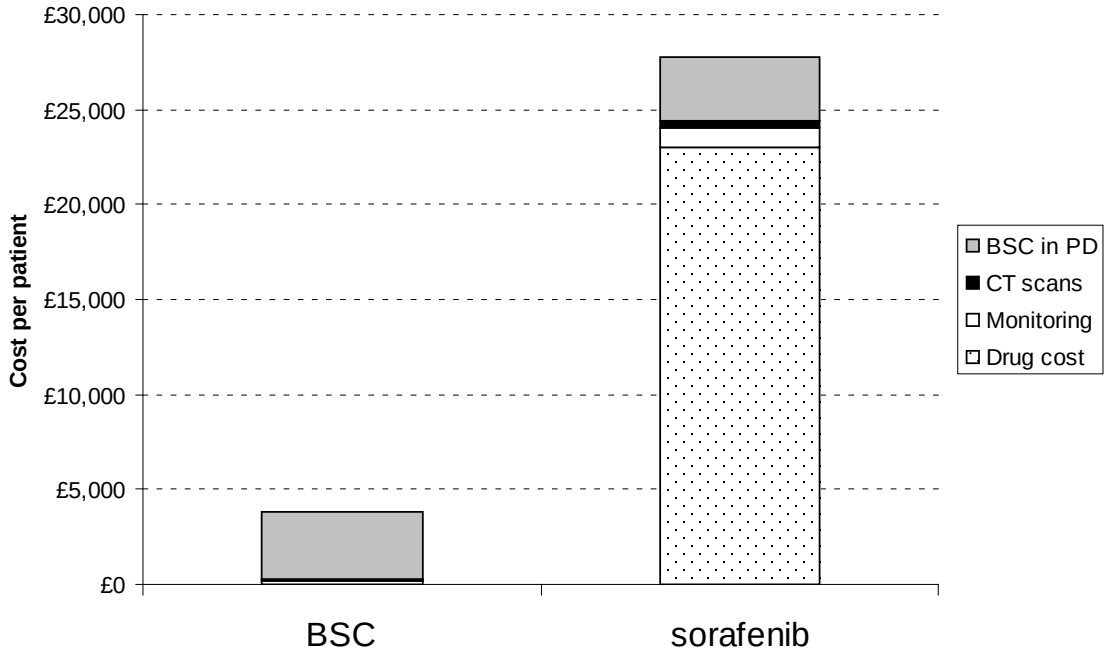
4.5.8. Research/policy question 4 - Cost effectiveness of sorafenib tosylate compared to best supportive care as second line therapy

Table 50 presents the mean estimates of costs and benefits for sorafenib and best supportive care (BSC), and the incremental benefits associated with sorafenib compared to BSC, in the patient group in whom treatment with cytokine based immunotherapy has failed, i.e. second line therapy. For sorafenib compared to BSC, the incremental life years and QALYs gained are 0.30 and 0.23 respectively, and the incremental cost is £24,001. Table 50 and Figure 24 (page 176) report the breakdown of the main components of the total cost estimates, with drug costs and the related medical management costs, making up the difference in mean total costs. Time on treatment (in the PFS health state) for sorafenib is 8.7 months. When compared to BSC sorafenib has an ICER of £78,960 per LYG and £102,498 per QALY gained.

Table 50: PenTAG base case cost-effectiveness analysis: sorafenib vs. BSC as second line therapy.

	BSC	sorafenib	sorafenib vs. BSC
Life Years	1.30	1.60	0.30
QALYs	0.91	1.15	0.23
Time on treatment (months)	n/a	8.7	n/a
Drug cost	£0	£23,058	£23,058
Drug admin	£0	£0	£0
Medical management	£248	£1,380	£1,132
Cost for BSC in PD health state	£3,549	£3,360	-£189
Total costs	£3,797	£27,797	£24,001
ICERs			
Cost / LYG			£78,960
Cost/QALY			**£102,498**

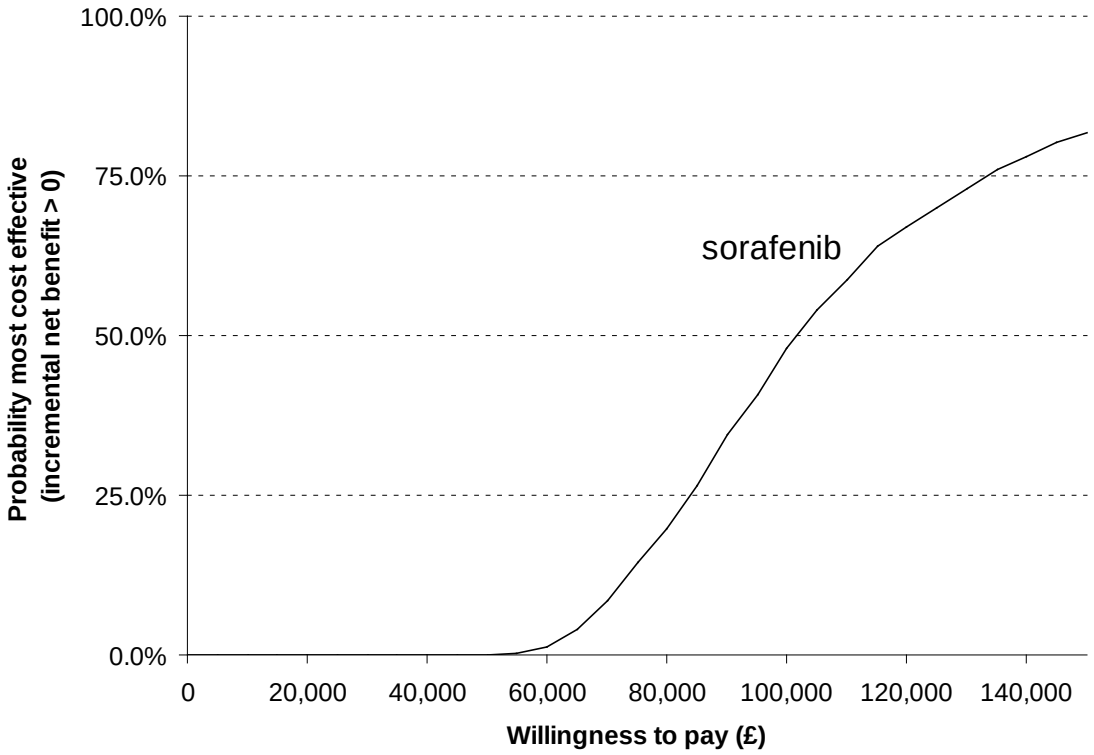
Figure 23: Breakdown of estimated mean total costs: sorafenib vs. BSC as second line therapy.



Probabilistic sensitivity analysis

Figure 25 incorporates parameter uncertainty in the base case estimates of cost-effectiveness (cost per QALY), using a CEAC derived using the net-benefit statistic against a range of potential values representing the willingness of the NHS to pay per QALY gained. See Appendix 9 (page 259) for detail on the probabilistic analysis undertaken. The figure shows that where the NHS is willing to pay £30,000 per QALY the probability that sorafenib is cost-effective compared to BSC is 0% (see cost-effectiveness plane presented in Appendix 8, page 256). Sorafenib is likely to be cost-effective compared to BSC only above a willingness to pay of approximately £100,000 per QALY.

Figure 24: Cost-effectiveness acceptability curve for sorafenib vs. BSC.



Deterministic sensitivity analysis

One-way sensitivity analysis is presented in Table 51 (page 179) and Figure 26 (page 181). The cost-effectiveness of sorafenib versus BSC is sensitive to variations in estimates of treatment effectiveness, cost of sorafenib (dose intensity assumption), and to a lesser extent the health state utilities used for PFS and PD health states. The ICER is only marginally influenced by the other parameters, including discounting, time horizon, and non-drug costs.

As discussed for sunitinib/bevacizumab plus IFN and temsirolimus (sensitivity analysis) the ICER is particularly sensitive to the estimate of the hazard ratio (HR) for overall survival (OS); from the clinical effectiveness review this is an uncertain parameter with a wide confidence interval. The ICER is sensitive to the HR for PFS, as discussed for sunitinib/bevacizumab and temsirolimus, the effect of the PFS HR on the ICER is counter-intuitive, with increased

effectiveness (lower HR) resulting in a higher ICER, and reduced effectiveness (higher HR) resulting in a lower ICER.

Although the available clinical effectiveness literature does not report on dose intensities for sorafenib (other than an assumption of 100%), where the dose intensity is varied to a level of 80% the ICER is reduced by £20,000 to £82,804.

The sensitivity analysis around the health state utility parameters (PFS and PD utilities) reinforces the finding from the effectiveness analysis that the overall survival data is the prominent driver for cost effectiveness, given the balancing of costs associated with the PFS health state when effectiveness dictates that patients remain in that state for a longer time (see discussion section 5, page 190). Sensitivity analysis is undertaken using alternative estimates from the data presented to NICE in the submission made by the manufacturer of sunitinib, and against the confidence intervals in the data used in the base case. In the sensitivity analysis, where the difference in utilities between PFS and PD increases to 0.13 from 0.08 (using PFS utility of 0.81, upper CI limit for PFS health state) the ICER reduces by £7,500 to £95,027. Where the difference in utility values between the two health states reduces to 0.02 from 0.08 (using PFS utility of 0.70, lower CI limit for PFS health state) the ICER increases by £10,000. Whereas when the utility difference between the two health states is zero (i.e. PD utility 0.76, using the upper limit of the 95% confidence interval), but with the PD health state value at a higher estimate (0.76 vs. 0.68) the ICER increases by only £1,700 to £104,214.

Table 51: Sensitivity analysis: sorafenib vs. BSC as second line therapy

	Base case	Sensitivity analysis	ICER Sorafenib vs. BSC
Base case	n/a	n/a	**£102,498**
General			
Time horizon	10 years	5 years	£103,867
Discounting	3.5% p.a. costs and benefits	0% p.a. costs and benefits	£98,211
Effectiveness			
Effectiveness: HR PFS	0.51	0.43 (lower 95% CI)	£115,264
		0.60 (upper 95% CI)	£91,373
Effectiveness: HR OS	0.72	0.54 (lower 95% CI)	£55,585
		0.94 (upper 95% CI)	£368,830
Cost			
Cost associated with death	£0	£3,923	£102,323
Cost for BSC in PD health state (per 6-weeks)	£435	£1,297*	£100,900
Cost of monitoring, outpatient costs (per 6-week cycle)	£154 sorafenib, £48 BSC	£0	£99,095
		£308	£103,131
Cost CT scan (per 6-week cycle)	£65 sorafenib, £32 BSC	£0	£101,224
		£130	£102,928
AE cost	£0 BSC, £11 sorafenib	£0 both treatments	£102,453
Dose intensity	100% sorafenib	80% sorafenib	£82,804
Health state utilities			
		0.78 PFS, 0.70 PD**	£99,549
		PFS utility 0.70 (lower 95% CI)	£112,350
		PFS utility 0.81 (upper 95% CI)	£95,027

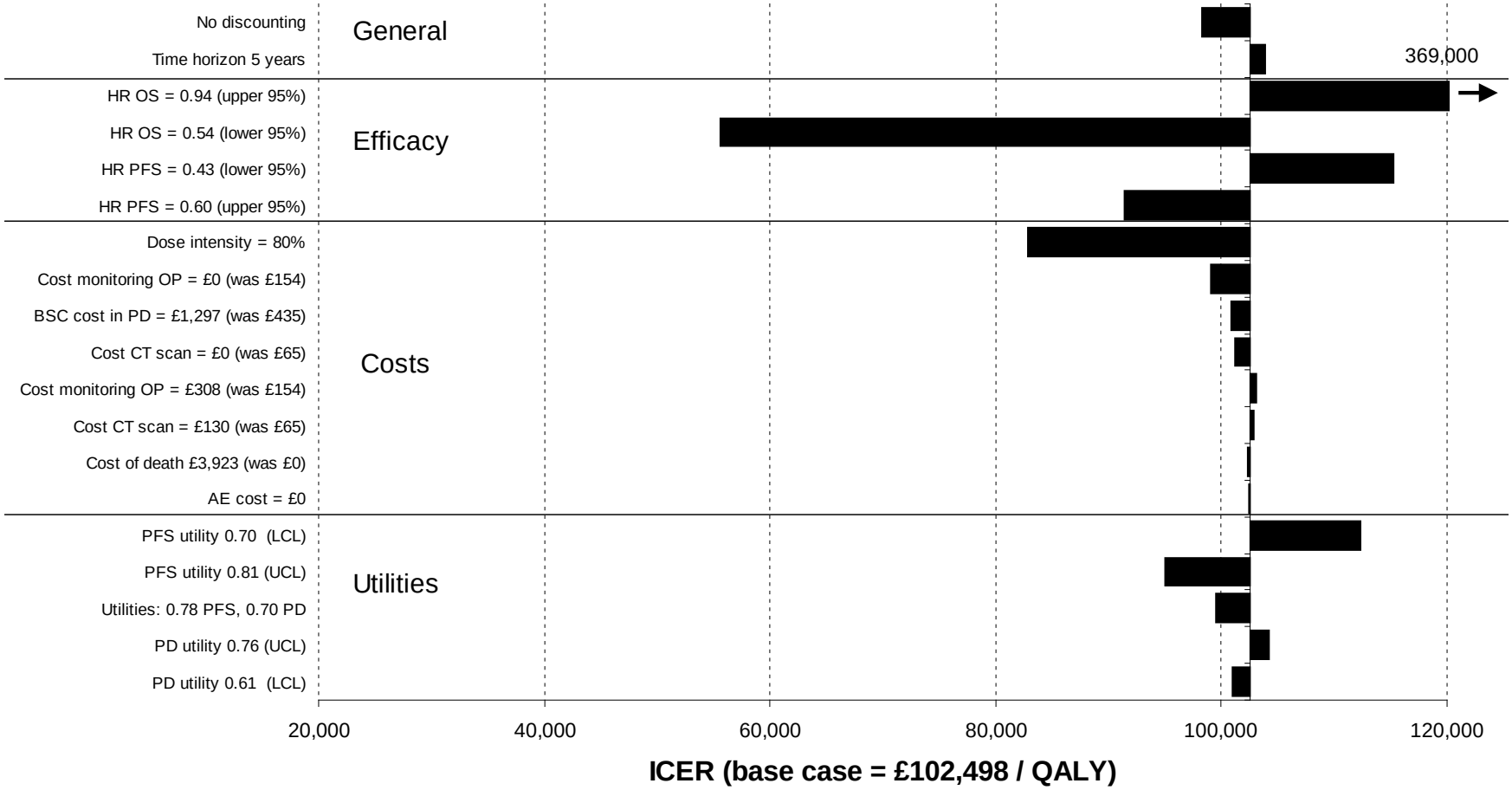
Utilities	0.76 PFS, 0.68 PD	PD utility 0.61 (lower 95% CI)	£100,923
		PD utility 0.76 (upper 95% CI)	£104,214
		0.62 PFS, 0.54 PD***	£124,704

* Based on Remak & Brazil (2004). [133]

** Taken from Motzer et al (2007) RCT.[111]

*** PenTAG assumptions

Figure 25: Sensitivity analysis: sorafenib vs. BSC as second line therapy.



LCL = lower confidence limit
UCL = upper confidence limit

4.6. Comparison of PenTAG CEA and manufacturer CEA

The preceding sections have presented a summary of the CEA presented by the manufacturers of drugs, in submissions to NICE, and detail on the CEA undertaken by PenTAG. Whilst there are some common aspects of methodology, in both model structure and data inputs, across manufacturer and PenTAG analyses, there are clear differences in some of the baseline assumptions and in the resulting cost effectiveness estimates. Whilst manufacturer submissions have been developed in isolation, PenTAG have sought to apply a common modelling approach across the policy questions. In all cases PenTAG presents base case estimates of cost per QALY that are higher than those presented in manufacturer submissions to NICE. Manufacturer and PenTAG differences, in base case cost per QALY estimates, are more marked in the assessment of cost-effectiveness for sunitinib versus IFN (1st line), and temsirolimus versus IFN (poor prognosis patient group). Cost per QALY estimates for bevacizumab plus IFN and sorafenib are higher in the PenTAG analysis, but not markedly so (when comparing bevacizumab analysis with 'dose cap' pricing scheme active in both models).

Table 52 presents summary cost per QALY estimates (base case) for manufacturer submissions and PenTAG cost-effectiveness analysis.

Table 52 Summary comparison of base case cost-effectiveness results from PenTAG and manufacturers economic analyses.

Comparison	Manufacturer base case cost per QALY	PenTAG base case cost per QALY
1st line treatment, suitable for immunotherapy		
Sunitinib vs. IFN	£28,546 PenTAG adjustment : Industry model using PenTAG fit of survival data for PFS, £48,052	£71,462 PenTAG model with first cycle of sunitinib free of charge to the NHS (Pfizer strategy), and using data from Motzer et al 2007 (sunitinib RCT) for baseline progression : £57,737
Bevacizumab plus IFN vs. IFN	£74,978 PenTAG adjustment : Industry model, 'without' dose cap pricing assumption, £108,329	£171,301 (base case) £90,584 (with 'dose cap' pricing)
1st line treatment, poor prognosis		
Temsirolimus vs. IFN	£55,814 PenTAG adjustment : Applying PenTAG assumptions on cost of administration for IFN to Wyeth model, £102,000 Applying PenTAG assumptions on cost for administration of IFN, and cost for temsirolimus (vial price), £121,175	£94,385
2nd line treatment		
Sorafenib vs. BSC	£90,630	£102,498

4.6.1. Sunitinib and bevacizumab (plus IFN) compared to IFN alone: CEA findings

When reviewing the cost effectiveness analysis and model submitted by Pfizer (for sunitinib compared to IFN), PenTAG have highlighted a number of differences in structural assumptions and data inputs which can explain the differences seen in the cost per QALY estimates. One of the differences between the Pfizer and PenTAG models is due to the judgments made over the data used to model the baseline progression for IFN alone. Here, PenTAG have chosen to use data on IFN progression from the RCT reported by Escudier and colleagues, whereas in the Pfizer base case analysis uses data on

IFN progression from the RCT reported by Motzer and colleagues, which whilst having a shorter follow-up for the overall survival data, is from a Pfizer study (which may explain their decision). PenTAG judge the data from Escudier and colleagues to be the most appropriate. However, where the PenTAG model is used with baseline progression modelled with data from Motzer and colleagues, as in the Pfizer model (but with a preferred/better fit, as discussed in section 4.5.4.3), the cost per QALY does decrease to £61,868. Therefore, we suggest that where the PenTAG model is used with the same baseline data as Pfizer assumptions (with adjusted fit for PFS data), and with the assumption that the first cycle of sunitinib is free of charge to the UK NHS, the estimates of cost per QALY (PenTAG £57,737 per QALY; Pfizer £48,052 per QALY) between the two models is similar (accepting small differences in a range of other data inputs e.g. duration of treatment with IFN alone).

The PenTAG review of the cost effectiveness analysis and model submitted to NICE by Roche, for comparison of bevacizumab plus IFN versus IFN alone, has highlighted a number of differences in structural assumptions and data inputs which can explain the differences seen in the cost per QALY estimates from Roche and the PenTAG analyses. The structures of the models (Roche and PenTAG) for disease progression are similar, and assumptions over health state utilities are the same in both models, so the estimates of life years and QALYs gained are similar. However, assumptions over costs, especially drug related costs, result in different cost effectiveness estimates.

Importantly, the pricing strategy employed by Roche, the bevacizumab 'dose cap' scheme, which they suggest will mean the UK NHS will not pay a product price beyond 10,000mg for an individual patient (where 10,000mg is exceeded in a one-year period), influences base case cost per QALY estimates in both analyses. Roche assume that the dose cap scheme is in place in their base case, whilst PenTAG (based on advice from NICE) have not assumed this for base case estimates (giving a comparison of £75K versus £171K per QALY). Where PenTAG assume the pricing strategy is 'in place / active' the base case cost per QALY is £90,584. Where PenTAG run the industry model, but without the pricing strategy the cost per QALY from the industry model increases to £108,329.

Another important difference between the PenTAG and Roche models is the use of data on dose intensity (discussed section 4.4.1.2). Dose intensity data are used to adjust the cost of bevacizumab and IFN. For bevacizumab, Roche use a dose intensity of 62%, vs. 88% in PenTAG model; for the IFN in the bevacizumab plus IFN arm, Roche use dose intensity of 80%, vs. 83% in the PenTAG model; for IFN monotherapy Roche use dose intensity data of 63%, vs. 86% in the PenTAG model. The Roche model uses dose intensity data different to that reported in the RCT of bevacizumab plus IFN compared to IFN.[106] When the RCT data is used (by PenTAG) in the Roche model (with RCT data almost identical to the data used in the PenTAG model), the cost per QALY from the Roche model increases from £75,000 to £117,000 (higher than that estimated by PenTAG, with the 'dose cap' pricing assumption).

There are a number of other differences between data inputs when comparing the models. For example, PenTAG's assumptions on the costs for drug administration, and medical management are higher than those in the Roche model, and the data used by PenTAG for the modelling of PFS and OS in bevacizumab plus IFN (vs IFN) is different (PenTAG use HRs of 0.63 & 0.75 respectively, Roche use HRs of 0.609 & 0.709). However, the main issues discussed above highlight that the two models are similar, when different structural and data judgments are taken into consideration.

4.6.2. Temsirolimus compared to IFN alone (poor prognosis): CEA findings

Where PenTAG have considered temsirolimus compared to IFN alone, in patients with poor prognosis, the report has reviewed the industry cost-effectiveness analysis and model (Wyeth), and has presented cost-effectiveness estimates using the PenTAG model. There are a number of key differences in the structure of the PenTAG and Wyeth models, and a number of different judgments over data inputs to the model. Therefore, the PenTAG estimates of cost per QALY are somewhat different to those presented in the Wyeth submission to NICE (PenTAG base case £94,385, Wyeth base case £55,814 per QALY).

Both the manufacturer model and the PenTAG model have used the same data on health state utilities (for the primary health states), and effectiveness data from the same RCT source (Hudes and colleagues)[112] to model disease progression. However, the Wyeth model uses patient level data from the trial to calculate time dependent transition probabilities, for both temsirolimus treatment and IFN treatment. On the other hand, PenTAG uses summary published trial data on baseline progression for IFN alone, and models treatment effectiveness using hazard ratios reported in the RCT. We have considered the fit of the survival curves (based on transit probabilities) estimated in the Wyeth model, and note that the fit is not precise/close in places compared to the empirical trial data. The PenTAG model predicts larger mean survival and QALYs in each of the treatment groups, and a higher incremental benefit from temsirolimus compared to IFN. Although model time horizons are different, Wyeth being 3yrs versus 10yrs for PenTAG, we do not believe this is a major issue.

Whilst there are clear differences in the health outcomes predicted in the two models, with the PenTAG model estimating greater benefits, the PenTAG model also makes different assumptions on resource use and costs, resulting in a much higher mean incremental cost (£22,272) compared to the Wyeth model (£7,493).

The difference between models in total costs and incremental costs, can be largely explained by assumptions on the drug cost for temsirolimus, and the cost associated with the administration of IFN. In the PenTAG model there is an assumption that for each dose of temsirolimus the NHS will use one

30mg vial of temsirolimus (the unit of purchase). Whilst the dose is 25mg, and there is some suggestion that this dose is adjusted downwards by dose intensity data, PenTAG assume that there is no opportunity to prevent waste (through vial sharing schemes) and accept that the 5mg overfill will be purchased but unused. The Wyeth model used the expected sales price for temsirolimus and estimates a cost per mg (e.g. based on price of 30mg vial divided by 30), therefore having lower product costs than seen in the PenTAG model. Where PenTAG use the Wyeth model and assume a 30mg cost per patient dose, the manufacturer model estimates a cost per QALY of £74,819.

The costs for the administration of IFN are high in the Wyeth model, compared to the assumptions made by PenTAG. As discussed in section 4.4.1.3, we disagree with the assumptions made in the manufacturer submission on costs for administration of IFN (we do not agree with the assumption that it will be administered in a hospital setting 3 times per week). Where we use the Wyeth model, but apply the PenTAG assumptions on cost for administration of IFN the cost per QALY (from the amended manufacturer model) increases from £55,814 to £102,000. With the Wyeth model amended (by PenTAG) to adjust the cost for temsirolimus (i.e. vial cost, per dose) and the cost for administration of IFN (as PenTAG assumptions) the cost per QALY is £121,175.

Where we have used the OS and PFS survival curves in the Wyeth submission (modelled using the transition probabilities in the manufacturer model) to predict disease progression in the PenTAG model, the cost per QALY estimates increase substantially, due to lower expected benefits. Whilst there are clear differences in the predicted disease progression, and the incremental benefits, with the Wyeth model predicting a profile of disease progression that is worse (e.g. higher mortality) than that seen in the PenTAG model, the differences in assumptions on resource use / cost indicate the potential convergence of the cost per QALY estimates from each of the models.

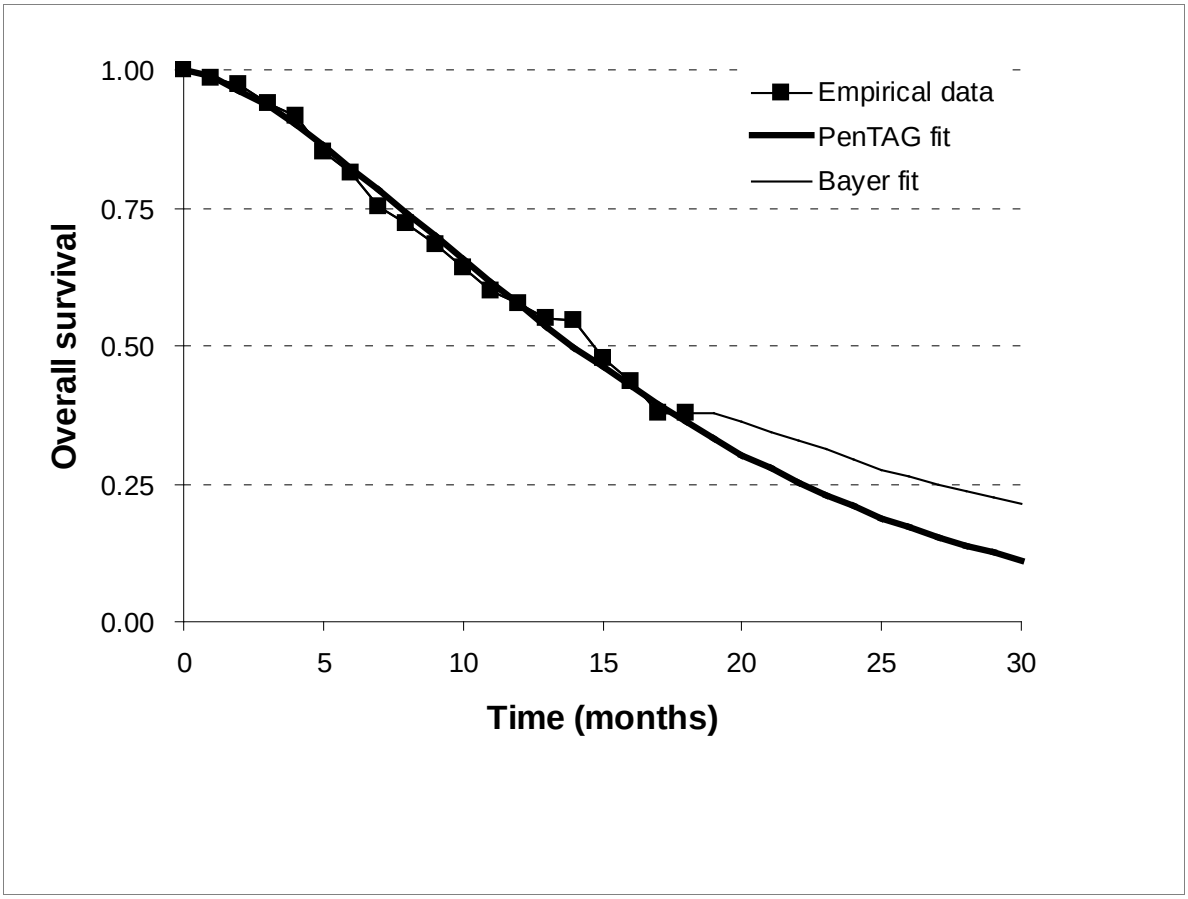
4.6.3. Sorafenib compared to best supportive care (2nd line treatment): CEA findings

In the PenTAG analysis a cost per QALY is estimated for sorafenib compared to BSC in 2nd line treatment for the patient group where patients are unsuitable for cytokine treatment. The manufacturer (Bayer) submission presents a cost per QALY for three patient groups; (1) patients unsuitable for cytokines and 2nd-line patients combined [as PenTAG], (2) 2nd-line patients only and (3) patients unsuitable for cytokines. Here, we discuss only patients unsuitable for cytokines and 2nd-line patients combined. The PenTAG base case estimate is £102,498 per QALY, which is higher than that of Bayer, at £90,630 per QALY .

The PenTAG and Bayer models use the same data to predict disease progression (RCT reported by Escudier and colleagues[113]). However, Bayer and PenTAG have used different approaches to model

disease progression. Bayer have modelled survival curves for sorafenib and BSC separately (using time dependent transition probabilities, derived from Kaplan-Meier data), for overall survival and PFS. PenTAG have modelled baseline disease progression (BSC) using Kaplan-Meier data from the RCT, and then modelled treatment effectiveness with sorafenib by applying the reported measures of clinical effectiveness (hazard ratios) in the RCT. This difference in approach leads to slight differences in the modelled disease progression, as shown in Figure 27 (page 188) with the PenTAG model predicting a greater level of mortality over time (a shorter tail to the PenTAG OS curve). The PenTAG model predicts lower survival, and lower incremental life years (see Table 53, page 189). The PFS profile is similar in the PenTAG and Bayer analyses. The incremental QALYs predicted by PenTAG are similar to those in the Bayer results, regardless of differences in mean life-years gained, as we have used different data on heath state utilities. In the PenTAG model, although fewer people survive, there is a greater utility gain in those that do survive, due to the value of 0.683 in the PD health state, compared to the Bayer input of 0.548 for PD. PenTAG use a value of 0.758 in PFS, compared to 0.737 in the Bayer analysis. We note that when we use the Bayer model, but adjust the health state values to reflect PenTAG assumptions the cost per QALY (Bayer model) falls from £90,630 to £80,135, which widens the gap in the ICER between PenTAG and Bayer results (with the disease progression noted above accounting for this).

Figure 26: Bayer and PenTAG fit to overall survival for BSC



Source: Escudier and colleagues, 2007[113]

The PenTAG and Bayer models both predict similar incremental total costs, although there are differences across the separate cost components (see Table 53, page 189). Bayer analysis reports higher costs for medical management than the PenTAG analysis. Bayer analysis assumes higher monthly costs for medical management in the PFS health state when patients are in the BSC treatment arm; Bayer use cost of £673 per month, compared with the PenTAG estimate of £58 per month. For sorafenib, Bayer assume a cost in PFS of £776 per month, compared with the PenTAG estimate of £158 per month. Bayer also apply higher costs for the progressive disease (PD) health state than PenTAG, £672 per month, compared to £314 per month. These assumptions on resource use for monitoring and medical management are uncertain, due to an absence of data. PenTAG have used advice from clinical experts. Bayer have also used surveys of clinicians (internet based surveys of 6 and 31 UK clinicians).

Table 53: Base case cost effectiveness analysis for sorafenib vs. BSC (2nd-line, unsuitable for cytokines): Comparison of PenTAG and manufacturer (Bayer) CEA.

	BSC		sorafenib		sorafenib vs. BSC	
	PenTAG	**Bayer**	**PenTAG**	**Bayer**	**PenTAG**	**Bayer**
Life Years	1.30	1.61	1.60	2.02	0.30	0.42
QALYs	0.91	0.96	1.15	1.22	0.23	0.26
Drug cost	£0	[redacted]	£23,058	[redacted]	£23,058	[redacted]
Drug admin	£0	[redacted]	£0	[redacted]	£0	[redacted]
Medical management	£248	[redacted]	£1,380	[redacted]	£1,132	[redacted]
BSC in PD	£3,549	[redacted]	£3,360	[redacted]	-£189	[redacted]
Total costs	£3,797	£13,230	£27,797	£37,079	£24,001	£23,849
Cost / LYG					£78,960	£57,456
ICER					**£102,498**	**£90,630**

§ calculated by PenTAG using Bayer's model.

5. Discussion and conclusions

This assessment has been necessarily constrained by the marketing authorisations of the interventions under review, which in turn dictated the scope of the assessment and the protocol and underlies our choice and derivation of appropriate research/policy questions on which to focus. We have wrestled with several important issues during this process namely, the definition of best supportive care, the definition of 'unsuitable' for treatment with interferon and the choice of comparators. We first discuss these issues and then for each of the four policy questions, the discussion is structured as follows:

- we present a summary of the findings from the systematic review of clinical effectiveness followed by an overview of the results from the PenTAG economic evaluation
- key factors influencing the results are then explored and discussed so as to aid interpretation
- the chief uncertainties in the economic evaluation are explored and discussed and we summarise the comparison of the PenTAG economic evaluations with those presented by the manufacturers,
- strengths and limitations of the assessment and their potential impact on the results are then considered and finally
- we provide a summary of our conclusions and what we consider the most important current priorities for further research.

Definition of best supportive care

We were unable to find any consistent definitions of 'best supportive care' in this clinical context. We were also unable to locate any trials of 'best supportive care' and understand the term to indicate that patients are receiving palliative care and monitoring. Several authors consider agents such as medroxyprogesterone and vinblastine to be 'placebo-equivalent' in trials of IFN versus control. However these agents are also considered as active treatments in some people. We have therefore estimated resource use and costs following consultation with our clinical expert advisory group, but recognise that this could be an area of wide variation both in clinical practice and patient need.

Definition of 'suitable for treatment with immunotherapy'

We interpreted 'suitable for treatment with IFN' as meaning that a patient so defined would not possess any clinical contraindications to treatment e.g. a history of depression or autoimmune disease. We did not consider people with intermediate or poor prognosis to be necessarily unsuitable for treatment with IFN.

However, it has become apparent since the publication of the PERCY Quattro trial of immunotherapy in patients with intermediate prognosis, which has been interpreted as showing no benefit of IFN in this patient group [38], that there is some variation around the UK in the management of people deemed to have intermediate or poor prognosis. In some centres, these people are offered treatment with IFN, in others they are considered to be 'unsuitable' for treatment with IFN and best supportive care therefore becomes their only treatment option.

Extrapolation of the results of the PERCY Quattro study [38] to this assessment is complex as the definition of intermediate prognosis differs from that used in the included trials.[106,111,113,115-117] However, using the MSKCC definition approximately 30% of patients in the included trials of first line therapy were considered to have favourable prognosis; approximately 50% of those in the second line trials[113,115-117] had favourable prognosis. The remainder of all included patients in this assessment had either intermediate or poor prognosis and could be considered, using alternative definitions, to be unsuitable for treatment with IFN.

Choice of comparators

We believed that it was important as far as possible to use current standard treatment as the comparator for all research questions - considering IFN to be the comparator for first line therapy in patients suitable for treatment with immunotherapy and best supportive care the comparator in all other situations. Our assessment does not take into account patient preference for treatment.

However, we recognise that a large proportion of people diagnosed with RCC in the UK will be deemed unsuitable for treatment with IFN as a result of clinical markers of prognosis and we therefore attempted to explore this issue further. We considered the validity of performing an indirect comparison between IFN and best supportive care in order to provide some estimate of the relative effectiveness and cost effectiveness of the new interventions against best supportive care. However, there are very few trials of IFN versus 'best supportive care' and those that have been performed do not provide results according to prognostic status.

Informal extrapolation of available data suggests that if it is assumed that there is no difference in the relative effectiveness of best supportive care and IFN in this population, and that the cost of best supportive care would be less than the cost of treatment with IFN, it is possible that the new interventions would be less likely to be considered cost effective at commonly used willingness to pay thresholds when compared to best supportive care. That is, if IFN is considered as an expensive equivalent of best supportive care, then the incremental costs of new drugs would all be greater when compared to best supportive care than when compared to IFN for no additional benefit.

5.1. Summary of main findings

5.1.1. Bevacizumab plus IFN and sunitinib compared with IFN as first line therapy

In this section we summarise the findings relevant to Research Question 1: In those who are suitable for treatment with immunotherapy, what is the clinical and cost effectiveness of bevacizumab plus IFN and sunitinib as first line therapy, using IFN as a comparator?

5.1.1.1. Clinical effectiveness (Section 3.2.2.2, page 51)

There is evidence from three good quality randomised clinical trials that sunitinib and bevacizumab plus IFN have clinically relevant and statistically significant advantages over treatment with IFN alone in terms of progression free survival and tumour response (see Table 12 and Table 13, pages 53 and 54). Compared with IFN treatment, both interventions are associated with a two-fold increase in progression free survival (from around 5 months to 11 months). [106,111] Unfortunately, there is little empirical data available to inform the effect of these interventions on overall survival. Moreover, further analysis of these trials is unlikely to add significantly to this particular evidence base as treatment crossover has occurred following interim analyses.

We were unable to locate any head-to-head comparison data for bevacizumab plus IFN versus sunitinib. Results of an indirect comparison suggest that sunitinib may be more effective than bevacizumab plus IFN (HR 0.67; 95% CI 0.50 to 0.89) in terms of progression free survival.

Data on adverse events suggest that the sunitinib is not associated with a greater frequency of adverse events than IFN, although the adverse event profiles are different (see Table 17, page 61). There were more grade 3 and 4 adverse events reported with bevacizumab plus IFN than with IFN in the AVOREN trial (mean number per patient 1.3 vs. 0.9 for the combination vs. IFN monotherapy respectively). It is not clear whether this difference was statistically significant.

There have been no published full-text papers in which EQ-5D data (health related quality of life data) collected during treatment with sunitinib, bevacizumab plus IFN or IFN alone is presented. The health state utilities used in the PenTAG model of cost effectiveness are further described in section 4.5.4.4 (page 141) and discussed in section 5.2.6.

All three trials were conducted primarily in people with clear cell carcinoma with MSKCC risk factors suggestive of a favourable or intermediate prognosis, who had undergone previous nephrectomy. Whether the results can be extrapolated to other patient groups is unclear.

5.1.1.2. PenTAG economic evaluation (Table 44)

Compared with the current standard therapy of IFN, the PenTAG economic analysis predicts an incremental benefit to patients receiving bevacizumab plus IFN of approximately a third of a life year at an incremental cost of £45,435. When quality of life is taken into account the base case cost per QALY for bevacizumab plus IFN compared with IFN monotherapy is £171,301 per QALY.

People receiving sunitinib accrue a slightly greater incremental benefit (approximately half a life year (giving 0.44 QALYs)) at a lower incremental cost (£31,185) producing a base case cost per QALY estimate for sunitinib versus IFN of £71,462 per QALY.

Probabilistic sensitivity analysis estimates that where the NHS is willing to pay £30,000 per QALY the probability that either intervention is cost effective compared to IFN is zero. Bevacizumab plus IFN is not likely to be considered cost effective compared to sunitinib or IFN at any reasonable willingness to pay threshold. Sunitinib is likely to be considered cost effective compared to bevacizumab plus IFN and IFN alone only above a willingness to pay threshold of approximately £75,000 per QALY.

In sensitiviy analyses, when applying pricing strategies stated by manufacturers, the cost per QALY estimates are £90,584 per QALY for bevacizumab plus IFN versus IFN and £65,362 per QALY for sunitinib versus IFN.

5.1.2. Sorafenib and sunitinib compared with best supportive care as first line therapy

In this section we address the findings relevant to Research Question 2: In those who are not suitable for treatment with immunotherapy what is the clinical and cost effectiveness of sorafenib tosylate and sunitinib, using best supportive care as a comparator?

This assessment is required to consider the interventions in relation to their marketing authorisations. Suitability for treatment with immunotherapy in this context is therefore defined in terms of contraindication to treatment with patients defined as being ‘unsuitable for treatment with immunotherapy’ having clinical contraindications to therapy e.g. autoimmune disease or a history of depression. We have not considered that patients defined as having a poor prognosis are ‘unsuitable’ for treatment with immunotherapy.

Unfortunately, we were unable to identify any studies of these interventions in people with a diagnosis of advanced and/or metastatic RCC deemed unsuitable for treatment with IFN which met the inclusion criteria of the review. We have therefore been unable to comment on the clinical effectiveness of

these interventions or to populate the PenTAG economic model to estimate the cost effectiveness of these interventions in this patient group.

The manufacturer of sorafenib (Bayer), present a commercial-in-confidence analysis of the cost effectiveness of sorafenib versus best supportive care in this patient population. A review and summary of this analysis can be found in section 4.4.1.4 (page 127)

5.1.3. Bevacizumab plus IFN or sorafenib or sunitinib or temsirolimus or best supportive care versus IFN

In this section we summarise the findings relevant to Research Question 3: In those with three or more of six poor prognostic factors what is the clinical and cost effectiveness of bevacizumab plus IFN, sorafenib, sunitinib, temsirolimus and best supportive care as first line therapy, using IFN as a comparator?

5.1.3.1. Clinical effectiveness (3.2.4.2, page 70)

Data from one large, good quality randomised clinical trial [112] indicates that treatment with temsirolimus has clinically relevant and statistically significant advantages over treatment with IFN (18MU three times weekly) in people with poor prognosis, in terms of progression free and overall survival (see section 3.2.4.2, page 70). This is the only comparison for which we have a robust estimate of overall survival. Compared with treatment with IFN, temsirolimus produces an increase in median overall survival from 7.3 to 10.9 months and a reduction in the risk of death of 22% (HR 0.73; 95% CI 0.58 to 0.92).

There is also some evidence to suggest that progression free survival may be prolonged by treatment with the combination of bevacizumab and IFN compared with IFN alone in this population. Although the difference between treatments is minimal (median progression free survival was 2.2 and 2.1 months during treatment with bevacizumab plus IFN and IFN alone respectively) and may not be considered clinically significant. In addition, the 95% confidence interval around the hazard ratio for the latter comparison crosses unity and may not be considered statistically significant.

We were unable to find any data on the use of sorafenib tosylate in this population, nor any head-to-head randomised trials of the new interventions, nor any comparisons with best supportive care. Unfortunately, due to differences in study and baseline population characteristics, we were unable to perform any indirect comparisons between treatments.

Data on adverse events suggest that temsirolimus is associated with a significantly lower frequency of serious (grade 3 and 4) adverse events than IFN.[112] According to a recently published systematic review between 1 and 20% of patients receiving temsirolimus reported grade 3 or 4 adverse events. The most commonly reported grade 3 and 4 adverse events were anaemia (20%), fatigue/asthenia (11%), hyperglycaemia (11%) and dyspnoea (9%), this includes both disease-related and drug-related adverse events.[120]

There have been no published full-text papers in which EQ-5D data (health related quality of life data) collected during treatment with temsirolimus or IFN is presented. However, the company submission suggests that EQ-5D data were collected during the trial of temsirolimus vs. IFN.[112] The health state utilities used in the PenTAG model of cost effectiveness are further described in section 4.5.4.4 (page 141) and discussed in section 5.2.6.

Results from this trial have also been presented according to tumour histology subtype and nephrectomy status.[112] There is a large amount of variation surrounding the estimates of effectiveness but nevertheless, the data suggest that temsirolimus may be more effective than IFN in all four subgroups (see section 3.2.4.2, page 70).

5.1.3.2. PenTAG economic evaluation (see section 4.5.7.2, page 165)

As a consequence of the paucity of suitable data available in people with poor prognosis, the only comparison for which we have been able to provide an estimate of cost effectiveness is temsirolimus versus IFN.

The PenTAG economic analysis predicts that people are in a period of progression free survival during which they receive treatment with temsirolimus for a mean of 7.6 months. In comparison, people receiving IFN do so for 4.6 months. The incremental benefit for temsirolimus is approximately half a life year (giving 0.24 QALYs) at an incremental cost of £22,272. The incremental cost per QALY estimate for the comparison of temsirolimus versus IFN is £94,385 per QALY.

The cost utility analyses performed in patient subgroups estimate incremental cost effectiveness ratios between £74,184 per QALY and £154,334 per QALY (Table 48, page 169). However, the effectiveness data on which these estimates are based is very uncertain with 95% confidence intervals either approaching or crossing unity in most cases. The validity of the subgroup analyses is further discussed on page 198 in section 5.2.2. These results should therefore be viewed with some caution.

The probabilistic analyses suggest that where the NHS is willing to pay £30,000 for an additional QALY, the probability that temsirolimus is cost effective compared to IFN is zero. Temsirolimus is

likely to be considered cost effective compared to IFN only above a willingness to pay threshold of approximately £95,000 per QALY.

5.1.4. Second line therapy: Sorafenib or sunitnib versus best supportive care

In this section we summarise the findings relevant to Research Question 4: In those in whom cytokine based immunotherapy has failed, what is the clinical and cost effectiveness of sorafenib tosylate and sunitinib, using best supportive care as a comparator?

5.1.4.1. Clinical effectiveness (Section 3.2.5.2, page 89)

Data from a large, good quality randomised clinical trial [113] and a randomised discontinuation trial [149] in which sorafenib was compared with placebo, suggest that sorafenib tosylate has clinically relevant and statistically significant advantages over best supportive care in terms of overall survival, progression free survival and tumour response. Data on median progression free survival is the most robust and in the randomised clinical trial [113] was 5.5 months in the sorafenib group and 2.8 months in the placebo group (see section 3.2.5.2, page 89).

We were unable to identify any comparative data for sunitinib in people in whom treatment with cytokine based immunotherapy has failed. Two single arm phase II trials suggest that sunitinib is efficacious in this patient group but extrapolation from uncontrolled trials is difficult.[85,116,117] No indirect comparison between treatments was possible as there was no common treatment arm.

Treatment with sorafenib is associated with a significantly increased frequency of hypertension and hand foot syndrome; 16 and 25% of people experienced these adverse events at grade 3 or 4 respectively during treatment with sorafenib in the main trial.[113]

Safety data suggest that the frequency of adverse events during second line therapy with sunitinib is no different from that reported during first line therapy.

All these trials were conducted in patients with metastatic clear cell RCC, the majority of whom had undergone previous nephrectomy and were classified as having favourable or intermediate prognosis according to the MSKCC risk score. Whether sorafenib or sunitinib have advantages over placebo in other patient groups is unclear.

5.1.4.2. PenTAG economic evaluation (section 4.5.8)

As we were unable to locate any comparative trials of sunitinib as second line therapy, we were only able to examine the cost effectiveness of sorafenib versus placebo (best supportive care) in this patient population.

The PenTAG model predicts an incremental benefit for sorafenib of approximately 0.3 life years (giving 0.23 QALYs) at an incremental cost of approximately £24,001 compared with placebo. The cost per QALY estimate for sorafenib versus placebo (best supportive care) is £102,498 per QALY.

The probabilistic sensitivity analysis suggests that were the NHS willing to pay £30,000 for an additional QALY the probability that sorafenib would be considered cost-effective compared with best supportive care is zero. Compared with best supportive care sorafenib is only likely to be considered cost effective above a willingness to pay of approximately £100,000 per QALY.

5.2. Uncertainties

In this section we discuss the key issues influencing the evaluation of clinical and cost effectiveness. We first consider issues that impact primarily on the assessment of clinical effectiveness, although their influence on the economic evaluation is also considered where appropriate. These include: the paucity of available overall survival data and the potential effect of the ensuing extrapolation of trial data; the validity of the sub-group analyses described in the report; and the generalisability of our findings to a wider patient population.

5.2.1. Extrapolation of trial data

In the assessment of both clinical and cost effectiveness we have only considered data collected during the randomised period of treatment prior to any interim analyses and crossover of patients from control to active treatments. This means that the evidence for an effect on overall survival used in the economic evaluation is immature and consequently uncertain (see section 5.2.4, page 199). However due to the loss of randomisation, the risk of confounding and the use of other active agents following disease progression, data collected prior to treatment crossover is the best data available. There is evidence of confounding in at least one of the included trials; final analysis of overall survival in the TARGETs trial [113], (after 48% (n=216) patients in the placebo group had crossed over to sorafenib treatment) produced a hazard ratio of 0.88 which was not statistically significant. Further analysis in which data from the crossed over patients were censored, produced a hazard ratio of 0.78 (p=0.0287).[98] Clearly the true effect of sorafenib in this trial lies somewhere between these two estimates. There is ongoing debate as to the validity of progression free survival as an endpoint with which to compare the effectiveness of interventions in oncology trials. On the one hand it is perhaps

unrealistic to expect to collect mature overall survival data given the multiple options for active treatment now available after a failed first line therapy. However, extension of progression free survival (during which a patient may receive an active agent and experience the associated adverse events) may have little clinical relevance if overall survival is not also suitably prolonged.

Use of data from pre-crossover only in the economic evaluation necessitates considerable extrapolation of trial data in order to populate the model for a time horizon of ten years. For the same trial [113], the survival curves used in the model are based on empirical data for the first 15 months or so, henceforth the curves rely on extrapolation.

5.2.2. Validity of sub-group analyses

The scope of this assessment required that we considered two sets of subgroups where data were available; according to tumour histology subtype (clear cell and non-clear cell RCC) and nephrectomy status. Two of the included trials provided data on these subgroups and where appropriate we have described and analysed this. However, although the subgroup analyses were pre-planned and they provide some indication as to the effectiveness and cost effectiveness of the interventions in different patient populations, we have reservations about the validity of these analyses. Primarily, the trials were not sufficiently powered to detect differences in effect in subgroups. For example in the trial of sunitinib versus IFN [111] only 10% of patients (n=77) in the trial had not undergone prior nephrectomy and in the trial of temsirolimus versus IFN [112] 17% had non clear cell RCC. Consequently, there is a large amount of imprecision in the hazard ratios; in most of the subgroup analyses the 95% confidence intervals approach or cross unity indicating that the results would not be considered statistically significant.

In addition, the division of patients according to tumour histology subtype does have a clinical basis but whilst a clear division can be made between patients in terms of nephrectomy status, the clinical relevance of this division is unclear. It is possible that division of the population according to nephrectomy status is confounded by other factors of disease status which underlie the reasons behind some people not undergoing surgery, such as the position of the primary tumour and the performance status of the patient.

5.2.3. Generalisability of results

All the trials included in the review of clinical effectiveness were conducted in patients with predominantly clear cell, metastatic RCC, the majority of whom had undergone previous nephrectomy and many of whom were of favourable and intermediate prognosis and good performance status. None of the studies recruited patients with brain metastases (unless neurologically stable) and few

patients with bone metastases were included (20% in the trial of bevacizumab plus IFN versus IFN [106] and 30% in the trial of sunitinib versus IFN[111]).

Whether the results of this assessment can be applied to other patient groups is unclear. Expanded access trials can provide some indication of the effectiveness of interventions in a wider patient population. Published results for sunitinib from an expanded access trial in approximately 2,000 patients, suggest that overall effectiveness may be reduced in a less highly selected population (estimates of median progression free survival of 8.9 months from the expanded access trial compared with 11 months from the randomised clinical trial[111]), but also provide evidence that sunitinib may be effective in previously unstudied populations such as those with brain metastases, people over the age of 65 years and those with an ECOG performance status of 2 or more.[119]

We now turn to the key issues which impact on the results of the economic evaluation, identified primarily in the deterministic sensitivity analysis. These include the estimates of treatment effectiveness, in particular overall survival, drug pricing (including variations in dose intensity and assumptions about wastage) and health values.

5.2.4. Effectiveness data

In the PenTAG economic evaluation, the effectiveness data used to model disease progression and cost-effectiveness comprises data on progression free and overall survival. Baseline disease progression, for IFN or BSC, has been modelled using Weibull survival analysis applied to empirical Kaplan-Meier data, with treatment effectiveness modelled using relative measures of treatment effectiveness i.e. hazard ratios for progression free and overall survival reported in the clinical trials.

Not surprisingly, in all comparisons the estimates of cost effectiveness are most sensitive to variations in the hazard ratios for overall survival. Due to the nature of the trials from which this data is derived, this data is also the most uncertain. For example, in the trial of sunitinib versus IFN, the hazard ratio for overall survival is 0.65 with 95% confidence intervals that range from 0.45 to 0.95.[111] This level of precision equates to possible variations in the effect of the drug from having very little effect to more than halving the risk of death. As might be expected the consequential effects on the incremental cost effectiveness ratio of sunitinib versus IFN are also large. Compared with a base case of £71,462 per QALY, varying the hazard ratio for overall survival between the upper and lower limits of the 95% confidence intervals produces results ranging from £39,759 per QALY (lower limit) to £263,363 per QALY (upper limit). For bevacizumab plus IFN (compared to IFN), temsirolimus (compared to IFN) and sorafenib (compared to best supportive care), there is a similar level of uncertainty around the estimate of the hazard ratio for overall survival, and similar marked swings in the cost per QALY estimates.

The sensitivity analyses for the hazard ratios for progression free survival have highlighted issues linked to the balancing of incremental costs and effects. In the PenTAG analysis, an increase in the size of the treatment effect (a lower hazard ratio for progression free survival) results in a worsening cost-effectiveness profile. In other words, improvements in progression free survival make the drugs less attractive in terms of value for money. This counter-intuitive effect is seen across all of the analyses undertaken by PenTAG, is apparent for both cost per QALY and cost per life-year analyses and can be explained partly by the relatively high incremental treatment costs (costs of the drug, drug administration and monitoring) associated with time spent in the progression free disease health state. In our modelling, these costs are shown to outweigh (dominate) the incremental benefits (life year gained, QALY gains) associated with spending a longer period of time in the progression free disease health state. When people move from progression free disease to the progressive disease health state they continue to benefit from treatment through the application of overall survival data. As the interventions have a significant treatment effect there is a difference in the predicted overall survival between groups. However, equal costs are incurred irrespective of treatment strategy (e.g. the cost incurred in the progressive disease state for people in the sunitinib cohort is equal to the cost incurred in the progressive disease state for people in the IFN cohort). Therefore, the balance of costs and effects associated with time in the progression free disease health state favours the baseline scenarios (either IFN or best supportive care). Consequentially, an improvement in progression free survival resulting in more time spent receiving treatment with a drug incurring a high incremental treatment cost leads to a higher estimate of cost effectiveness.

None of the manufacturer submissions to NICE have explicitly presented sensitivity analyses using alternative assumptions for hazard ratios for progression free survival. We have performed these sensitivity analyses using the manufacturer models for sunitinib (Pfizer) and sorafenib (Bayer), and observed the same counter-intuitive effect.

Sensitivity analysis against the hazard ratios for overall survival (OS) shows a more intuitive scenario. As expected, when the hazard ratio for overall survival is reduced (i.e. there is a greater treatment benefit), the cost per QALY decreases and the intervention would be more likely to be considered cost effective.

It is interesting to note that whilst the effectiveness of treatments against outcomes for progression free survival has been used to emphasise the potential clinical benefits from treatment, it is the much less certain data on effectiveness against overall survival that is driving the estimates of incremental cost effectiveness.

5.2.5. Drug pricing

There are several elements to the assumptions made about drug pricing within the PenTAG economic evaluation; the use of pricing strategies, assumptions about wastage and dose intensity and the costs associated with administration of drugs. Due to the relatively high cost of the new interventions, variations in the price of the drug for whatever reason have a relatively large impact on the estimates of cost effectiveness.

Pricing strategies

Two of the manufacturers (Pfizer and Roche) of interventions (sunitinib and bevacizumab plus IFN) in this assessment indicate that pricing strategies will be available for these agents in the UK. As expected, reduction in the total cost of the drug has large implications for the resulting cost effectiveness estimates, particularly in the comparison of bevacizumab plus IFN versus IFN where the incremental cost effectiveness ratio is reduced from £171,301 per QALY to £90,584 (PenTAG analysis) with the incorporation of the manufacturers pricing strategy. Multi-way sensitivity analyses in which the pricing strategy for bevacizumab is applied together with variation in the hazard ratios for overall and progression free survival are shown in Table 46 (page 162). Given the best estimates for the effectiveness of treatment (lower limits of 95% confidence intervals for overall and progression free survival) and the presence of the dose capping scheme the cost effectiveness ratios for the comparison of bevacizumab plus IFN versus IFN alone become £49,190 per QALY and £91,973 per QALY respectively.

The manufacturers pricing strategy for sunitinib has similar although less marked effects (Table 45, page 159).

Dose intensity

We have assumed in the model that people would be exposed to the same dose intensity of treatment as reported in the clinical trials from which the effectiveness data arises. As might be expected, increasing or decreasing the dose intensity of the intervention produces the expected increase or decrease in the cost effectiveness ratio. We did not identify any data with which to clarify any possible relationship between dose intensity and the effectiveness of treatment, e.g. higher dose intensity leading to a better response to treatment, and it is unclear whether it would be realistic to expect higher dose intensities than those reported during trials due to the close monitoring provided within the context of a randomised clinical trial. Presumably, higher compliance with treatment would be associated with a greater incidence of adverse events since the primary reason for dose interruption or discontinuation in the trials was the incidence of unacceptable toxicity. However, as seen in the multi-way sensitivity analyses in which increases in drug costs were varied together with an increase in the

effectiveness of treatment (a decrease in the hazard ratio), if this could be achieved we might expect the estimates of incremental cost effectiveness to decrease.

Wastage assumptions

Temsirolimus is produced in 30mg vials, 25mg of which is needed per patient per treatment; there is therefore the potential for vial sharing between patients. Following consultation with our clinical experts, who advised that vial sharing was unlikely to occur on a regular basis due to the number of patients necessary, the short shelf life of the product, the route of administration (i.v. infusion) and the need for prior treatment with anti-histamine, we assumed that no vial sharing occurred in the base case analysis. Due to the potential cost-saving implications of vial sharing, it is not surprising that when this is varied to assume 100% vial sharing i.e. no wastage that the incremental cost effectiveness ratio is reduced (from a base case of £94,385 per QALY to £81,687 per QALY). This analysis takes no account of additional pharmacy resources required to implement vial sharing.

Drug administration costs

In the comparison of temsirolimus versus IFN, variation in the cost of administration of both agents and the consequent incremental difference in costs has a large effect on the cost effectiveness estimate. In the base case the difference in the administration costs for temsirolimus and IFN is £5,848 (see Table 47, page 165) and forms a substantial component of the total cost difference. We have based our assumptions on the cost of administration of IFN on the opinions of our expert advisory group who reported that IFN is predominantly administered at home. If we assume that IFN is administered in the hospital setting (as in the evaluation performed by the manufacturer of temsirolimus) and is thus associated with higher administration costs, the incremental cost between treatments becomes smaller and the resulting cost effectiveness estimates are also reduced.

5.2.6. Utilities

As described in section 4.5.4.4, we identified two sources of possible health state utilities and were unsure as to the relationship, if any, between these data sets. We were not convinced that the difference in utility values obtained in the two trials [111,112] could be explained by differences in performance status and were concerned that we might be introducing a lack of continuity into the modelling of the policy questions by choosing to use health state values from different sources in different questions. However, in the absence of other data, there was no persuasive alternative and we acknowledge the limitations in the data used.

The sensitivity of cost per QALY estimates to changes in health state utilities is connected to the impact of effectiveness measures (hazard ratios for progression free and overall survival) on cost

effectiveness. As discussed in section 5.2.4, overall survival is a major driver in the cost-effectiveness analysis and has a greater impact than progression free survival. In the same way, sensitivity analyses on health state values demonstrate that variations in the health state value for the progressive disease health state have a bigger impact on cost per QALY estimates, than variations in the utility interval between the progressive disease and progression free health states, due to the balancing of incremental costs and benefits. That is, where the difference in the utility interval between 'living' health state values, is varied in sensitivity analysis, this has a lesser impact on the cost effectiveness estimate than changing the absolute value used for the progressive disease state (i.e. the difference between alive in progressive disease and dead).

5.3. Comparison of PenTAG cost effectiveness analysis with those produced by manufacturers

We have reviewed the four economic evaluations submitted by the manufacturers of interventions in this assessment. We have not carried out an exhaustive audit of each of the models, but we have concentrated on reviewing the assumptions underlying the model structure and the data used to populate them, and provide a summary in section 4.4 on page 105.

The cost effectiveness estimates produced in the PenTAG economic evaluation are higher than the manufacturer base case estimates in all cases (although in two of the four analyses the results are similar). Whilst there are some common aspects of methodology, in both model structure and data inputs across manufacturer and PenTAG analyses, there are also clear differences in the resulting cost effectiveness estimates. These are reviewed and summarised in section 4.6. Where a potential area for divergence between models has been identified, exploration of both the PenTAG and manufacturer models, with incorporation of the alternative data, has indicated that it is possible to see similar results across models, when the differences are taken into account.

Whilst the manufacturers have been able to present economic evaluations of their products in isolation, we have used a similar modelling framework across all research questions. However, there are several analyses included in the company submissions which we have not undertaken due to an absence of reliable effectiveness data e.g. comparison of sunitinib versus best supportive care in second line treatment and comparison of sorafenib versus best supportive care as first line therapy in people unsuitable for treatment with IFN.

5.4. Strengths of the assessment

This is the first analysis of the effectiveness and cost effectiveness of bevacizumab plus IFN, sorafenib tosylate, sunitinib and temsirolimus to inform policy in the UK NHS setting. We were unable to find any other fully published economic evaluations of these interventions.

Comprehensive, explicit and systematic literature searches including hand searching of conference proceedings, were performed to locate evidence both for the review of clinical effectiveness and to inform the economic modelling study.

Overall survival data for these interventions is scarce and unlikely to become available with IFN as a comparator, as the agents are now readily available in Europe and the US and used as first line therapy for metastatic RCC. Careful consideration of the empirical survival data was therefore necessary, with attempts to fit the most appropriate survival curves to best extrapolate the available immature data.

Extensive analyses of the uncertainty of the model were performed with one-way, multi-way and probabilistic sensitivity analyses.

5.5. Limitations of the assessment

Model-based cost effectiveness analyses are an inevitable consequence of the need to integrate a range of information about a wide variety of factors to support policy making decisions on new technologies. These relate to the natural history of disease, the efficacy and effectiveness of interventions, the treatment pathway and the resultant life expectancy and quality of life in different disease states and with different treatments.

We have already alluded to several limitations of this work including the constraint of the assessment by the marketing authorisations of the products leading to difficulties with the derivation of research questions and the subsequent applicability of these questions to the RCC population, and the uncertainty of the overall survival and health state utility data. In this section we discuss some further issues which we believe may be limitations of the assessment. These include, the availability of clinical effectiveness data for all potential comparisons, issues surrounding patient preference, consideration of the sequencing of treatments, some of the structural modelling assumptions used in the PenTAG model and the scarcity of available information on resource use and costs.

We were not able to identify data to inform on all the potential interventions relevant to each policy question and despite attempts to perform indirect comparison where head-to-head data were not available from randomised clinical trials this was only possible for the comparison of bevacizumab plus IFN versus sunitinib as first line therapy in patients suitable for treatment with IFN. As a result of

this lack of primary clinical effectiveness data we have been unable to fully inform the policy questions.

As is common in health technology assessment, we use summary data, not individual patient data, to model treatment effectiveness. We have estimated progression free and overall survival for baseline treatment by fitting Weibull curves to Kaplan-Meier data. It is preferable to fit Weibull curves from individual patient data using the method of maximum likelihood[150] and this may have led to more precise estimates of cost effectiveness. Individual patient data was used in one of the four company submissions (Wyeth[125]). As a result of the structural assumptions we have made in the PenTAG economic evaluation, modelling is driven by data on overall survival and progression free survival. This was a necessary consequence of the available clinical data but it does mean that time in progressive disease has been indirectly calculated (the difference between overall survival and time spent in progressive disease). We have also been unable to identify any published data on time spent in progressed disease during treatment with the interventions with which to calibrate the outputs from the model.

There is a scarcity of published data available to inform resource use and costs associated with treatment of RCC especially in terms of the provision of best supportive care and the monitoring and medical management of people with RCC, both during treatment (progression free disease) and during progressed disease. As is the case with most modelling studies, we have therefore adopted some simplifying assumptions. We acknowledge that this could be considered a limitation of the evaluation. However, we feel that the use of simplifying assumptions (which are adopted in a similar way cross all interventions) has enabled us to examine the relationships between effectiveness, costs and utilities without additional uncertainty and complexity.

As more interventions become available for the treatment of metastatic RCC, the sequencing of treatment will become more important. We chose to model first and second line treatment separately rather than produce an overall model of RCC as we felt that this was the most appropriate way to address the research questions in the context of the protocol, without introducing additional unnecessary uncertainty. Currently, the only licensed treatment options for second line therapy are sorafenib and best supportive care, although this is an area of much primary research activity (see Appendix 12, page 272). In our evaluation, people in progressive disease receive best supportive care only. As clinical effectiveness data becomes available for the use of these interventions as second line and subsequent treatment options emerge, the treatment pathway will inevitably become more complex, necessitating further evaluation.

As required by NICE, the assessment takes no account of individual patient preference for treatment. This may be particularly important when comparing an oral therapy taken at home with one which is

administered as an intravenous infusion in hospital. It is possible that this type of information would be captured within utility values, but we do not believe that this is the case with the values that we have used. We might anticipate that patient preference would be for an oral tablet taken at home but we found no published sources of data to inform on this or on patient preference for receiving IFN at home rather than in the hospital setting. Relatedly, we have not considered the disutility of adverse events associated with treatment and have used disease specific rather than treatment specific utility values in the evaluation. We felt that this was most appropriate given the sparsity of available information on health state values in RCC. Although the frequency of adverse events experienced during treatment is generally lower with the new interventions than with IFN, the adverse event profile is different. We have no data to inform as to the impact that this might have on utility values. Furthermore, we have taken no account of emerging concerns over long-term safety in the case of sunitinib.

5.6. Other relevant factors

All of the interventions in this assessment have been granted orphan drug status. However, where NICE have consulted on the methods for the assessment and appraisal of orphan drugs they have suggested no difference in the process or methodological guidance for the assessment of clinical and cost effectiveness.

5.7. Conclusions

We conclude that there is evidence to suggest that treatment with bevacizumab plus IFN and sunitinib has clinically relevant and statistically significant advantages over treatment with IFN alone in patients with metastatic RCC. There is also evidence to suggest that, in people with three of six risk factors for poor prognosis, temsirolimus has clinically relevant advantages over treatment with IFN and sorafenib tosylate is superior to best supportive care as second line therapy. The frequency of adverse events associated with bevacizumab plus IFN, sunitinib and temsirolimus is comparable with that seen during treatment with IFN, although the adverse event profiles are different. Treatment with sorafenib is associated with a significantly increased frequency of hypertension and hand foot syndrome.

The PenTAG cost effectiveness analyses suggests that the probability that any of the interventions would be considered cost effective at a willingness to pay threshold of £30,000 per QALY approaches zero.

5.7.1. Suggested research priorities

There are clear gaps in the evidence base needed to fully appraise the clinical and cost effectiveness of these four interventions in accordance with their marketing authorisations. Further randomised clinical trials in the following areas would therefore be useful:

- in patients unsuitable for treatment with IFN either as a result of contraindications or who have been defined as having intermediate and poor prognosis and may not benefit from IFN, trials of sorafenib, sunitinib, bevacizumab and best supportive care, and
- comparative trials of sunitinib and sorafenib as second line therapy.

In the current evidence base there is large amount of uncertainty surrounding the estimates of overall survival, primarily due to early crossover of people receiving control treatment following interim analyses. It is unrealistic and perhaps unethical to expect that further randomised clinical trials would be performed using IFN or best supportive care as a comparator in these interventions that are now widely used in Europe and the US. As the interventions provide little possibility of a cure and in the absence of unconfounded estimates of overall survival from RCTs, further understanding of the impact of the interventions on health related quality of life during progression free survival and progressed disease would facilitate the decision making process for clinicians and patients.

Research on current treatment pathways and current practice (e.g. in the use of interferon) would reduce the level of uncertainty in future studies modelling the cost-effectiveness of drugs for treatment of renal cancer.

As more agents are introduced for the treatment of metastatic RCC, the issues of treatment sequencing become more evident and raise many additional research questions surrounding the combination and order of treatments to provide maximum benefit in each patient population.

When modelling treatment of RCC there are methodological challenges when using summary data (survival analysis) from clinical trials, and research to explore the impact of using aggregated data compared to individual patient level data would be helpful.

Appendix 1: Literature search strategies

Search strategy for clinical effectiveness

The Medline search strategy was translated and run in:
MEDLINE (Ovid) – 1950 to September week 3 2007
EMBASE (Ovid) – 1980 to 2007 week 39
Cochrane CENTRAL Register of Controlled Trials (CCTR) – 2007 Issue 3
Cochrane Database of Systematic Reviews (CDSR) – 2007 Issue 3
HTA database (in Cochrane Library) – 2007 Issue 3
(ISI Web of Science) Science Citation Index – 1981 to 26/09/07
(ISI Web of Science) Proceedings – 1980 to 01/10/07
BIOSIS – 1985 to 01/10/07

MEDLINE OVID 1950 –September week 3 2007
Searched 26/09/2007
1 exp Carcinoma, Renal Cell/
2 (renal cell carcinoma$ or cell renal carcinoma$ or renal carcinoma$ or kidney carcinoma$ or kidney cell carcinoma$ or renal adenocarcinoma$ or kidney adenocarcinoma$ or adenocarcinoma$ renal or adenocarcinoma$ kidney$).mp.
3 (hypernephroma$ or nephroid carcinoma$ or hypernephroid carcinoma$ or kidney hypernephroma$ or kidney pelvic carcinoma$ or kidney pyelocarcinoma$ or renal hypernephroma$ or grawitz tumo?r$ or renal cell neoplasm$ or renal cell cancer$ or renal tumo?r$ or carcinoma chromophobe cell kidney$ or chromophobe cell kidney carcinoma$).mp.
4 exp kidney neoplasms/
5 (cancer$ adj2 kidney$1).ti,ab.
6 (neoplasm$1 adj2 kidney$1).ti,ab.
7 (neoplasm$1 adj2 renal).ti,ab.
8 (cancer$ adj2 renal).ti,ab.
9 (tumo?r$1 adj2 kidney$1).ti,ab.
10 (tumo?r$1 adj2 renal).ti,ab.
11 or/1-10
12 (bevacizumab or avastin or sorafenib or nexavar or sunitinib or sutent or torisel or temsirolimus or "CCI-779").mp.
13 11 and 12
14 limit 13 to humans
15 (editorial or letter).pt.
16 14 not 15

Search strategy for cost-effectiveness
This search strategy was translated and run in:
MEDLINE (Ovid) – 1950 to September week 3 2007
EMBASE (Ovid) – 1980 to 25/09/07
Cochrane CENTRAL Register of Controlled Trials (CCTR) – 2007 Issue 3
(ISI Web of Science) Science Citation Index – 1981 to 24/10/07
BIOSIS – 1985 to 24/10/07
(ISI Web of Science) Proceedings – 1980 to 24/10/07
NHS EED – 1995 to 24/10/07
NRR – 2000 to 24/10/07
Conferences searched on Internet, including ECCO 14, ASCO, ISPOR and ISOP

MEDLINE (Ovid) 1950 – September week 3 2007
Searched 25/09/2007

Search one: for specific drug interventions linked to RCC

1 exp Cost-Benefit Analysis/ or exp Economics, Pharmaceutical/ or exp Drug Costs/ or exp Models, Economic/
2 exp "Fees and Charges"/
3 (economic$ or price or pricing or pharmacoeconomic$ or pharmaeconomi$).tw.
4 (cost or costly or costing$ or costed).tw.
5 (cost$ adj2 (benefit$ or utilit$ or utilis$ or minim$)).tw.
6 (expenditure$ not energy).tw.
7 (value adj2 (money or monetary)).tw.
8 budget$.tw.
9 (economic adj2 burden$).tw.
10 "resource use".ti,ab.
11 exp economics/
12 exp economics hospital/
13 exp economics pharmaceutical/
14 exp economics nursing/
15 exp economics dental/
16 exp economics medical/
17 exp "costs and cost analysis"/
18 value of life/
19 exp models economic/
20 cost of illness/
21 or/1-20
22 letter.pt.
23 editorial.pt.
24 comment.pt.
25 or/22-24
26 21 not 25
27 (bevacizumab or avastin or sorafenib or nexavar or sunitinib or sutent or torisel or temsirolimus or "CCI-779").mp.
28 CCI-779.rn.
29 27 or 28
30 26 and 29
31 exp carcinoma renal cell/
32 (renal cell carcinoma$ or cell renal carcinoma$ or renal carcinoma$ or kidney carcinoma$ or kidney cell carcinoma$ or renal adenocarcinoma$ or kidney adenocarcinoma$ or adenocarcinoma$ renal or adenocarcinoma$ kidney$).ti,ab.
33 (kidney$1 adj2 cancer).ti,ab.
34 (hypernephroma$ or nephroid carcinoma$ or hypernephroid carcinoma$ or kidney hypernephroma$ or kidney pelvic carcinoma$ or kidney pyelocarcinoma$ or renal hypernephroma$ or grawitz tumo?r$ or renal cell cancer$ or renal tumo?r$ or carcinoma chromophobe cell kidney$ or chromophobe cell kidney carcinoma$).ti,ab.
35 or/31-34
36 30 and 35

Search two: for interferon interleukin plus cost filter plus RCC

1 exp Cost-Benefit Analysis/ or exp Economics, Pharmaceutical/ or exp Drug Costs/ or exp Models, Economic/
2 exp "Fees and Charges"/
3 (economic$ or price or pricing or pharmacoeconomic$ or pharmaeconomi$).tw.
4 (cost or costly or costing$ or costed).tw.
5 (cost$ adj2 (benefit$ or utilit$ or utilis$ or minim$)).tw.

6 (expenditure$ not energy).tw.
7 (value adj2 (money or monetary)).tw.
8 budget$.tw.
9 (economic adj2 burden$).tw.
10 "resource use".ti,ab.
11 exp economics/
12 exp economics hospital/
13 exp economics pharmaceutical/
14 exp economics nursing/
15 exp economics dental/
16 exp economics medical/
17 exp "costs and cost analysis"/
18 value of life/
19 exp models economic/
20 cost of illness/
21 or/1-20
22 letter.pt.
23 editorial.pt.
24 comment.pt.
25 or/22-24
26 21 not 25
27 exp carcinoma renal cell/
28 (renal or kidney$1).ti,ab.
29 (carcinoma$ or cancer$ or tumo?r$1 or adenocarcinoma$ or pyelocarcinoma$).ti,ab.
30 28 and 29
31 26 and 27 and 30
32 limit 31 to (humans and english language)
33 exp Interleukin-2/
34 exp Interferon-alpha/
35 32 and (33 or 34)
36 exp Interferon-alpha/ec [Economics]
37 exp Interferon Alfa-2b/ec [Economics]
38 exp Interleukin-2/ec [Economics]
39 or/36-38
40 27 and 30 and 39
41 35 or 40
42 limit 41 to (humans and english language)

Search three: for broad disease area search and cost filter

1 exp economics/
2 exp economics hospital/
3 exp economics pharmaceutical/
4 exp economics nursing/
5 exp economics dental/
6 exp economics medical/
7 exp "Costs and Cost Analysis"/
8 Cost Benefit Analysis/
9 value of life/
10 exp models economic/
11 exp fees/ and charges/
12 exp budgets/
13 (economic$ or price$ or pricing or financ$ or fee$ or pharmacoeconomic$ or pharma economic$).tw.
14 (cost$ or costly or costing$ or costed).tw.
15 (cost$ adj2 (benefit$ or utilit$ or minim$ or effective$)).tw.

16 (expenditure$ not energy).tw.
17 (value adj2 (money or monetary)).tw.
18 budget$.tw.
19 (economic adj2 burden).tw.
20 "resource use".ti,ab.
21 or/1-20
22 (news or letter or editorial or comment).pt.
23 21 not 22
24 exp Kidney Neoplasms/
25 exp carcinoma renal cell/
26 (renal or kidney$1).tw.
27 (neoplasm$ or carcinoma$ or cancer$ or tumo?r$ or adenocarcinoma$ or pyelocarcinoma$).tw.
28 26 and 27
29 or/24-25,28
30 23 and 29
31 limit 30 to (humans and english language)
32 limit 31 to animals
33 31 not 32
34 from 33 keep 1-833
35 (renal adj (neoplasm$ or carcinoma$ or cancer$ or tumo?r$ or adenocarcinoma$ or pyelocarcinoma$)).tw.
36 (kidney$1 adj (neoplasm$ or carcinoma$ or cancer$ or tumo?r$ or adenocarcinoma$ or pyelocarcinoma$)).tw.
37 35 or 36
38 (renal adj2 (neoplasm$ or carcinoma$ or cancer$ or tumo?r$ or adenocarcinoma$ or pyelocarcinoma$)).tw.
39 (kidney$1 adj2 (neoplasm$ or carcinoma$ or cancer$ or tumo?r$ or adenocarcinoma$ or pyelocarcinoma$)).tw.
40 38 or 39
41 or/24-25,37
42 or/24-25,40
43 23 and 41
44 limit 43 to (humans and english language)
45 limit 44 to animals
46 44 not 45
47 23 and 42
48 limit 47 to (humans and english language)
49 limit 48 to animals
50 48 not 49

Search strategy for quality of life

This search strategy was translated and run in:
Ovid MEDLINE(R)
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
EMBASE – 1980 to 2007 week 42
PsycINFO including PsycARTICLES 2000 – Present

Ovid MEDLINE(R) <1950 to October Week 2 2007>.
Searched 23/10/07
1 (renal or kidney$).ti,ab.
2 (cancer$ or neoplasm$ or carcinoma$ or tumo?r$1 or adenocarcinoma$ or pyelocarcinoma$ or hypernephroma$ or nephroid carcinoma$).ti,ab.
3 1 and 2
4 Carcinoma, Renal Cell/
5 (renal cell carcinoma or renal cancer$ or RCC).ti,ab.
6 Kidney Neoplasms/

7 or/3-6
8 value of life/
9 quality adjusted life year/
10 quality adjusted life.ti,ab.
11 (qaly$ or qald$ or qale$ or qtime$).ti,ab.
12 disability adjusted life.ti,ab.
13 daly$.ti,ab.
14 health status indicators/
15 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab.
16 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab.
17 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab.
18 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab.
19 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty of sftwenty or shortform twenty of short form twenty).ti,ab.
20 (euroqol or euro qol or eq5d or eq 5d).ti,ab.
21 (hql or hqol or h qol or hrqol or hr qol).ti,ab.
22 (hye or hyes).ti,ab.
23 health$ year$ equivalent$.ti,ab.
24 ((health or cost$) adj3 utilit$).ti,ab.
25 (hui or hui1 or hui2 or hui3).ti,ab.
26 disutil$.ti,ab.
27 rosser.ti,ab.
28 quality of well being.ti,ab.
29 quality of wellbeing.ti,ab.
30 qwb.ti,ab.
31 willingness to pay.ti,ab.
32 standard gamble$.ti,ab.
33 time trade off.ti,ab.
34 time tradeoff.ti,ab.
35 tto.ti,ab.
36 (index adj2 well being).mp.
37 (quality adj2 well being).mp.
38 ((multiattribute$ or multi attribute$) adj3 (health ind$ or theor$ or health state$ or utilit$ or analys$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
39 quality adjusted life year$.mp.
40 (15D or 15 dimension$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
41 (12D or 12 dimension$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
42 rating scale$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
43 linear scal$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
44 linear analog$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
45 visual analog$.mp. [mp=title, original title, abstract, name of substance word, subject heading word]
46 (categor$ adj2 scal$).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
47 or/8-46 (100636)
48 (letter or editorial or comment).pt.

49 47 not 48
50 49 and 7
51 (Assessment of Quality of life at the End of Life or AQEL).ti,ab.
52 (Functional Assessment of Chronic Illness Therapy Measurement System or FACIT).ti,ab.
53 (Functional Living Index Emesis or FLIE).ti,ab.
54 (Functional Living Index Cancer or FLIC).ti,ab.
55 (Palliative Care Assessment or PACA).ti,ab.
56 (Palliative Care Outcome Scale or POS).ti,ab.
57 (Quality of Life Cancer Scale or QOL-CA).ti,ab.
58 Quality of Life Questionnaire Core 30 Items.ti,ab.
59 (Functional Assessment of Cancer Therapy or FACT-G).ti,ab.
60 (Fact Kidney Symptom Index or FKSI).ti,ab.
61 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60
62 7 and 61
63 50 or 62
64 limit 63 to (humans and english language)

Search strategy for model parameters

This search strategy was translated and run in:
Ovid MEDLINE(R)
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations
EMBASE – 1980 to 2007 week 42

Ovid MEDLINE(R) <1950 to October Week 2 2007>.
Searched 24/10/07
1 exp models, economic/
2 markov chains/
3 exp models, statistical/
4 monte carlo method/
5 "Proportional Hazards Models"/
6 ((Prognosis or natural history or disease progress$ or disease course) adj5 (model$ or simulat$)).ti,ab.
7 1 or 2 or 3 or 4 or 5 or 6
8 ((renal or kidney$) adj2 (cancer$ or neoplasm$ or carcinoma$ or tumo?r$1)).ti,ab.
9 (renal cell carcinoma or renal cancer$).ti,ab.
10 Carcinoma, Renal Cell/
11 *Kidney Neoplasms/
12 8 or 9 or 10 or 11
13 7 and 12
14 limit 13 to (humans and english language and yr="1990 - 2007")

Appendix 2: Data extraction forms

These are available in separate PDF files.

Appendix 3: Method of indirect comparison

According to this method, it is possible to simultaneously compare three treatments A, B and C, where data is available from direct comparisons of treatments A and B (from trial X) and treatments A and C (from trial Y) providing the baseline population characteristics of the patients in the two trials are similar. Denoting HRBAPFS as the hazard ratio for PFS between treatments A and B from trial X, and HRCAPFS as the hazard ratio for PFS between treatments A and C from trial Y, the indirect comparison of hazard ratios for PFS between treatments B and C, HRBCPFS is given as;

$$HR_{BC}{}^{PFS} = \frac{HR_{BA}{}^{PFS}}{HR_{CA}{}^{PFS}}, \text{ or } \ln(HR_{BC}{}^{PFS}) = \ln(HR_{BA}{}^{PFS}) - \ln(HR_{CA}{}^{PFS})$$

and similarly for OS. The standard error of ln(HR) between treatments B and C for PFS is then given as;

$$SE[\ln(HR_{BC}{}^{PFS})] = \sqrt{\{SE[\ln(HR_{BA}{}^{PFS})]\}^2 + SE\{[\ln(HR_{CA}{}^{PFS})]\}^2}$$

and similarly for OS. Although this method is able to partially account for baseline risk and other prognostic factors of participants in the individual trials the results may not be as robust or reliable as those obtained from a direct head-to-head comparison in a randomised clinical trial and should thus be interpreted with caution.[83,151,152]

Appendix 4: Table of excluded studies with rationale

Table 54: Table of excluded studies with rationale

Papers excluded	Reason for exclusion
Amato (2005)[153]	Not a relevant intervention
Anon. (2006)[67]	Not a relevant intervention
Atkins et al. (2004)[154]	Not a relevant intervention
Choueiri (2007)[155]	Results mixed for different interventions
Chouhan et al. (2007)[156]	Not a clinical trial or SR
Escudier (2007)[157]	Not a clinical trial or SR
Escudier et al. (2007)[158]	Not a relevant intervention
George (2007)[159]	Not a clinical trial or SR
Gore & Escudier (2006)[160]	Not a clinical trial or SR
Hughes (2006)[73]	No relevant comparison
Jain et al. (2006)[161]	Not a clinical trial or SR
Kane et al. (2006)[162]	Not a clinical trial or SR
Lamuraglia et al. (2006)[163]	Not a clinical trial or SR
Lara & Quinn (2003)[164]	Not a relevant intervention
Le (2007)[66]	Not a clinical trial or SR
Mancuso & Sternberg (2006)[165]	Not a clinical trial or SR
Margolin (2007)[166]	Not a clinical trial or SR
McKeage & Wagstaff (2007)[71]	Not a clinical trial or SR
Medioni (2007)[167]	Not a clinical trial or SR
Montorsi (2007)[168]	Not a clinical trial or SR
Motzer (2000)[36]	Not a relevant intervention
Motzer (2006)[169]	Not a clinical trial or SR
Motzer (2006)[170]	Not a clinical trial or SR
Motzer et al. (2006)[116]	No relevant comparison
Motzer et al. (2006)[117]	Not a RCT or CCT
Patard (2007)[171]	Not a clinical trial or SR
Patel (2007)[172]	Not a clinical trial or SR
Peralba et al. (2003)[173]	Not a clinical trial or SR
Quan & W.D.Y. (2006)[174]	Not a clinical trial or SR

Raymond E. (2004)[175]	Not a RCT or CCT
Rini & Small (2005)[176]	Not a clinical trial or SR
Rini (2004)[177]	Not a clinical trial or SR
Rini (2005)[178]	Not a clinical trial or SR
Rini (2005)[64]	Not a clinical trial or SR
Rini (2007)[179]	Not a relevant intervention
Rini et al. (2006)[180]	Not a RCT or CCT
Rodriguez (2006)[181]	Not a RCT or CCT
Ryan & Mack (2007)[182]	Not a RCT or CCT
Schoffski et al. (2006)[62]	Not a clinical trial or SR
Schrader (2006)[183]	Not a clinical trial or SR
Shih & Lindley (2006)[65]	No relevant comparison
Skolarikos (2007)[184]	No relevant outcomes
Strumberg et al. (2007)[185]	No relevant comparison
Yang (2003)[186]	Not a relevant intervention
Yang (2004)[187]	Not a relevant intervention

Appendix 5: Review of clinical effectiveness – supplementary tables

Table 55: Study characteristics: bevacizumab plus IFN versus sunitinib versus IFN as first line therapy

Study	Escudier, et al. 2007[106]	Motzer, et al. 2007[111]	Rini, et al. 2008[101]
Participants	**Inclusion criteria:** Age ≥ 18 years Confirmed RCC with >50% clear cell histology Total or partial nephrectomy (if resection margins clearly negative of disease) Karnofsky performance status of ≥ 70% Measurable or non-measurable disease (according to RECIST criteria) Normal hepatic, haematopoietic and renal function **Exclusion criteria:** Prior systemic treatment for metastatic RCC disease Evidence of brain metastases Ongoing full dose oral or parenteral anticoagulant or anti-platelet aggregation treatment Recent major surgical procedures Uncontrolled hypertension on medication Clinically significant cardiovascular disease Chronic corticosteroid treatment	**Inclusion criteria:** Age ≥ 18 years; Metastatic renal-cell carcinoma with a clear-cell histologic component, confirmed by the participating centers The presence of measurable disease An Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 Adequate haematological, coagulation, hepatic, renal, and cardiac function **Exclusion criteria:** Prior systemic treatment for metastatic RCC disease Evidence of brain metastases Evidence of uncontrolled hypertension or clinically significant cardiovascular events or disease during the preceding 12 months	**Inclusion criteria:** Metastatic clear cell RCC No further details available **Exclusion criteria:** Prior systemic treatment for metastatic RCC disease Evidence of CNS metastases Evidence of vascular disease blood pressure above 160/90 or a history of thrombosis within one year Ongoing treatment with anticoagulant therapy
Interventions	**Bevacizumab or placebo:** bevacizumab 10mg/kg body weight i.v. every two weeks **IFN:** IFN-2a 9MIU s.c.	**Sunitinib**: 50mg orally once daily for 4 weeks followed by 2 weeks without treatment **IFN**: 9MIU s.c. three times	**Bevacizumab:** bevacizumab 10mg/kg body weight i.v. every two weeks **IFN:** IFN-2a 9MIU s.c.

	three times per week for a maximum of 52 weeks No dose reductions of bevacizumab/placebo allowed IFN dose could be reduced to 6MIU or 3MIU to manage grade 3 and above adverse events if necessary. All treatment stopped on evidence of disease progression, unacceptable toxicity or withdrawal of consent Other antineoplastic therapies were allowed subsequent to progression or toxicity	per week. A reduced dose of 3MIU was administered in the first week and 6MIU in the second week, with the full dose of 9MIU thereafter. Dose reductions to 37.5mg and then to 25mg daily of sunitinib and to 6MIU and then to 3MIU three times per week of IFN were allowed for the management of severe adverse events. All treatment stopped on evidence of disease progression, unacceptable adverse events or withdrawal of consent	three times per week
Study objectives	To determine whether first-line bevacizumab plus interferon improves efficacy compared with interferon alone	To evaluate the efficacy of sunitinib compared with interferon alpha	To investigate the addition of bevacizumab to initial IFN therapy
Outcomes	**Primary**: overall survival **Secondary**: progression-free survival, overall response rate (according to RECIST), and safety	**Primary**: progression-free survival, defined as the time from randomisation to the first documentation of objective disease progression or to death from any cause whichever occurred first **Secondary**: objective tumour response rate (according to RECIST), overall survival, patient-reported outcomes, and safety	**Primary:** overall survival **Secondary:** progression free survival (defined from the date of randomisation to the date of progression according to RECIST criteria or death due to any cause), overall response and safety
Analysis	Efficacy was assessed by intention-to-treat. For the safety analysis, patients were assigned to treatment groups on the basis of treatment received, with patients in the placebo arm receiving one or more doses of bevacizumab being assigned to the bevacizumab arm The study was designed to have 80% power for the log rank test to detect an improvement in overall survival with an HR of 0.76, assuming an	Efficacy (primary endpoint) was assessed by intention-to-treat. A blinded central review of radiological images was used to assess the primary endpoint and the objective response rate. Safety analyses were performed on the basis of the treatment actually received The study was designed to have 90% power for the log rank test to detect a clinically relevant increase in progression free survival from 4.7 to 6.2 months in patients treated with	The study was designed with 86% power to detect a 30% decrease in hazard rate assuming a two-sided significance level of 0.05

	improvement of median survival from 13 months to 17 months, at a two sided alpha level of 0.05. One interim analysis was planned based on 250 deaths after which the study was unblinded and patients in the IFN arm who had not progressed were offered bevacizumab plus IFN. Results of the interim analysis are presented in this paper and represent an interim analysis of OS and a final analysis of PFS Patients without an event were censored on the day of last follow-up assessment or the last day of study drug administration, if no follow-up assessment was done.	sunitinib, at a two sided alpha level of 0.05. Three scheduled interim analyses were planned; this paper provides the results of the second analysis, after which the study was unblinded and patients in the IFN group with progressive disease were allowed to crossover into the sunitinib group	

Table 56: Summary of adverse events (any grade): bevacizumab plus IFN versus sunitinib versus IFN as first line therapy

Study	**Escudier, et al. 2007[106] ***		**Motzer, et al. 2007[111] ¶**	
Intervention	**BEV + IFN**	**IFN + Placebo**	**Sunitinib**	**IFN**
n	**337**	**304**	**375**	**375**
	% of patients		**% of patients**	
Diarrhoea	20	15	53	12
Fatigue	33	27	51	51
Nausea			44	33
Stomatitis			25	2
Vomiting			24	10
Hypertension	26	9	24	1
Hand–foot syndrome			20	1
Mucosal inflammation			20	1
Rash			19	6
Asthenia	32	28	17	20
Dry skin			16	5
Skin discoloration			16	0
Changes in hair colour			14	1
Epistaxis			12	1
Pain in a limb			11	3
Headache	23	16	11	14
Dry mouth			11	6
Decline in ejection fraction			10	3
Pyrexia	45	43	7	34
Chills			6	29
Myalgia			5	16
Influenza-like illness	24	25	1	7
Dyspnoea	13	13		
Bleeding	33	9		
Anorexia	36	30		
Depression	12	10		
Leukopenia			78	56
Neutropenia	7	7	72	46
Anaemia	10	13	71	64

Increased creatinine			66	49
Thrombocytopenia	6	4	65	21
Lymphopenia			60	63
Increased lipase			52	42
Increased aspartate aminotransferase			52	34
Increased alanine aminotransferase			46	39
Increased alkaline phosphatase			42	35
Increased uric acid			41	31
Hypophosphatemia			36	32
Increased amylase			32	28
Increased total bilirubin			19	2
Proteinuria	18	3		
Venous thromboembolic event	3	<1		
Treatment discontinuation due to an adverse event	28	12	8	13
Deaths due to an adverse event	2	2		

* Adverse events and laboratory abnormalities that occurred with a frequency of 2% or more ¶ Adverse events and selected laboratory abnormalities that occurred in at least 10% of patients in the sunitinib group.

Table 57: Adverse events leading to discontinuation of study medication: bevacizumab plus IFN versus IFN as first line therapy

Study	**Escudier, et al. 2007[107]**	
Intervention	**BEV+ IFN**	**IFN + placebo**
n	**337**	**304**
	No. of patients (%)	**No of patients (%)**
General disorders	31 (9)	13 (4)
Renal and urinary disorder	16 (5)	3 (<1)
Gastrointestinal disorder	13 (4)	4 (1)
Nervous system disorder	9 (3)	6 (2)
Infections	8 (2)	3 (<1)
Psychiatric disorders	5 (1)	6 (2)
Blood and lymphatic system disorders	6 (2)	3 (<1)
Metabolism and nutrition disorder	5 (1)	3 (<1)
Vascular disorder	7 (2)	1 (<1)

Table 58: Study characteristics: temsirolimus versus IFN as first line therapy in patients with poor prognosis

Study	**Hudes, et al. 2007[112]**
Participants	**Inclusion criteria:** Histologically confirmed advanced renal cell carcinoma (stage IV or recurrent disease) A karnofsky performance score of 60 or more At least three of the following six poor prognostic factors a serum lactate dehydrogenase level of more than 1.5 times the upper limit of the normal range a haemoglobin level below the lower limit of the normal range a corrected calcium level of more than 10mg per decilitre a time from initial diagnosis of RCC to randomisation of less than one year a Karnofsky score of 60 or 70 or metastases in multiple organs Measurable disease (according to RECIST criteria) Adequate bone marrow, renal, and hepatic functions **Exclusion criteria:** Prior systemic therapy Evidence of brain metastases unless neurologically stable and not requiring corticosteroids after surgical resection or radiotherapy
Interventions	**Temsirolimus**: 25 mg i.v. weekly **IFN**: IFN-2α 18 MIU s.c three times per week **Temsirolimus plus IFN**: Temsirolimus 15 mg i.v. weekly plus IFN-α at a starting dose of 3 MIU s.c three times per week rising to 6 MU s.c. three times per week Dose reduction without treatment interruption was permitted at the discretion of the treating physician to manage grade 2 adverse events. Treatment was withheld for grade 3 or 4 adverse events and restarted at a reduced dose after recovery to grade 2 or lower. For the combination-therapy group, one or both agents were withheld, depending on the adverse event. Patients who received temsirolimus received premedication with 25 to 50mg of intravenous diphenhydramine or a similar H_1 blocker 30 minutes before each weekly infusion as prophylaxis against an allergic reaction. Patients in the IFN group who were unable to tolerate 9MIU or 18 MIU received the highest tolerable dose which could be 3MIU, 4.5 MIU or 6 MIU. All treatment stopped on evidence of disease progression, symptomatic deterioration or intolerable adverse events.
Study objectives	To compare temsirolimus and temsirolimus plus IFN with IFN alone in metastatic renal cell carcinoma
Outcomes	**Primary**: overall survival **Secondary**: progression-free survival, objective response rate, clinical benefit rate, and adverse events
Analysis	Efficacy (overall survival) was calculated on an intention-to-treat basis. No information is provided on the method of analysis of secondary endpoints. All patients who received any treatment were included in the safety analysis. The study (200 patients per group) was designed to have 80% power to detect an improvement in overall survival of 40% for each comparison with the use of a two-sided stratified log-rank test at an overall 2.5% level of significance

	Two interim analyses were planned after approximately 164 and 430 deaths and a final analysis, if necessary, after a total of 504 deaths had occurred; this paper provides the results of the second analysis (after 446 patients had died)

Table 59: Proportion of patients reporting adverse events (all grades): temsirolimus versus IFN as first line therapy in patients with poor prognosis

Study	**Hudes, et al.[112]**		
Intervention	**Temsirolimus**	**IFN**	***Temsirolimus plus IFN***
n	**208**	**200**	***208***
Asthenia	51	64	*62*
Rash	47	6	*21*
Anaemia	45	42	*61*
Nausea	37	41	*40*
Anorexia	32	44	*38*
Pain	28	16	*20*
Dyspnoea	28	24	*26*
Hyperlipidemia	27	14	*38*
Infection	27	14	*34*
Diarrhoea	27	20	*27*
Peripheral oedema	27	8	*16*
Hyperglycaemia	26	11	*17*
Cough	26	14	*23*
Hypercholesterolemia	24	4	*26*
Fever	24	50	*60*
Abdominal pain	21	17	*17*
Stomatitis	20	4	*21*
Constipation	20	18	*19*
Back pain	20	14	*15*
Vomiting	19	28	*30*
Weight loss	19	25	*32*
Headache	15	15	*22*
Increased creatinine level	14	10	*20*
Thrombocytopenia	14	8	*38*
Chills	8	30	*34*
Increased aspartate amino-transferase level	8	14	*21*
Neutropenia	7	12	*27*
Leukopenia	6	17	*31*

Listed are all grade adverse events occurring in at least 20% of patients. The analysis did not include patients who underwent randomisation but received no treatment: seven in the IFN group, one in the temsirolimus group and two in the combination therapy group.

Table 60: Study characteristics: sorafenib versus sunitinib versus best supportive care as second line therapy

Study	Escudier, et al. 2007[113]	Ratain, et al. 2006[115]	Motzer, et al. 2006[116]	Motzer, et al. 2006[117]
Participants	**Inclusion criteria:** Age ≥ 18 years Histologically confirmed metastatic clear cell renal-cell carcinoma Evidence of progression after one systemic treatment within the previous 8 months An ECOG performance status of 0 or 1 MSKCC risk status of low or intermediate Life expectancy of at least 12 weeks Adequate bone marrow, liver, pancreatic, and renal function **Exclusion criteria:** Evidence of brain metastases Previous exposure to VEGF pathway inhibitors	**Inclusion criteria:** Age ≥ 18 years Histologically or cytologically confirmed metastatic refractory cancer At least one measurable tumour An ECOG performance status of 0 or 1 Life expectancy of at least 12 weeks Adequate bone marrow, liver, and renal function **Exclusion criteria:** Evidence of CNS involvement Other serious medical problems Previous use of a Ras inhibitor	**Inclusion criteria:** Age ≥ 18 years Histologically confirmed metastatic clear-cell RCC Prior nephrectomy Measurable disease Failure of one previous cytokine-based therapy due to disease progression An ECOG performance status of 0 or 1 Adequate organ function **Exclusion criteria:** Evidence of brain metastases Evidence of significant cardiac events within the previous 12 months	**Inclusion criteria:** Histologically confirmed metastatic RCC Measurable disease Failure of one cytokine based therapy because of disease progression or unacceptable toxicity An ECOG performance status of 0 or 1 Normal serum amylase and lipase A normal adrenocorticotropic hormone stimulation test Adequate haematologic, hepatic, renal, and cardiac function. **Exclusion criteria:** Evidence of brain metastases Evidence of cardiac dysrhythmia, prolongation of QTc interval, or any significant cardiac event within the previous 12 months
Interventions	**Sorafenib:** 400mg (or placebo) orally twice daily. Dose reductions to 400mg once daily and then 400mg every other day were permitted to manage adverse events. All treatment stopped on	*Run in period* **Sorafenib:** 400mg orally twice daily. Dose reductions/interruptions were permitted to manage adverse events	**Sunitinib:** 50 mg orally once a day in repeated 6-week cycles (4 consecutive weeks of treatment followed by 2 weeks off treatment) Dose reduction for toxicity was allowed (to 37.5 mg/d then 25	**Sunitinib:** 50 mg orally once a day in repeated 6-week cycles (4 consecutive weeks of treatment followed by 2 weeks off treatment) Dose escalation by 12.5 mg/d (up to 75 mg/d) was permitted in

	evidence of disease progression or withdrawal from the study as a result of adverse events or death	*Randomisation period* Patients with a reduction in tumour size of less than 25% were randomly assigned to either sorafenib at current dose or matching placebo. Patients with a reduction in tumour size of more than 25% continued to receive sorafenib (current dose) Patients with disease progression discontinued treatment During the randomisation period patients whose disease progressed while on placebo were offered sorafenib	mg/d) to manage adverse events All treatment stopped on evidence of disease progression, unacceptable toxicity, or withdrawal of consent	the absence of treatment-related toxicity Dose reduction was allowed (to 37.5 mg/d and then to 25 mg/d) to manage adverse events All treatment was stopped on evidence of disease progression, unacceptable toxicity, or withdrawal of consent
Study objectives	To determine the effects if sorafenib on progression free survival and overall survival in patients with advanced clear cell renal cell carcinoma in whom one previous systemic therapy had failed	To evaluate the effects of sorafenib on tumour growth in patients with metastatic renal cell carcinoma	To confirm the anti-tumour efficacy of sunitinib as second-line treatment in patients with metastatic clear-cell RCC	To assess the clinical efficacy and safety of sunitinib in patients with cytokine refractory metastatic RCC
Outcomes	**Primary:** overall survival **Secondary:** progression-free survival, best overall response rate (according to RECIST criteria)	**Primary:** the percentage of randomly assigned patients remaining progression free at 12 weeks following randomisation **Secondary:** progression-free survival (PFS) after random assignment (randomized subset only), overall PFS (from start of treatment), tumour response rate and safety	**Primary:** overall objective response rate (assessed according to RECIST) **Secondary:** duration of response, progression-free survival, overall survival, and safety	**Primary:** objective tumour response rate (according to RECIST) **Secondary:** time to progression and safety

Analysis	Efficacy (overall survival) was assessed by intention-to-treat. No details as to how patients were censored for analysis of overall survival are provided. The study was designed to have 90% power to detect a 33.3% difference in survival between the two groups at a two-sided alpha level of 0.04 after 540 patients had died. An interim analysis of progression free survival was planned after disease had progressed in approximately 363 patients. A further interim analysis of overall survival was performed prior to crossover.	The primary endpoint was assessed by intention to treat The study was designed to have 81% power to detect a drug effect that corresponded to a reduction in the progression rate from 90% to 70% 12 weeks after randomisation	This is an open-label, single-arm phase II clinical trial The study was designed to have 90% power to detect an objective response rate for sunitinib of 15% or more using an overall 2-sided significance level of 0.05	This is an open-label, single arm phase II clinical trial Sample size was determined using Simon's Minimax two-stage design. The study was designed to have 85% power to evaluate the hypothesis that the objective response rate was greater than or equal to 15% at an alpha level of 5%

Table 61: Adverse events: any grade: sorafenib versus sunitinib versus best supportive care as second line therapy

Study	**Escudier, et al. 2007[113]**		**Ratain, et al. 2006[115]**	**Motzer, et al. 2006[116]**	**Motzer, et al. 2006 [117]**
	sorafenib	**placebo**	**sorafenib**	**sunitinib**	**sunitinib**
n	451	452	202	106	63
			% of patients		
Allergy / immunology			**10**		
Cardiovascular general			**56**		
Hypertension	17	2	43	16	5
Ejection fraction decline	NR	NR	NR	NR	11
Blood / bone marrow			**31**		
Decreased haemoglobin	8	7	27	NR	NR
Constitutional symptoms			**90**		
Fatigue	37	28	73	28	38
Weight loss	10	6	33	NR	NR
Other symptoms	10	6	22	NR	NR
Fever	NR	NR	12	NR	NR
Gastrointestinal			**95**		
Diarrhoea	43	13	58	20	24
Nausea	23	19	30	13	19
Anorexia	16	13	47	12	6
Vomiting	16	12	24	10	13
Constipation	15	11	32	NR	NR
Dysgeusia	NR	NR	NR	9	NR
Dyspepsia	NR	NR	NR	16	16
Stomatitis	NR	NR	NR	13	19
Mucosal inflammation	NR	NR	NR	12	NR
Other symptoms	NR	NR	29	NR	NR
Neurology/sensory neuropathy			**68**		
Abdominal pain	11	9	19	NR	NR
Headache	10	6	19	NR	NR
Joint pain	10	6	12	NR	NR
Bone pain	8	8	NR	NR	NR
Tumour pain	6	5	NR	NR	NR

Muscle pain	NR	NR	11	NR	NR
Pain, other	NR	NR	58	7	NR
Pulmonary			**63**		
Cough	13	14	28	NR	NR
Dyspnoea	14	12	38	NR	NR
Pulmonary, other	NR	NR	18	NR	NR
Dermatologic			**93**		
Rash or desquamation	40	16	66	3	NR
Hand-foot skin reaction	30	7	62	15	NR
Alopecia	27	3	53	NR	NR
Pruritis	19	6	NR	NR	NR
Dry skin	NR	NR	23	NR	NR
Flushing	NR	NR	16	NR	NR
Dermatitis	NR	NR	NR	NR	8
Dermatology, other			**43**		
Renal / genitourinary			**25**		
Creatinine	NR	NR	14	NR	14
Creatine kinase	NR	NR	NR	NR	15
Haemorrhage	NR	NR	22	NR	NR
Hepatic			**29**		
ALT	NR	NR	11	NR	8
AST	NR	NR	11	NR	NR
Infection/febrile neutopenia			**37**		
Infection without neutropenia	NR	NR	37	NR	NR
Musculoskeletal			**14**		
Metabolic / laboratory			**42**		
Neutropenia	NR	NR	NR	42	45
Lipase increased	NR	NR	NR	28	24
Anaemia	NR	NR	NR	26	37
Thrombocytopenia	NR	NR	NR	21	18
Lymphopenia	NR	NR	NR	NR	72
Hyperamylasemia	NR	NR	NR	NR	10
Total bilirubin	NR	NR	NR	NR	5
Hyperglycaemia	NR	NR	17	NR	NR
Hyperuricaemia	NR	NR	13	NR	NR
Hypophosphataemia	NR	NR	15	NR	NR

Appendix 6: Critical appraisal of industry submissions

Table 62: Comparison of manufacturer (Pfizer) submission CEA models of sunitinib versus IFN / BSC in 1st line and 2nd line use with NICE reference case requirements

NICE reference case requirement		Reviewer comment 1st Line analysis/model	Reviewer comment 2nd Line analysis/model
Decision problem	As per the scope developed by NICE (esp. technologies & patient group)	✓ Only two of four new drugs	✓ All 2nd-line drugs and BSC considered
Comparator	Alternative therapies routinely used in the UK NHS	✓ Interferon-alpha	✓ BSC
Perspective on costs	NHS and PSS	✓	✓
Perspective on outcomes	All health effects on individuals	✓	✓
Type of economic evaluation	Cost-effectiveness analysis	✓	✓
Synthesis of evidence on outcomes	Based on a systematic review	✓ Single RCT for comparison of sunitinib with IFN, single RCT for comparison of bevacizumab+IFN with IFN	✓ Single-arm trial for sunitinib, various trials for BSC
Measure of health benefits	QALYs	✓	✓
Description of health states for QALY calculations	Use of a standardised and validated generic instrument	✓ EQ-5D from Phase III RCT	✓ EQ-5D from single-arm sunitinib trial
Method of preference elicitation for health state values	Choice-based method (e.g. TTO, SG, not rating scale)	✓	✓
Source of preference data	Representative sample of the UK public	✓	✓
Discount rate	3.5% pa for costs and health effects	✓	✓

Table 63: Critical appraisal checklist of the Pfizer economic evaluation for sunitinib versus interferon in 1st line use.

Dimension of quality			Comments
Structure			
S1	Statement of decision problem/objective	✓	Cost-effectiveness modelling of first-line use of sunitinib versus IFN in a patient population with advanced RCC, low or intermediate prognosis. NICE is the primary decision maker.
S2	Statement of scope/perspective	✓	NHS perspective. Model inputs are consistent with the perspective. Scope of model stated and justification given. Outcomes consistent with perspective and scope of model.
S3	Rationale for structure	✓	The model structure, based on the health states: PFS, PD and death, has been described clearly, and is consistent with the progression of RCC. Weibull models are common in survival analysis, allowing for time-dependent transition probabilities.
S4	Structural assumptions	✓	Model assumptions are given. Weibull regression models were fitted to PFS and OS of the Phase III RCT (Motzer et al 2007[111]).
S5	Strategies / comparators	?	Sunitinib was compared with IFN which is appropriate. Pfizer do not perform an indirect comparison between sunitinib and bevacizumab+IFN, although they do present a comparison of bevacizumab+IFN versus IFN.
S6	Model type	✓	This type of model based on survival curves is frequently used in this type of decision problem.
S7	Time horizon	✓	Treatment is administered whilst patients are in PFS, and is well described. The model time horizon is lifetime, which is appropriate.
S8	Disease states / pathways	✓	The disease states: first-line PFS, PD and death reflect the underlying biological progress of the disease are those generally accepted for this decision question.
S9	Cycle length	✓	The cycle length of approx. 4 days is short enough to capture the complexities of the natural history of the disease.
Data			
D1	Data identification	?/✓	Data identification methods are described. The data for the important parameters (transition probabilities and utilities) have been taken from the main Phase III RCT. Data on utilities are not transparent.
D2	Pre-model data analysis	?/✓	Data for calculating the costs of administration, routine follow-up, diagnostic tests, BSC, death, and treating adverse events.
D2a	Baseline data	✓	Pfizer have used the OS data from the Phase III trial of sunitinib, which is reasonable, but we caution that given this data is immature, the cost-effectiveness estimates are subject to a good deal of uncertainty. To address this uncertainty, Pfizer have used other sources of OS data for IFN. However, we believe that it is unwise to use OS data from one trial and PFS

			from a different trial, due to lack of consistency. Furthermore, Pfizer have used the HR of sunitinib vs. IFN from the Phase III trial of sunitinib, which is also subject to uncertainty, due to the immaturity of the data, but this is the only data available for this parameter. The model patient population was defined to be the same as in the Phase III trial of sunitinib, which is a reasonable assumption.
D2b	Treatment effects	?	As stated in the previous point, Pfizer have used the OS HR between sunitinib and IFN which is based on immature data, and therefore subject to large uncertainty.
D2c	Quality of life weights (utilities)	?/✓	Utilities were derived from EQ-5D data collected during the Motzer et al (2007) RCT[111] from approximately 600 patients. However, data is unpublished, therefore assessment of detail/methods not possible.
D3	Data incorporation	?	Data incorporated in the model are referenced and generally well described. However, there are several references cited in the report for which full details not given in the reference list. Data incorporation is transparent. For the PSA, the choice of distribution for each parameter has been described and justified. However, we note that the description of the variables incorporated in the report does not match those actually used in the model.
D4	Assessment of uncertainty	?/✓	All types of uncertainty have been addressed.
D4a	Methodological	X	Pfizer have used a single type of model.
D4b	Structural	✓	Structural uncertainties, such as the use of alternative OS curves for IFN, have been modelled.
D4c	Heterogeneity	✓	Pfizer model no patient subgroups. However, given the data available, this is reasonable. For example, there is insufficient data to model the following patient subgroups: clear cell, non-clear cell, nephrectomy, no nephrectomy, good prognosis, intermediate prognosis.
D4d	Parameter	?	Extensive univariate and PSA performed. However, the description of the variables incorporated in the PSA in the report does not match those actually used in the model.
Consistency			
C1	Internal consistency	X	No evidence has been presented to indicate that the mathematical logic of the model has been tested.
C2	External consistency	?	The results of the model were not calibrated against independent data, although it is not clear that such independent data exists. The results of the model have not been compared with those of other models of metastatic RCC, although these other models have been reported only in abstract form.

✓ indicates 'clear', X indicates 'concerns', and ? indicates 'uncertain/unknown'

Checklist structure from Phillips and colleagues [135]

Table 64: Pfizer cost-effectiveness results per patient for bevacizumab+IFN versus IFN

	Bevacizumab + IFN-α	**IFN-α**	**Incremental**
Benefits			
Life years gained	2.30	1.85	0.45
Progression free years gained	0.84	0.61	0.23
Time in progressed state	1.46	1.23	0.22
QALYs gained	1.65	1.31	0.34
Costs			
Drug acquisition	£40,0002	£3,667	£36,335
Administration costs	£1,341	£0	£0
Follow-up	£0	£2,296	-£2,296
Diagnostic tests	£426	£296	£159
Adverse events	£5	£1	£4
Supportive care	£13,051	£11,670	£1,380
Total costs	£54,984	£18,01	£36,923
Cost effectiveness			*Bevacizumab + IFN-α vs IFN-α*
Incremental cost per life year gained			£81,754
Incremental cost per progression free years gained			£162,110
Incremental cost per QALY			£107,357

Table 65: Critical appraisal checklist of the Pfizer economic evaluation for sunitinib versus BSC in 2nd line use

Dimension of quality			Comments
Structure			
S1	Statement of decision problem/objective	✓	Cost-effectiveness modelling of 2nd-line use of sunitinib versus BSC in a patient population with advanced RCC. NICE is the primary decision maker.
S2	Statement of scope/perspective	✓	NHS perspective. Model inputs are consistent with the perspective. Scope of model stated and justification given. Outcomes consistent with perspective and scope of model.
S3	Rationale for structure	✓	The model structure, based on the health states: PFS, PD and death, has been described clearly, and is consistent with the progression of RCC. Weibull models are common in survival analysis, allowing for time-dependent transition probabilities.
S4	Structural assumptions	X	Model assumptions are given. Weibull regression models were fitted to PFS and OS for sunitinib from a single-arm trial. Weibull models were fitted for BSC from several different trials. However, we believe that it is invalid to model sunitinib from one trial and BSC from different trials, because randomization is broken.
S5	Strategies / comparators	✓	Sunitinib was compared with BSC which is appropriate. Pfizer do not perform an indirect comparison between sunitinib and sorafenib, although they do present a comparison of sorafenib versus BSC.
S6	Model type	✓	This type of model based on survival curves is frequently used in this type of decision problem.
S7	Time horizon	✓	Sunitinib is administered whilst patients are in PFS, and is well described. The model time horizon is lifetime, which is appropriate.
S8	Disease states / pathways	✓	The disease states: PFS, PD and death reflect the underlying biological progress of the disease are those generally accepted for this decision question.
S9	Cycle length	✓	The cycle length of approx. 1 to 10 weeks is short enough to capture the complexities of the natural history of the disease.
Data			
D1	Data identification	?	Data identification methods are described. The data for the important parameters (transition probabilities and utilities) for sunitinib have been taken from a single-arm trial, and for BSC from several different trials. However, we believe that it is not appropriate to use data from different trials for the two treatment arms.
D2	Pre-model data analysis	✓	The methodology for calculating the costs of routine follow-up, diagnostic tests, BSC, death, and treating adverse events are stated.

D2a	Baseline data	X	Pfizer have used the sunitinib OS data from the single-arm trial of sunitinib. This data is not mature, hence the cost-effectiveness estimates are subject to a good deal of uncertainty. As Pfizer acknowledge, the two main sources of BSC survival data have important limitations. Furthermore, Pfizer do not state why they did not model PFS and OS for sunitinib from the other single-arm trial of sunitinib, trial A6181006. The model patient population was inconsistent between sunitinib and BSC.
D2b	Treatment effects	X	See above.
D2c	Quality of life weights (utilities)	?/✓	Utilities were derived from EQ-5D data collected during the single-arm trial of sunitinib. However, data is unpublished, therefore assessment of detail/methods not possible. The PFS utility for BSC was assumed equal to the baseline utility of this trial, and the PD utility for BSC was assumed equal to that of sunitinib, which seems appropriate.
D3	Data incorporation	✓	Data incorporated in the model are referenced and generally well described. However, there are several references cited in the report for which full details not given in the reference list. Data incorporation is transparent. For the PSA, the choice of distribution for each parameter has been described and justified.
D4	Assessment of uncertainty	✓	All types of uncertainty have been addressed.
D4a	Methodological	X	Pfizer have used a single type of model.
D4b	Structural	✓	Structural uncertainties, such as the use of alternative OS curves for BSC, have been modelled.
D4c	Heterogeneity	✓	Pfizer modelled no patient subgroups. However, given the data available, this is reasonable.
D4d	Parameter	✓	Extensive univariate and PSA performed.
Consistency			
C1	Internal consistency	X	No evidence has been presented to indicate that the mathematical logic of the model has been tested.
C2	External consistency	?	The results of the model were not calibrated against independent data, although it is not clear that such independent data exists. The results of the model have not been compared with those of other models of metastatic RCC, although these other models have been reported only in abstract form.

✓ indicates ‘clear’, X indicates ‘concerns’, and ? indicates ‘uncertain/unknown’

Checklist structure from Phillips and colleagues [135]

Table 66: Pfizer base case per patient results of 2nd-line sunitinib vs BSC

	sunitinib	BSC	Incremental
Benefits			
Life years gained	1.52	0.75	0.77
Progression free years gained	0.96	0.42	0.54
Time in progressed state	0.56	0.33	0.23
QALYs gained	1.14	0.55	0.60
Costs			
Drug acquisition	£18,715	£0	£18,715
Follow-up	£1,516	£0	£1,516
Diagnostic tests	£699	£0	£699
Adverse events	£65	£0	£0
Supportive care	£6,956	£5,468	£1,488
Total costs	£27,855	£5,468	£22,387
Cost effectiveness			*sunitinib vs BSC*
Incremental cost per life year gained			£29,061
Incremental cost per progression free years gained			£41,817
Incremental cost per QALY			£37,519

Table 67: Pfizer per patient results of exploratory analysis of 2nd-line sorafenib vs BSC

	Sorafenib	**BSC**	**Incremental**
Benefits			
Life years gained	1.66	1.31	0.35
Progression free years gained	0.60	0.41	0.19.
Time in progressed state	1.06	0.89	0.17
QALYs gained	1.18	0.91	0.27
Costs			
Drug acquisition	£16,971	£0	£16,971
Follow-up	£944	£0	£944
Diagnostic tests	£416	£0	£416
Adverse events	£0	£0	£0
Supportive care	£10,504	£9,424	£1,080
Total costs	£28,835	£9,424	£19,411
Cost effectiveness			*Sorafenib vs BSC*
Incremental cost per life year gained			£54,750
Incremental cost per progression free years gained			£103,813
Incremental cost per QALY			£73,078

Table 68: Comparison of Roche's model of bevacizumab+IFN versus IFN in 1st line use with NICE reference case requirements

NICE reference case requirement		Reviewer comment
Decision problem	As per the scope developed by NICE (esp. technologies & patient group)	✓ bevacizumab+IFN vs. IFN in 1st-line
Comparator	Alternative therapies routinely used in the UK NHS	✓ IFN
Perspective on costs	NHS and PSS	✓
Perspective on outcomes	All health effects on individuals	✓
Type of economic evaluation	Cost-effectiveness analysis	✓
Synthesis of evidence on outcomes	Based on a systematic review	✓ Avoren RCT[106] for bevacizumab+IFN vs. IFN
Measure of health benefits	QALYs	✓
Description of health states for QALY calculations	Use of a standardised and validated generic instrument	✓ EQ-5D from Motzer et al (2007)[111] RCT of sunitinib vs. IFN
Method of preference elicitation for health state values	Choice-based method (e.g. TTO, SG, not rating scale)	✓
Source of preference data	Representative sample of the UK public	✓
Discount rate	3.5% pa for costs and health effects	✓

Table 69: Critical appraisal checklist of the Roche economic evaluation for bevacizumab plus IFN versus IFN in 1st line use

Dimension of quality			Comments
Structure			
S1	Statement of decision problem/objective	✓	Cost-effectiveness modelling of 1st-line use of bevacizumab plus IFN versus IFN in a patient population with advanced RCC. NICE is the primary decision maker.
S2	Statement of scope/perspective	✓	NHS perspective. Model inputs are consistent with the perspective. Scope of model stated and justification given. Outcomes consistent with perspective and scope of model.
S3	Rationale for structure	?/✓	The model structure, based on the health states: PFS, PD and death, has been described clearly, and is consistent with the progression of RCC. Gompertz curves are common in survival analysis, allowing for time-dependent transition probabilities. However, we believe that log-logistic curves in sensitivity analysisare inappropriate due to their long tails.
S4	Structural assumptions	✓	Model assumptions are given. Gompertz and log-logistic curves were fitted to PFS and OS for bevacizumab plus IFN and IFN from the appropriate RCT. The HR for OS is used correctly.
S5	Strategies / comparators	?	Bevacizumab plus IFN was compared with IFN which is appropriate. However, although sunitinib is available for treating patients in 1st-line RCC, Roche do not perform an indirect comparison between bevacizumab plus IFN and sunitinib
S6	Model type	✓	This type of model based on survival curves is frequently used in this type of decision problem.
S7	Time horizon	✓	The duration of treatment is well described. The model time horizon is lifetime, which is appropriate.
S8	Disease states / pathways	✓	The disease states: PFS, progressed and death reflect the underlying biological progress of the disease are those generally accepted for this decision question.
S9	Cycle length	✓	The cycle length of 1 month is short enough to capture the complexities of the natural history of the disease.
Data			
D1	Data identification	✓	Data identification methods are described. The data for the important parameters (survival probabilities and utilities) for bevacizumab plus IFN have been taken from appropriate RCTs.
D2	Pre-model data analysis	?	Pre-model data analysis, e.g. cost of AEs, is generally reasonable. However, we are sceptical of Roche's calculation of the dose intensities. The values estimated are lower than those published in the relevant RCT.
D2a	Baseline data	?	Roche have used the PFS and OS data from the main RCT of bevacizumab plus IFN vs. IFN. This data is not mature, hence the cost-effectiveness estimates are subject to a good deal of

			uncertainty, due to extrapolation. As mentioned above, we do not believe that it is appropriate to model survival by the log-logistic curve, because the tail is too long. Half-cycle corrections have been used.
D2b	Treatment effects	?	Treatment effects are taken from the main RCT. Roche use the PFS HR of 0.709 for the safety population, instead of the value of 0.79 quoted in Escudier et al (2007).[106] The value used is not quoted in Escudier et al (2007)[106], and results in a lower ICER for bevacizumab+IFN vs. IFN. The treatment effects are assumed to continue after data-cutoff in the main RCT, which is reasonable.
D2c	Quality of life weights (utilities)	?/✓	Given that utilities are not available from the main RCT of bevacizumab plus IFN vs. IFN, Roche have used utilities from EQ-5D data collected during the RCT of sunitinib vs. IFN. Utilities were assumed independent of treatment, which is reasonable. Data used remain unpublished.
D3	Data incorporation	✓	Data incorporated in the model are referenced and generally well described. Data incorporation is transparent. For the PSA, the choice of distribution for each parameter has been described and justified.
D4	Assessment of uncertainty	✓	All types of uncertainty have been addressed.
D4a	Methodological	X	Roche have used a single type of model
D4b	Structural	?	Roche have only assessed the structural uncertainty of using different mathematical functions for the survival curves.
D4c	Heterogeneity	✓	Roche modelled no patient subgroups. However, given the data available, this is reasonable.
D4d	Parameter	X	Roche have performed a PSA, but not univariate sensitivity analysis on parameters.
Consistency			
C1	Internal consistency	X	Roche provide no evidence to indicate that the mathematical logic of the model has been tested.
C2	External consistency	?	The results of the model were not calibrated against independent data, although it is not clear that such independent data exists. The results of the model have not been compared with those of other models of metastatic RCC, although these other models have been reported only in abstract form.

✓ indicates 'clear', X indicates 'concerns', and ? indicates 'unclear/unknown'

Checklist structure from Phillips and colleagues [135]

Table 70: Comparison of Wyeth's model with NICE reference case requirements

NICE reference case requirement		**Reviewer comment**
Decision problem	As per the scope developed by NICE (esp. technologies & patient group)	✓ Only one of four new drugs
Comparator	Alternative therapies routinely used in the UK NHS	✓ IFN and BSC
Perspective on costs	NHS and PSS	✓
Perspective on outcomes	All health effects on individuals	✓
Type of economic evaluation	Cost-effectiveness analysis	✓
Synthesis of evidence on outcomes	Based on a systematic review	✓ Single RCT for comparison with IFN, single RCT for comparison with BSC
Measure of health benefits	QALYs	✓
Description of health states for QALY calculations	Use of a standardised and validated generic instrument	✓ EQ-5D from Phase III RCT.
Method of preference elicitation for health state values	Choice-based method (e.g. TTO, SG, not rating scale)	✓
Source of preference data	Representative sample of the UK public	✓
Discount rate	3.5% pa for costs and health effects	✓

Table 71: Critical appraisal checklist of the Wyeth economic evaluation

Dimension of quality			Comments
Structure			
S1	Statement of decision problem/objective	✓	Cost-effectiveness modelling of first-line use of temsirolimus versus IFN and BSC in a patient population with advanced RCC and poor prognosis. NICE is the primary decision maker.
S2	Statement of scope/perspective	✓	NHS perspective. Model inputs are consistent with the perspective. Scope of model stated and justification given. Outcomes consistent with perspective and scope of model.
S3	Rationale for structure	✓	The model structure, based on the health states: PFS, PD and death, has been described reasonably clearly, and is consistent with the progression of RCC. Weibull models are common in survival analysis, allowing for time-dependent transition probabilities.
S4	Structural assumptions	?	Model assumptions are given. Weibull regression models were fitted to PFS and post-progression survival outcomes of the Phase III clinical trial (post-progression survival is defined as time from progression to death). However, the estimation of transition probabilities between health states from regression analyses is not described in the report. It is not clear why the transition probabilities PFS to PD should equal the probabilities from PD to PD.
S5	Strategies / comparators	?	Temsirolimus was compared with IFN which is appropriate. Temsirolimus is also compared with and BSC, but we are unsure of the robustness of this comparison.
S6	Model type	✓	This type of Markov state transition model is frequently used in this type of decision problem.
S7	Time horizon	✓	The duration of treatment is well described. The model time horizon is 3 years, which is long enough to follow the great majority of patients to death.
S8	Disease states / pathways	?	The disease states: first-line PFS, PD and death are those generally accepted for this decision question. However, as stated above, the derivation of transition probabilities is opaque.
S9	Cycle length	✓	The cycle length of 1 month is short enough to capture the complexities of the natural history of the disease.
Data			
D1	Data identification	✓	Data identification methods are described. The data for the important parameters (transition probabilities and utilities) have been taken from the main Phase III RCT, but some of this data is unpublished.
D2	Pre-model data analysis	?/✓	The use of regression to derive the transition probabilities seems reasonable, but is not described in sufficient detail. The method for calculating the costs of treatment initiation, routine follow-up, disease progression, BSC, terminal care, and treating

			adverse events seems reasonable.
D2a	Baseline data	?	The model patient population was defined to be the same as in the Phase III trial of temsirolimus, which is a reasonable assumption. As explained above, the calculation of transition probabilities is not described sufficiently clearly.
D2b	Treatment effects	X	The model relative treatment effects have not been described. In particular, we cannot tally the HR for overall survival implicit in the model with that given in Hudes et al (2007).[112] Similarly for the subgroup analyses. Wyeth assume that the Weibull function, extrapolated beyond the trial time period, accurately describes survival beyond the trial period, which is reasonable, especially since OS is almost completely (~80%) mature at data cutoff.
D2c	Quality of life weights (utilities)	?/✓	Utilities were derived primarily from EQ-5D data collected during Hudes et al (2007) RCT[112] from approximately 280 patients. Utility data was used in the Q-TWiST framework. Data used not published
D3	Data incorporation	✓	Data incorporated in the model are referenced and generally well described. Data incorporation is transparent. For the PSA, the choice of distribution for each parameter has been described and justified.
D4	Assessment of uncertainty	?	Not all types of uncertainty have been addressed.
D4a	Methodological	X	Wyeth have used a single type of model
D4b	Structural	X	Not assessed.
D4c	Heterogeneity	✓	The model was applied to the following patient subgroups: clear cell, non-clear cell and nephrectomy, no nephrectomy.
D4d	Parameter	✓	Extensive univariate and PSA performed.
Consistency			
C1	Internal consistency	X	No evidence has been presented to indicate that the mathematical logic of the model has been tested.
C2	External consistency	X	The results of the model were not calibrated against independent data. Importantly, the model predictions of PFS and OS curves do not agree with the Kaplan-Meier curves reported in Hudes et al (2007).[112] The results of the model have not been compared with those of other models of metastatic RCC, although these other models have been reported only in abstract form.

✓ indicates 'clear', X indicates 'concerns', and ? indicates 'unclear/unknown'

Checklist structure from Phillips and colleagues [135]

Table 72: Wyeth clear cell and non-clear cell subgroup results.

Health Outcomes 36 month time horizon	**Temsirolimus Clear Cell**	**IFN Clear Cell**	**Temsirolimus Non-clear Cell**	**IFN Non-clear Cell**	**Incremental Clear Cell**	**Incremental Non-clear cell**
Mean progression-free life years - discounted	0.60	0.46	0.64	0.25	0.140	0.388
Mean life years - discounted	1.01	0.85	1.12	0.66	0.161	0.458
Mean QALYs - discounted	0.50	0.39	0.55	0.29	0.109	0.260
Treatment Costs (Discounted)						
1st-line drugs	£12,729	£2,721	£13,621	£1,163	£10,008	£12,458
1st-line administration	£3,176	£7,333	£3,399	£3,284	-£4,157	£115
Toxicities	£857	£982	£857	£982	-£124	-£124
Dx/Tx initiation and routine follow-up	£2,285	£1,941	£2,369	£1,415	£345	£954
Progression	£510	£391	£404	£425	£119	-£21
Post-progression (2nd line + BSC)	£2,881	£2,743	£3,424	£2,899	£138	£524
Death	£10,991	£11,028	£10,527	£11,127	-£38	-£600
Total Costs	**£33,429**	**£27,139**	**£34,601**	**£21,296**	**£6,291**	**£13,305**
Incremental Cost effectiveness Ratios (ICERS)						
Total Costs	£33,429	£27,139	£34,601	£21,296	£6,291	£13,305
Total Life years	1.01	0.85	1.12	0.66	0.161	0.458
Total QALYs	0.50	0.39	0.55	0.29	0.109	0.260
			Cost per life year		**£39,188**	**£29,035**
			Cost per QALY		**£57,731**	**£51,159**

Table 73: Wyeth nephrectomy and no nephrectomy subgroups results

Health Outcomes-36 month time horizon	**temsirolimus** Nephrectomy	**IFN** Nephrectomy	**temsirolimus** No nephrectomy	**IFN** No nephrectomy	**Incremental** Nephrectomy	**Incremental** No nephrectomy
Mean progression-free life years - discounted	0.58	0.42	0.64	0.41	0.161	0.225
Mean life years - discounted	0.99	0.83	1.12	0.83	0.162	0.296
Mean QALYs -discounted	0.49	0.38	0.56	0.38	0.110	0.177
Treatment Costs (Discounted)						
1st-line drugs	£12,274	£2,432	£13,705	£2,369	£9,841	£11,337
1st-line administration	£3,062	£6,589	£3,420	£6,425	-£3,526	-£3,005
Toxicities	£857	£982	£857	£982	-£124	-£124
Dx/Tx initiation and routine follow-up	£2,241	£1,844	£2,375	£1,822	£397	£553
Progression	£510	£400	£454	£395	£110	£59
Post-progression (2nd line + BSC)	£2,878	£2,877	£3,109	£2,525	£1	£584
Death	£11,006	£11,015	£10,515	£11,115	-£9	-£600
Total Costs	**£32,828**	**£26,139**	**£34,436**	**£25,631**	£6,690	£8,805
Incremental Cost effectiveness Ratios (ICERS)						
Total Costs	£32,828	£26,139	£34,436	£25,631	£6,690	£8,805
Total Life years	0.99	0.83	1.12	0.83	0.162	0.296
Total QALYs	0.49	0.38	0.56	0.38	0.110	0.177
			Cost per life year		**£41,188**	**£29,792**
			Cost per QALY		**£60,575**	**£49,690**

Table 74: Temsirolimus vs BSC results from Wyeth model

Health Outcomes-36 month time horizon	**temsirolimus**	**BSC**	**Incremental**
Mean progression-free life years - discounted	0.61	0.33	0.285
Mean life years - discounted	1.02	0.64	0.381
Mean QALYs - discounted	0.51	0.30	0.205
Treatment Costs (Discounted)			
1st-line drugs	£12,957	£458	£12,499
1st-line administration	£3,233	£0	£3,233
Toxicities	£857	£0	£857
Dx/Tx initiation and routine medical follow-up	£2,310	£2,612	-£302
Progression	£467	£369	£98
Post-progression (2^{nd} line + BSC)	£2,884	£2,201	£683
Death	£10,903	£11,291	-£388
Total Costs	£33,612	£16,932	£16,680
Incremental Cost effectiveness Ratios (ICERS)			
Total Costs	£33,612	£16,932	£16,680
Total life years	1.02	0.64	0.381
Total QALYs	0.51	0.30	0.205
		Cost per life year	**£43,746**
		Cost per QALY	**£81,201**

Table 75: Comparison of Bayer's model of sorafenib versus BSC in 2nd-line use and cytokine unsuitable patients with NICE reference case requirements

NICE reference case requirement		**Reviewer comment**
Decision problem	As per the scope developed by NICE (esp. technologies & patient group)	✓ sorafenib vs. BSC in 2nd-line and cytokine unsuitable patients
Comparator	Alternative therapies routinely used in the UK NHS	✓ BSC
Perspective on costs	NHS and PSS	✓
Perspective on outcomes	All health effects on individuals	✓
Type of economic evaluation	Cost-effectiveness analysis	✓
Synthesis of evidence on outcomes	Based on a systematic review	✓ Escudier et al (2007) RCTof sorafenib vs.BSC[113]
Measure of health benefits	QALYs	✓
Description of health states for QALY calculations	Use of a standardised and validated generic instrument	?/✓ EQ-5D survey of RCC clinicians
Method of preference elicitation for health state values	Choice-based method (e.g. TTO, SG, not rating scale)	✓
Source of preference data	Representative sample of the UK public	✓
Discount rate	3.5% pa for costs and health effects	✓

Table 76: Main per patient results of Bayer cost-effectiveness analyses of sorafenib vs. BSC and sunitinib vs. sorafenib.

	Sorafenib - BSC			Sunitinib - sorafenib
Sorafenib vs. BSC	**2nd-line & cytokine unsuitable combined**	**2nd-line only**	**cytokine unsuitable only**	
Increase in OS (years)	0.46	[redacted]	[redacted]	[redacted]
Increase in PFS (years)	0.19	[redacted]	[redacted]	[redacted]
Increase in QALYs	0.26	[redacted]	[redacted]	[redacted]
Cost per LYG	£57,456	[redacted]	[redacted]	[redacted]
Cost per QALY	**£90,630**	[redacted]	[redacted]	[redacted]
Prob. cost-effectiveness WTP £30,000 / QALY	0.0%	[redacted]	[redacted]	not given
Incremental costs				not given
Total costs	£23,849	£23,033	£27,175	
drug cost †	[redacted]	[redacted]	[redacted]	
drug administration †	[redacted]	[redacted]	[redacted]	
AEs †	[redacted]	[redacted]	[redacted]	
PFS excl. cost of sorafenib †	[redacted]	[redacted]	[redacted]	
PD †	[redacted]	[redacted]	[redacted]	

† calculated by PenTAG from Bayer's model.

Table 77: Bayer results for sorafenib versus BSC by subgroup

		Mean PFS (months)			Mean OS (months)		
Subgroup	**Value**	**Placebo**	**Sorafenib**	**Difference**	**Placebo**	**Sorafenib**	**Difference**
Age	≥65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Motzer score	Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nephrectomy	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline ECOG	0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline ECOG	1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior IL-2/Interferon	No (unsuitable)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Prior IL-2/Interferon	Yes (failed)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastasis in Lung at BL	No	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Metastasis in Liver at BL	Yes	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diagnosis time at BL	≥1.5 years	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BL: baseline							

		QALYs		Life years		Cost		ICER	
Subgroup	**Value**	**Placebo**	**Sorafenib**	**Placebo**	**Sorafenib**	**Placebo**	**Sorafenib**	**QALY**	**LYG**
Age	≥65	[redacted]	[redacted]	[redacted]	[redacted]	£10,484	£36,078	[redacted]	[redacted]
Motzer score	Intermediate	[redacted]	[redacted]	[redacted]	[redacted]	£10,450	£33,884	[redacted]	[redacted]
Nephrectomy	Yes	[redacted]	[redacted]	[redacted]	[redacted]	£11,686	£35,515	[redacted]	[redacted]
Baseline PS (avg utility)	0	[redacted]	[redacted]	[redacted]	[redacted]	£13,043	£37,368	[redacted]	[redacted]
Baseline PS (PS 0 utility)	0	[redacted]	[redacted]	[redacted]	[redacted]	£13,043	£37,368	[redacted]	[redacted]
Baseline PS (avg utility)	1	[redacted]	[redacted]	[redacted]	[redacted]	£10,554	£30,550	[redacted]	[redacted]
Baseline PS (PS 1 utility)	1	[redacted]	[redacted]	[redacted]	[redacted]	£10,554	£30,550	[redacted]	[redacted]
Prior IL-2/Interferon	No (unsuitable)	[redacted]	[redacted]	[redacted]	[redacted]	£11,408	£38,583	[redacted]	[redacted]
Prior IL-2/Interferon	Yes (failed)	[redacted]	[redacted]	[redacted]	[redacted]	£13,230	£36,263	[redacted]	[redacted]
Metastasis in Lung at BL	No	[redacted]	[redacted]	[redacted]	[redacted]	£14,177	£40,471	[redacted]	[redacted]
Metastasis in Liver at BL	Yes	[redacted]	[redacted]	[redacted]	[redacted]	£11,339	£36,154	[redacted]	[redacted]
Diagnosis time at BL	≥1.5 years	[redacted]	[redacted]	[redacted]	[redacted]	£14,177	£42,896	[redacted]	[redacted]
BL: baseline									

Table 78: Critical appraisal checklist of the Bayer economic evaluation of sorafenib versus BSC in 2nd line use and for patients unsuitable for cytokine treatment

Dimension of quality			Comments
Structure			
S1	Statement of decision problem/objective	✓	Cost-effectiveness modelling of sorafenib vs. BSC in 2nd line use and for patients unsuitable for cytokine treatment in a patient population with advanced RCC. NICE is the primary decision maker.
S2	Statement of scope/perspective	✓	NHS perspective. Model inputs are consistent with the perspective. Scope of model stated and justification given. Outcomes consistent with perspective and scope of model.
S3	Rationale for structure	✓	The model structure, based on the health states: progression-free survival, progressed and death, has been described clearly, and is consistent with the progression of RCC. Exponential curves are used to extrapolate OS for sorafenib and BSC, which is a valid method. However, it might have been useful to extrapolate with the Weibull distribution, since this is more flexible than the exponential distribution.
S4	Structural assumptions	?/✓	Model assumptions are given. The structural assumptions for utilities are described however, use of data from a survey of clinicians is a weakness.
S5	Strategies / comparators	✓	All feasible options have been evaluated.
S6	Model type	✓	This type of model based on survival curves is frequently used in this type of decision problem.
S7	Time horizon	✓	Treatment is given whilst in PFS, and is well described. The model time horizon is ten years, which is long enough to follow the great majority of patients to death.
S8	Disease states / pathways	✓	The disease states: PFS, progressed and death reflect the underlying biological progress of the disease are those generally accepted for this decision question.
S9	Cycle length	✓	The cycle length of 1 month is short enough to capture the complexities of the natural history of the disease.
Data			
D1	Data identification	?	Data identification methods are described. The data for the important parameters (PFS and OS curves and utilities) have been taken from the main RCT. However, the sources of the unit costs in PFS and PD and for AEs given in the Excel model and in Appendix 3.2 of the report are not provided. Costs were modelled at the following times: treatment initiation, routine monthly follow-up, disease progression, BSC and terminal care / death. At each of these times, costs were categorized as outpatient, inpatient, laboratory tests and radiological exams. Unit costs were taken from standard UK

			sources (NHS Reference Costs,[139] BNF,[70] and CIPFA[188]). We are concerned that resource use was obtained from a US perspective, although it was adjusted to a UK setting. Also, only five physicians were consulted.
D2	Pre-model data analysis	✓	Pre-model data analysis, e.g. cost of AEs, resource use in PFS and PD is good.
D2a	Baseline data	?	Bayer have correctly used the PFS and OS data from the main RCT of sorafenib vs. BSC. OS is not fully mature, hence Bayer have extrapolated using an exponential curve, which is valid. Half-cycle corrections have not been used.
D2b	Treatment effects	✓	Treatment effects are taken from the main RCT. HRs are not used in the data for all patients combined. Instead, the sorafenib and BSC curves have been fitted separately, which is reasonable. The treatment effects are assumed to continue after data-cutoff in the main RCT, which is reasonable.
D2c	Quality of life weights (utilities)	?/✓	Given that utilities are not available from the main RCT of sorafenib vs. BSC, Bayer have used utilities from EQ-5D data from a survey of clinicians. Utilities were assumed independent of treatment. Data used are unpublished. Small health valuation surveys of clinicians are not methodologically sound.
D3	Data incorporation	✓	Data incorporated in the model are referenced and generally well described. The exception is that the sources of the unit costs in PFS and PD and for AEs given in the Excel model and in Appendix 3.2 of the report are not provided. For the PSA, the choice of distribution for each parameter has been described and justified.
D4	Assessment of uncertainty	?	Not all types of uncertainty have been addressed.
D4a	Methodological	X	Bayer have used a single type of model.
D4b	Structural	X	Bayer have not investigated structural uncertainty.
D4c	Heterogeneity	✓	Bayer modelled ten patient subgroups.
D4d	Parameter	✓	Bayer have performed a PSA and univariate sensitivity analysis on parameters.
Consistency			
C1	Internal consistency	X	Bayer provide no evidence to indicate that the mathematical logic of the model has been tested.
C2	External consistency	?	The results of the model were not calibrated against independent data, although it is not clear that such independent data exists. The results of the model have not been compared with those of other models of metastatic RCC, although these other models have been reported only in abstract form.

✓ indicates 'clear', X indicates 'concerns', and ? indicates 'uncertain/unknown'

Checklist structure from Phillips and colleagues [135]

Appendix 7: Overall survival and progression-free survival model fitting

For a direct comparison between two treatments, Weibull curves were calculated as follows. First, Weibull curves were fitted separately to the PFS and OS Kaplan-Meier curves corresponding to a chosen baseline treatment from the appropriate RCT as follows. The Weibull survival function is;

$$S(t) = \exp\left(-\lambda t^{\gamma}\right)$$

at time t, with scale parameter λ, shape parameter γ and hazard;

$$h(t) = \gamma\lambda t^{\gamma-1}$$

If $\gamma > 1$, the hazard increases with time, and if $0 < \gamma < 1$, it decreases with time. Parametric curves can be fitted to empirical Kaplan-Meier data using simple regression by transforming the survivor function to a linear function.[142,189] Accordingly, linearising;

$$\log\left(-\log(S(t))\right) = \log(\lambda) + \gamma\log(t)$$

from which parameters γ and λ are estimated. As a word of caution, outlier points are often found in this regression equation for values of S(t) slightly less than 1, i.e. for very small t. In this case, -log(S(t)) is fractionally greater than 0, and hence log[-log(S(t))] is very large and negative. In this case, such outlier points were omitted from the regression. As a check, the fit of the estimated Weibull function to the Kaplan-Meier curve was inspected for reasonableness.

Second, a Weibull curve was assumed for the other treatment in the direct comparison between two treatments. This curve was obtained by application of the hazard ratio to the

baseline survival curve for the first treatment.[142] In particular, γ for the second treatment was set equal to γ for the first treatment, and λ for the second treatment was calculated as λ for the baseline treatment multiplied by the hazard ratio between the two treatments. This method allows for uncertainty in the HRs for the PSA. Very occasionally, using this method, at large time t, the number of patients in PFS is modelled to exceed the number of patients alive. Therefore, to avoid this, we imposed the constraint that at any time t, the number of patients in PFS was limited to the number of patients alive.

Now consider a simultaneous comparison between three treatments A, B and C, in particular, between sunitinib, bevacizumab plus IFN and IFN. Suppose trial X compares treatments A and B and trial Y compares A and C. Weibull curves were calculated for PFS and OS for each of treatments A, B and C as follows. For the common treatment A, Weibull curves were fitted separately for OS and PFS from one of the two trials, as described above, to give parameters λ_A^{PFS}, λ_A^{OS}, γ_A^{PFS}, γ_A^{OS}. OS and PFS Weibull curves for treatment B were obtained by application of the hazard ratios HR_{BA}^{OS} and HR_{BA}^{PFS} from trial X respectively, as described above, i.e. $\lambda_B^{PFS} = HR_{BA}^{PFS}.\lambda_A^{PFS}$, $\gamma_B^{PFS} = \gamma_A^{PFS}$, $\lambda_B^{OS} = HR_{BA}^{OS}.\lambda_A^{OS}$, $\gamma_B^{OS} = \gamma_A^{OS}$. Similarly, OS and PFS Weibull curves for treatment C were obtained by application of the hazard ratios HR_{CA}^{OS} and HR_{CA}^{PFS} from trial Y respectively.

For each treatment, we now have the number of patients in PFS and PD at each model cycle. The probabilities of transition between the three health states depend on time. However, it is neither possible nor necessary to calculate these probabilities. Transition probabilities should be calculated only in order to estimate the number of patients in the health states at any time. However, we calculate these as explained above. It is not possible to calculate the time-dependent transition probabilities indicated by the arrows in Figure 10 (page 132), because, at each time, there are three unknown transition probabilities, but only two independent equations containing these three probabilities. Expressed differently, we do not know what proportion of the patients that die in each cycle come from PFS or PD. Transition probabilities can only be calculated if we know the health states of individual patients over time, as described in Billingham and colleagues.[189]

Appendix 8: Cost-Effectiveness Analysis Results: Cost-effectiveness planes to complement cost-effective analysis presented in the report

Scatter plots (cost effectiveness planes) are shown in Figure 28, Figure 29 and Figure 30 (pages 256, 257 and 258). In all cases, notice that incremental total costs and benefits are highly correlated. This is because we assume that, for each treatment, the PFS HR and OS HR are correlated. Therefore, when the model samples a low PFS HR, thus incurring a higher incremental drug cost (as drugs are taken whilst in PFS), then a low OS HR is sampled, thus incurring a higher incremental lifespan and hence incremental QALYs.

Figure 27: Simulations of mean incremental total costs vs. benefits for sunitinib vs. IFN and bevacizumab plus IFN vs. IFN. Willingness to pay of £20,000 / QALY and £30,000 / QALY are shown by the dotted and continuous lines respectively.

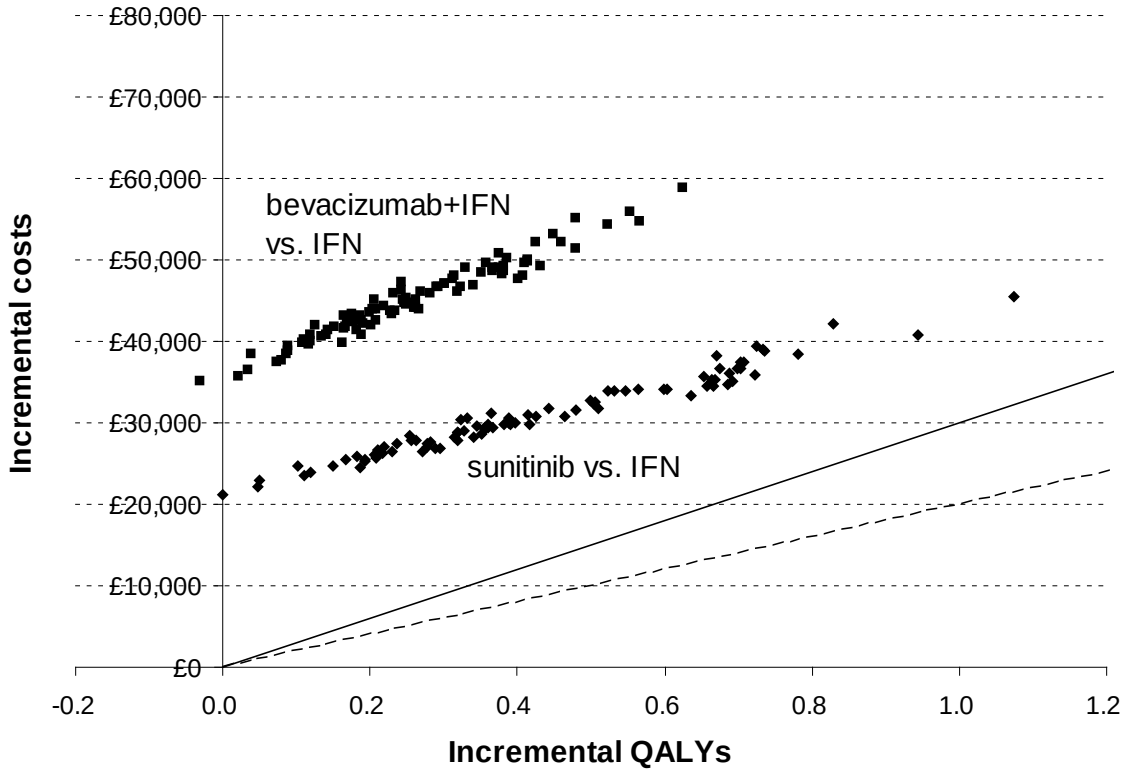


Figure 28: Simulations of mean incremental total costs vs. benefits for all patients for temsirolimus vs. IFN. Willingness to pay of £20,000 / QALY and £30,000 / QALY are shown by the dotted and continuous lines respectively.

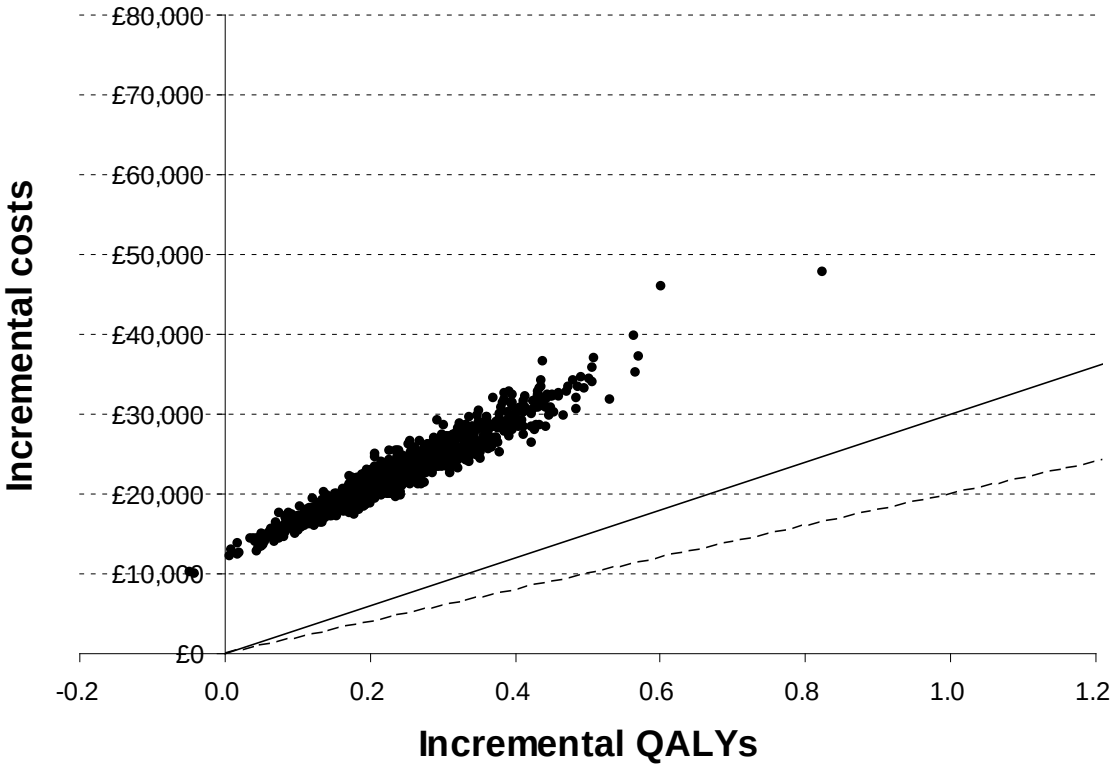
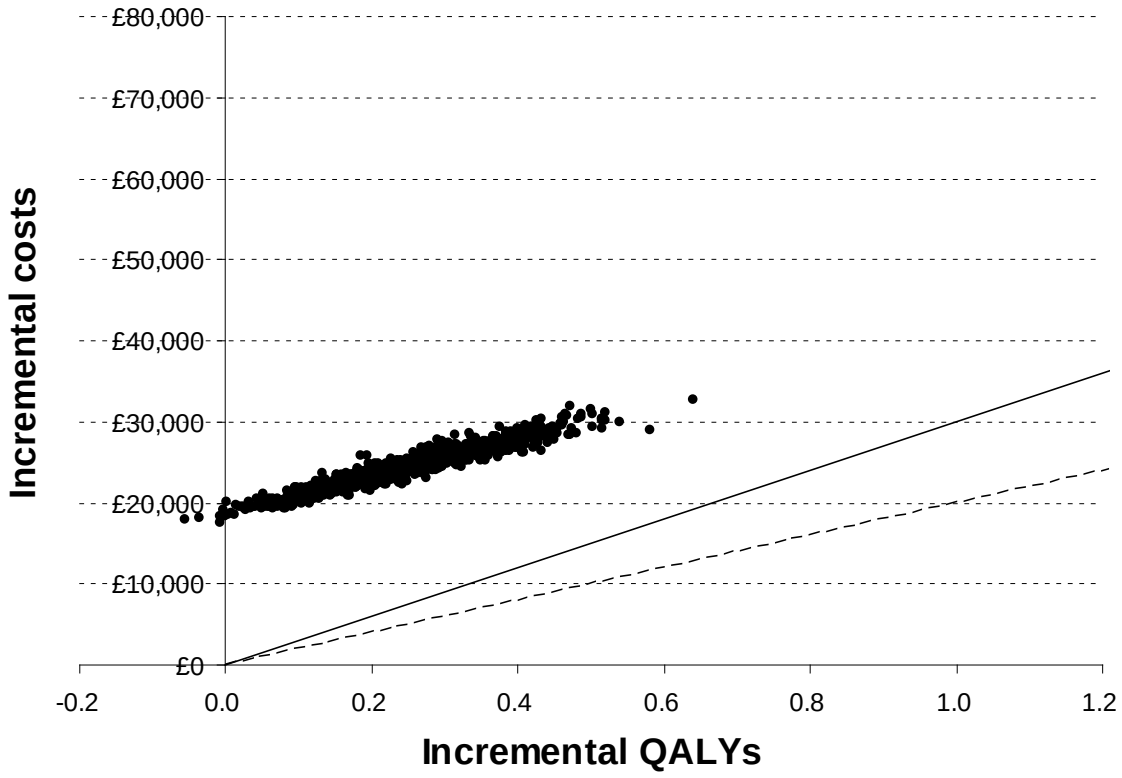


Figure 29: Simulations of mean incremental total costs vs. benefits for sorafenib vs. BSC. Willingness to pay of £20,000 / QALY and £30,000 / QALY are shown by the dotted and continuous lines respectively.



Appendix 9: Probabilistic sensitivity analysis

We performed Monte Carlo simulations to explore the impact of uncertainty in the model parameters on cost-effectiveness. Means, standard errors and statistical distributions for these parameters are given in Table 79.

For each treatment, we assumed that the OS and PFS HRs were perfectly correlated, which seems more realistic than completely uncorrelated. The two parameters of the Weibull distribution, $\ln(\lambda)$ and γ, for baseline PFS and separately for OS were drawn from bivariate normal distributions, using the method of Cholesky matrix decomposition. The variance-covariance matrices used in the matrix decomposition were estimated from linear regression of $\ln(-\ln S(t))$ against $\ln(t)$, described in Appendix 7, where $S(t)$ is the survival function at time t.

For simplicity, AE costs were assumed deterministic because their impact on cost-effectiveness analysis is very small.

Table 79: Stochastic parameters used in PenTAG model

Parameter type	Parameter	Mean cost per 6-weeks (s.e.)	Statistical distribution
Effectiveness	Weibull: λ, γ	See Table 80	bivariate normal§
	Hazard ratios	See Table 81	lognormal
Health state utilities	All utilities	See Table 82	beta§
Costs	Drug acquisition	Not stochastic	n/a
	Adverse events	Not stochastic	n/a
	Drug administration	IFN: £112 (£7), bevacizumab: £590 (£52), temsirolimus: £1,179 (£105)†	gamma§
	Medical management	PFS BSC: £81 (£3), PFS All drug treatments: £223 (£9), PD All treatments (drugs & BSC) : £435 (£22)†	gamma§

§ Recommended by Briggs and colleagues.[190]

† Standard errors (s.e.) calculated from the interquartile ranges and number of data submissions given in [145] and [139], except for the costs taken from [146], the cost of BSC in PD and the cost of administration of IFN, which were estimated by assuming the average ratio of standard error to mean, 0.06, over all other costs.

Table 80: Base case parameters of Weibull distribution used in PenTAG model

Policy question	Treatment	PFS		OS	
		λ	γ	λ	γ
1st-line (not poor prognosis)	**IFN**	0.132	1.004	0.011	1.447
	sunitinib	0.055	1.004	0.007	1.447
	bevacizumab plus IFN	0.083	1.004	0.008	1.447
1st-line (poor prognosis)	**IFN**	0.542	0.582	0.127	0.829
	temsirolimus	0.401	0.582	0.092	0.829
2nd-line & unsuitable IFN	**BSC**	0.262	0.943	0.013	1.502
	sorafenib	0.134	0.943	0.010	1.502

NB: Time measured in months

Table 81: Hazard ratios used in PenTAG model

Policy question	Treatment	PFS	OS
1st-line (not poor prognosis)	**sunitinib vs. IFN**	0.42 (0.33 - 0.52)	0.65 (0.45 - 0.94)
	bevacizumab plus IFN vs. IFN	0.63 (0.52 - 0.75)	0.75 (0.58 - 0.97)
1st-line (poor prognosis)	**temsirolimus vs. IFN**	0.74 (0.60 - 0.91)	0.73 (0.58 - 0.92)
2nd-line & unsuitable IFN	**sorafenib vs. BSC**	0.51 (0.43 - 0.60)	0.72 (0.54 - 0.94)

NB: 95% confidence intervals given in brackets.

Table 82: Health state utilities used in PenTAG model

Policy question	Treatments	Health state	Base case (s.e.) *	Source / Justification
1st-line (not poor prognosis)	IFN, sunitinib, bevacizumab plus IFN	PFS	0.78 (0.01)	Pfizer submission[136]
		PD	0.70 (0.02)	
1st-line (poor prognosis)	IFN, temsirolimus	PFS	0.60 (0.06**)	Wyeth submission[125]
		PD	0.45 (0.04**)	
2nd-line & unsuitable IFN	Sorafenib, BSC	PFS	0.76 (0.03)	Pfizer submission[136]
		PD	0.68 (0.04)	

* s.e. derived from s.d. and number of patients from RCTs, reported in industry submissions.

** s.e. estimated as 10% of mean.

Appendix 10: Cohort composition

Figure 30: Cohort compositions for policy Question 1. Dark grey indicates PFS, light grey indicates PD and white indicates death.

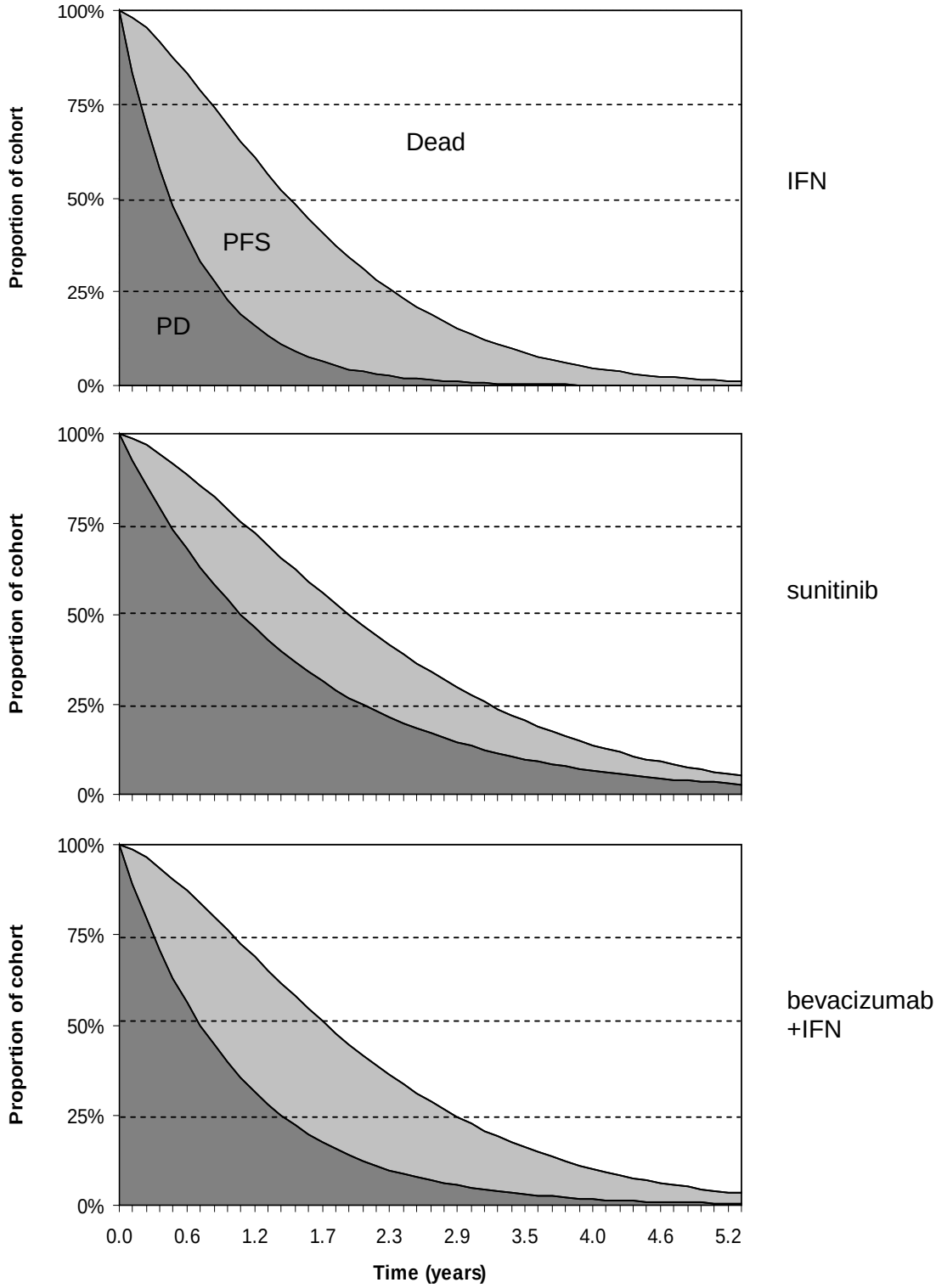


Figure 31 Cohort compositions for policy Question 2.

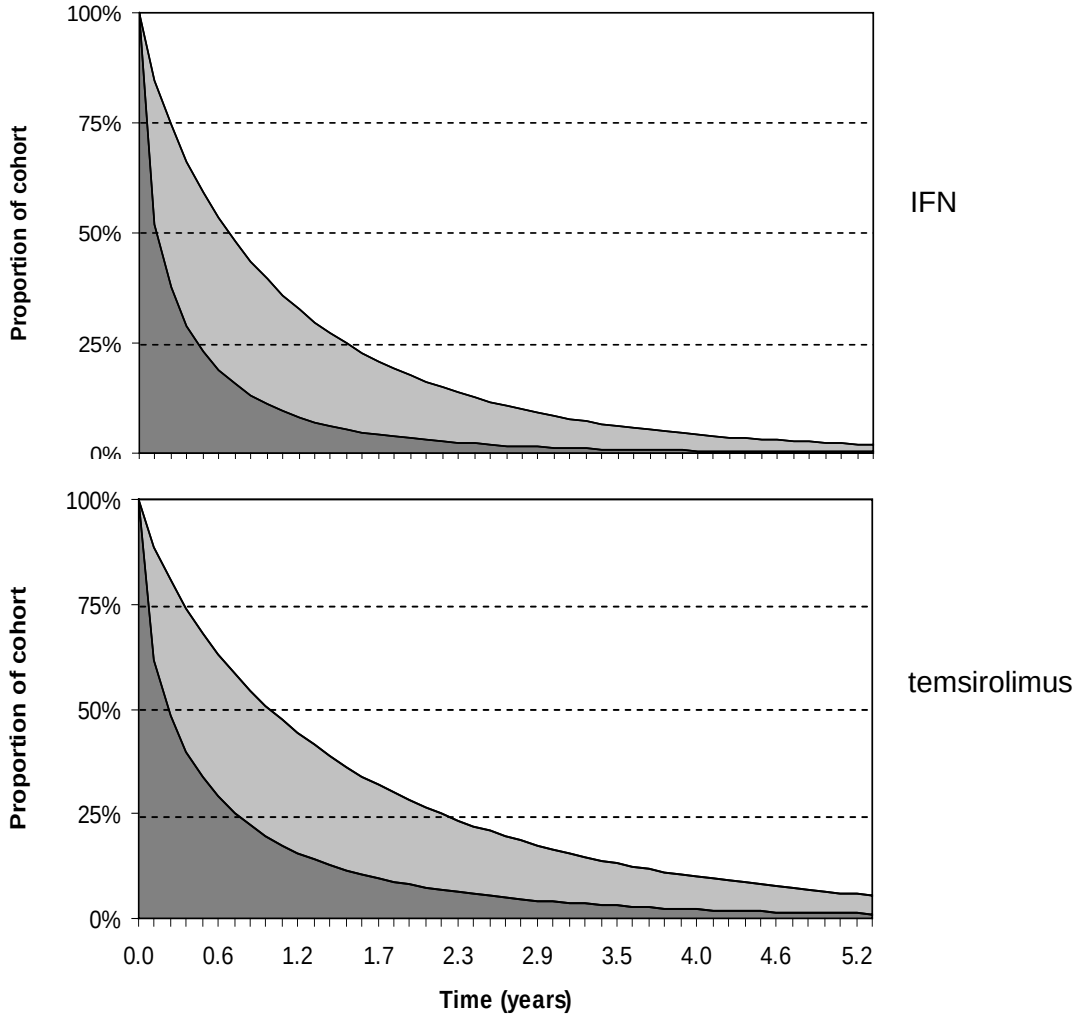
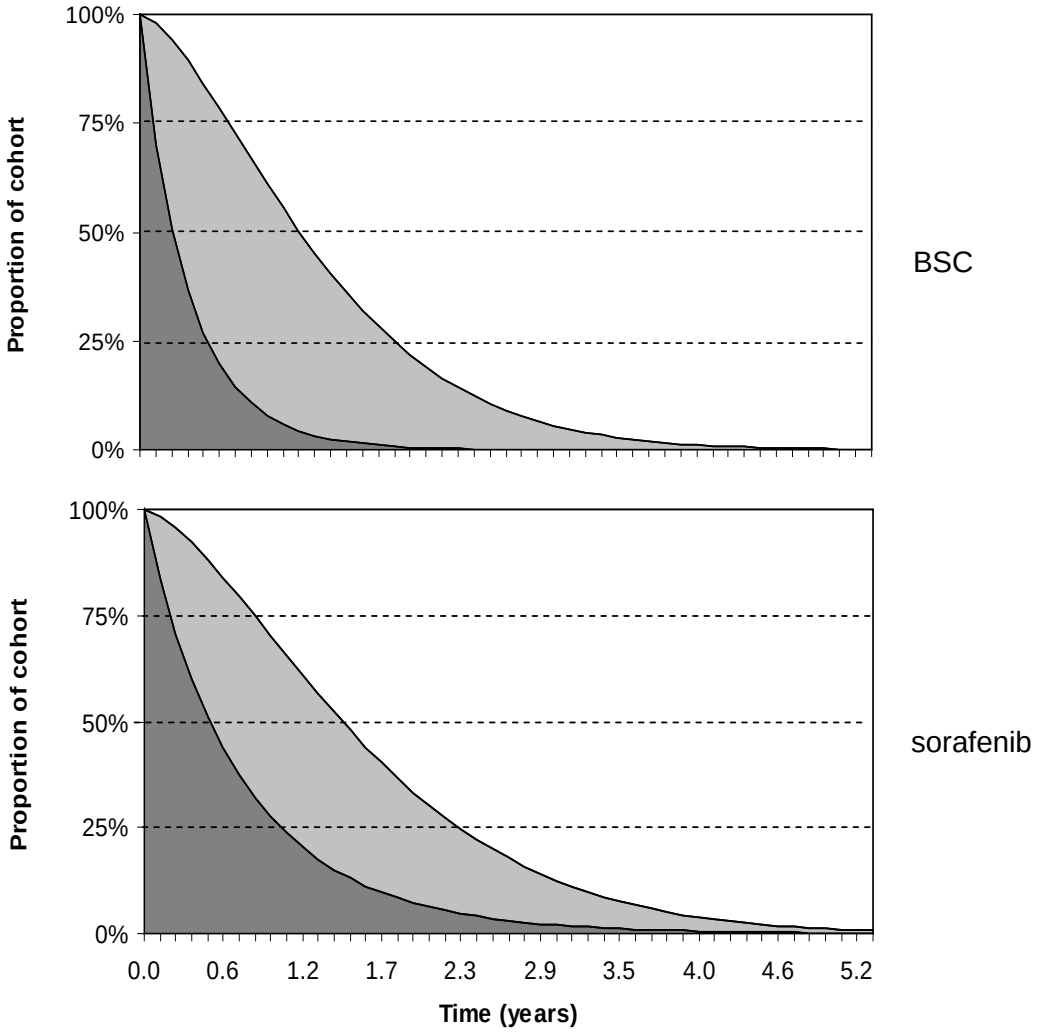
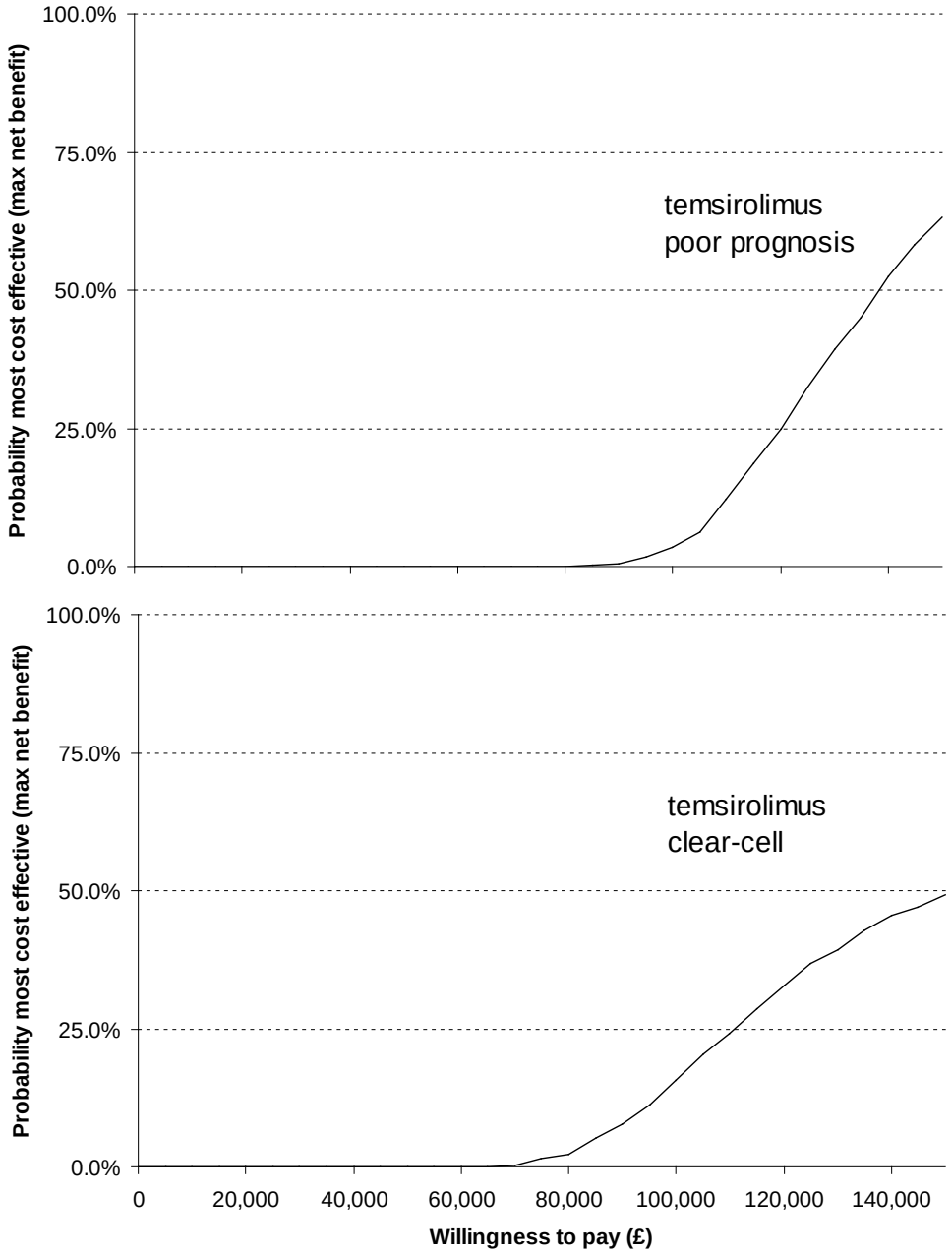


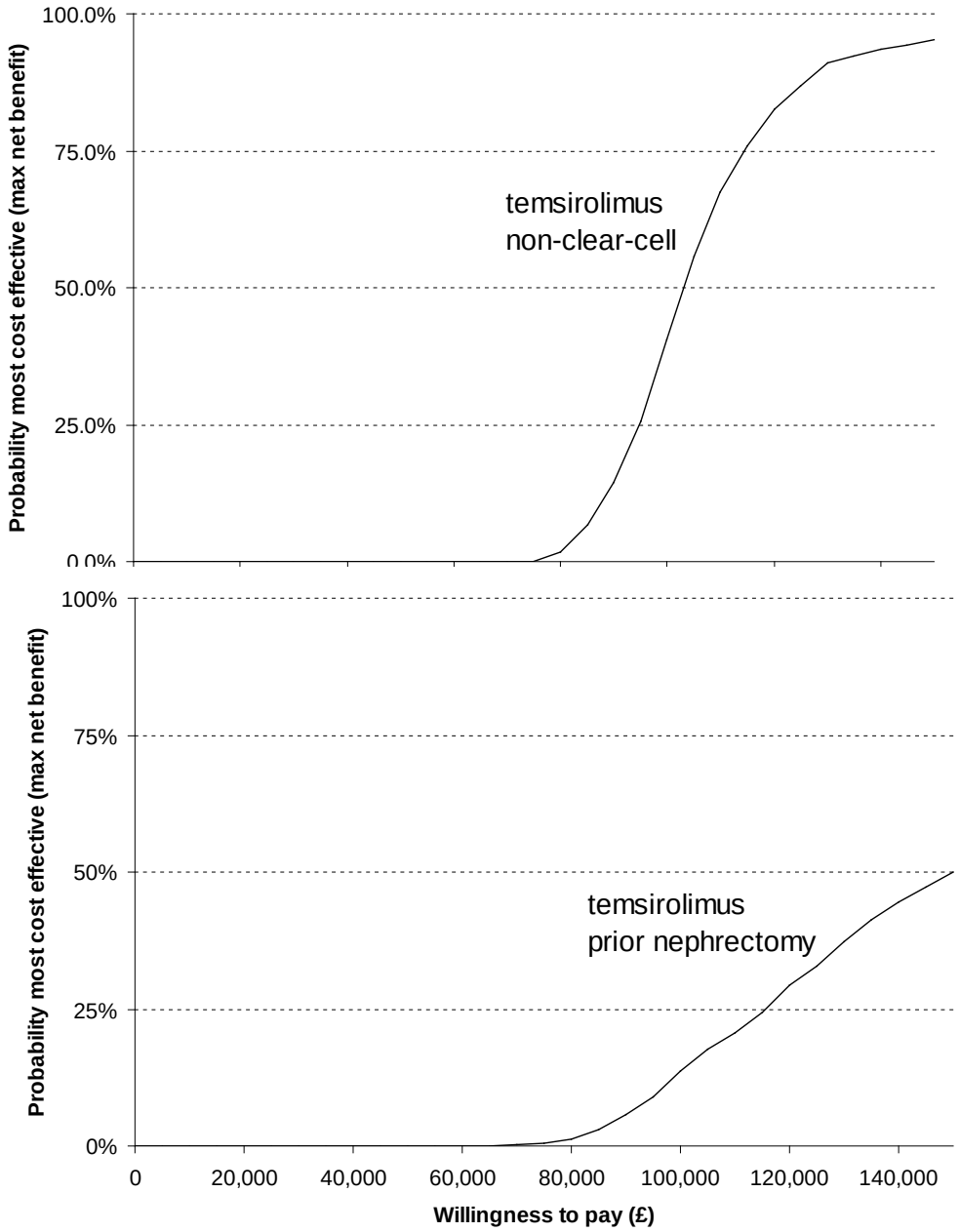
Figure 32: Cohort compositions for policy Question 3

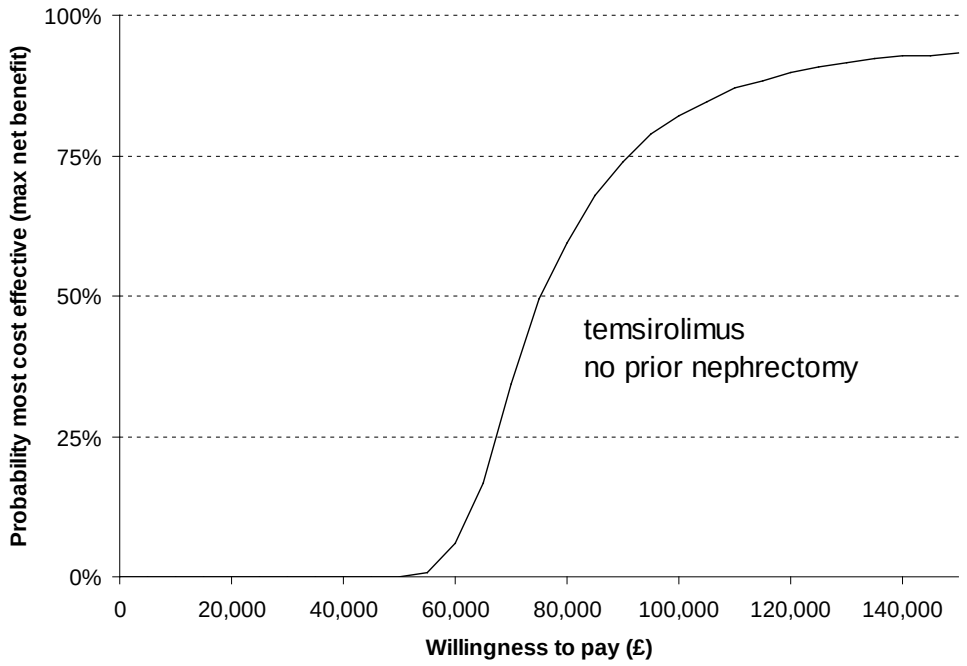


Appendix 11: Cost-effectiveness acceptability curves for patient subgroups for temsirolimus vs. IFN

Figure 33: Cost-effectiveness acceptability curves for patient subgroups for temsirolimus vs. IFN




100.0%
75.0%
50.0%
25.0%
0.0%
Probability most cost effective (max net benefit)
temsirolimus
non-clear-cell
100%
75%
50%
25%
0%
Probability most cost effective (max net benefit)
temsirolimus
prior nephrectomy
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
Willingness to pay (£)


100%
75%
50%
25%
0%
Probability most cost effective (max net benefit)
temsirolimus
no prior nephrectomy
0
20,000
40,000
60,000
80,000
100,000
120,000
140,000
Willingness to pay (£)

Appendix 12: Ongoing / unpublished trials of bevacizumab, sorafenib, sunitinib and temsirolimus for renal cell carcinoma

Trial name	Register / identifier number	Established/ anticipated sample size	Status
SORCE: A phase III Randomised Controlled Study Comparing Sorafenib With Placebo In Patients With Resected Primary Renal Cell Carcinoma at High or Intermediate Risk of Relapse	NCT00492258	1656	Recruiting
Randomized Phase IIb Study of Sorafenib Dose Escalation in Patients With Previously Untreated Metastatic Renal Cell Carcinoma (RCC)	NCT00557830	170	Recruiting
Open Label, Non-Comparative Treatment Protocol for the Use of Sorafenib in Patients With Advanced Renal Cell Carcinoma	NCT00111020	2622	Active, not recruiting
A Randomised, Open-Label, Multi-Centre Phase II Study of BAY 43-9006 (Sorafenib) Versus Standard Treatment With Interferon Alpha-2a in Patients With Unresectable and/or Metastatic Renal Cell Carcinoma	NCT00117637	Not reported	Active, not recruiting
A Phase II Study of BAY 43-9006 Prior to and Following Nephrectomy in Patients With Metastatic Renal Cell Carcinoma	NCT00110344	30	Terminated
A Randomized Phase II Trial Of Sunitinib Administered Daily For 4 Weeks, Followed By 2-Week Rest Vs. 2-Week On And 1-Week Off In Metastatic Renal Cell Carcinoma	NCT00570882	72	Recruiting
A Randomized Open Label Multicenter Phase II Study of First Line Therapy With Sorafenib in Association With IL-2 vs Sorafenib Alone in Patients With Unresectable and/or Metastatic Renal Cell Carcinoma	NCT00609401	90	Recruiting
A Randomized Trial of Temsirolimus and Sorafenib as Second-Line Therapy in Patients With Advanced Renal Cell Carcinoma Who Have Failed First-Line Sunitinib Therapy	NCT00474786	476	Recruiting
Pre-Operative Administration of Sorafenib in Patients With Metastatic Renal Cell Carcinoma Undergoing Cytoreductive Nephrectomy	NCT00480389	30	Recruiting

Dynamic-Contrast Enhanced MRI Pharmacodynamic Study of BAY 43-9006 in Metastatic Renal Cell Carcinoma	NCT00606866	57	Active, not recruiting
A Phase I/II Study of Sorafenib and RAD001 in Patients With Metastatic Renal Cell Carcinoma	NCT00384969	73	Recruiting
A Phase I/II Study of Sorafenib and Palliative Radiotherapy in Patients With Advanced Renal Cell Carcinoma and Symptomatic Bony Metastases	NCT00609934	36	Recruiting
A Multicenter Uncontrolled Study of Sorafenib in Patients With Unresectable and/or Metastatic Renal Cell Carcinoma	NCT00586105	40	Active, not recruiting
A Phase II, Multi-Centre, Open-Label Study to Assess the Efficacy, Safety, Tolerability and Pharmacokinetics of Intrapatient Dose Escalation of Sorafenib as First Line Treatment for Metastatic Renal Cell Carcinoma	NCT00618982	80	Not yet recruiting
An Open-Label, Non-Comparative, Treatment Protocol for the Use of BAY 43-9006 (Sorafenib) in Patients With Advanced Renal Cell Carcinoma	NCT00478114	15	Recruiting
Extension Study for BAY 43-9006 in Japanese Patients With Renal Cell Carcinoma	NCT00586495	95	Active, not recruiting
An Open Label, Non Comparative, Phase III Study of the Raf Kinase Inhibitor BAY 43-9006 as a Subsequent to First Line Therapy in Patients With Advanced Renal Cell Carcinoma	NCT00492986	1164	Active, not recruiting
A Randomized, Double Blinded, Multi-Center Phase 2 Study to Estimate the Efficacy and Evaluate the Safety and Tolerability of Sorafenib in Combination With AMG 386 or Placebo In Subjects With Metastatic Clear Cell Carcinoma of the Kidney	NCT00467025	150	Recruiting
A Randomized Discontinuation Trial to Determine the Clinical Benefit of Continuation of Sorafenib Following Disease Progression in Patients With Advanced Renal Cell Carcinoma	NCT00352859	260	Terminated
Phase II Clinical Trial, Non-Randomized, Multicentre, on the Combination of Gemcitabine, Capecitabine and Sorafenib (Bay 43-9006) in Treatment of Patients With Unresectable and/or Metastatic Renal Cell Carcinoma (RCC)	NCT00496301	40	Recruiting
A Phase 1/2, Open-Label, Dose Escalation Study to Assess the Safety and Pharmacokinetics of Recombinant Interleukin 21 (rIL-21) Administered Concomitantly With Sorafenib (Nexavar) in Subjects With Metastatic Renal Cell Carcinoma	NCT00389285	48	Recruiting
A Phase II Study of Sorafenib in Patients With Metastatic Renal Cell Carcinoma	NCT00496756	23	Recruiting

A Phase II Study of Sorafenib in Patients With Metastatic Renal Cell Carcinoma	NCT00445042	44	Recruiting
The BeST Trial: A Randomized Phase II Study of VEGF, RAF Kinase, and mTOR Combination Targeted Therapy (CTT) With Bevacizumab, Sorafenib and Temsirolimus in Advanced Renal Cell Carcinoma [BeST]	NCT00378703	360	Recruiting
Phase I/II Trial of RAD001 Plus Nexavar® For Patients With Metastatic Renal Cell Carcinoma	NCT00448149	55	Recruiting
ASSURE: Adjuvant Sorafenib or Sunitinib for Unfavorable Renal Carcinoma	NCT00326898	1332	Recruiting
Mechanistic Evaluations on Sorafenib Induced Hypophosphatemia in Patients With Advanced Renal Cell Carcinoma	NCT00622479	50	Not yet recruiting
A Phase 2 Study of Sorafenib (BAY 43-9006) in Metastatic Renal Cell Cancer to the Brain	NCT00301847	44	Active, not recruiting
Phase I/II Trial of Sorafenib (Nexavar) and RAD001 (Everolimus) in the Treatment of Patients With Advanced Clear Cell Renal Cell Carcinoma	NCT00392821	81	Recruiting
A Phase II Neoadjuvant Clinical Trial to Evaluate the Efficacy of BAY 43-9006 (Sorafenib) in Metastatic Renal Cell Carcinoma	NCT00126659	45	Active, not recruiting
A Phase II Clinical Trial to Evaluate the Efficacy of BAY 43-9006 With or Without Low Dose Interferon in Metastatic Renal Cell Carcinoma	NCT00126594	80	Active, not recruiting
A Phase I/II Trial of BAY 43-9006 Plus Gemcitabine and Capecitabine in the Treatment of Patients With Advanced Renal Cell Carcinoma	NCT00121251	35	Recruiting
A Phase I/II Trial of BAY 43-9006 in Combination With Bevacizumab in Patients With Advanced Renal Cell Cancer	NCT00126503	58	Recruiting
A Phase II Study of the RAF-Kinase Inhibitor BAY 43-9006 (NSC0724772, IND 69,896) in Combination With Interferon-α2B in Patients With Advanced Renal Cancer	NCT00101114	Not reported	Completed

Source: www.ukcrn.org.uk/index/clinical/portfolio_new/P_search.html, www.controlled-trials.com/mrct/, www.clinicaltrials.gov/, www.controlled-trials.com/ukctr/

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