NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Overview

Bevacizumab, sorafenib, sunitinib and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma

The overview is written by members of the Institute's team of technical analysts. It forms part of the information received by the Appraisal Committee members before the first committee meeting. The overview summarises the evidence and views that have been submitted by consultees and evaluated by the Assessment Group, and highlights key issues and uncertainties. To allow sufficient time for the overview to be circulated to Appraisal Committee members before the meeting, it is prepared before the Institute receives consultees' comments on the assessment report. These comments are therefore not addressed in the overview.

A list of the sources of evidence used in the preparation of this document is given in appendix A.

1 Background

1.1 The condition

Renal cell carcinoma (RCC), also called renal adenocarcinoma or hypernephroma, is a highly vascular type of kidney cancer usually originating in the lining of the tubules of the kidney. RCC accounts for 90% of kidney cancers and approximately 3% of all adult cancers. In England and Wales, kidney cancer is the eighth most common cancer in males and the 14th most common in females, making it nearly twice as common in men as in women. Kidney cancer most commonly affects adults aged 50–80 years.

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 2004, 5745 cases of newly diagnosed kidney cancer were registered in England and Wales. The incidence begins to rise over the age of 40 and is highest in those over 65.

The most common histological types of RCC are clear cell carcinoma, also known as conventional or non-papillary RCC (approximately 75% of cases), and non-clear cell carcinoma; type I papillary RCC, type II papillary RCC and chromophobe RCC. Clear cell carcinoma produces vascular endothelial growth factor (VEGF) and spreads early. Staging of RCC uses the American Joint Cancer Committee (AJCC) Tumour-Node-Metastasis (TNM system). This staging system is based on the combination of tumour size and extent of spread from the kidneys. TNM classifications are combined to produce stages I–IV and describe a patient's overall disease stage. This appraisal is concerned with advanced and metastatic RCC (stage III and IV). Stage III denotes disease that is locally advanced and/or has spread to regional lymph nodes. There are several combinations of T and N categories included in this stage. Stage IV includes several combinations of T, N and M and denotes that metastasis has occurred.

The most common presenting symptoms of advanced RCC are blood in the urine (haematuria), a palpable mass in the flank or abdomen and abdominal pain. Other non-specific symptoms include fever, night sweats, malaise and weight loss. Approximately 25% of patients present with advanced and/or metastatic disease, representing around 1400 new patients per year. An estimated 50% of patients who have curative resection for earlier stages will develop recurrent and/or metastatic disease. Without treatment, these patients have a median survival of only 6–12 months and a 2-year survival rate of 10–20%.

The prognosis following the diagnosis of metastatic disease is poor and only about 10% of people diagnosed with stage IV RCC live for 5 years after initial diagnosis. Anatomical, histological, clinical and molecular factors all influence the prognosis in patients with RCC.

1.2 Current management

There are currently no treatments that can reliably be expected to cure advanced and/or metastatic RCC. The primary objectives of medical intervention are therefore relief of physical symptoms and maintenance of

function. Surgery is the principle potentially curative therapeutic approach for the treatment of RCC. However, the success of surgery depends on the stage of disease. The standard approach is radical nephrectomy, which includes removal of the entire kidney together with Gerota's fascia (a sheath of fibrous tissue). Removal of the ipsilateral adrenal gland and regional lymph nodes may also be necessary. Radical or partial nephrectomy may be performed in patients with metastatic disease. When metastasis is limited, surgery may have some success.

Metastatic RCC is largely resistant to chemotherapy, radiotherapy and hormonal therapy. Chemotherapy alone is not considered effective in patients with metastatic RCC, with the most extensively studied agents, floxuridine and fluorouracil, giving response rates ranging from 0 to 20%. Vinblastine and hormonal agents such as medroxyprogesterone acetate (MPA) have produced similarly disappointing results, as have combinations of chemotherapy and immunotherapy.

The cytokine interferon alfa-2a (IFN-α) is the most commonly used immunotherapy in England and Wales. However improvements in median survival have not been observed for patients with advanced RCC receiving IFN-α. The combination of IFN-α and nephrectomy has been shown to be superior, in terms of median survival, to IFN-α alone in patients with metastatic RCC. In the USA, the preferred option for immunotherapy of advanced and/or metastatic RCC is high-dose interleukin-2 (IL-2). The toxicity of IL-2 is substantially higher than that of IFN-α. Moreover, high-dose IL-2 treatment requires administration on an inpatient basis with intensive supportive care. Commonly experienced adverse effects of both IFN-α and IL-2 include flu-like symptoms, tiredness and depression.

The NICE cancer service guideline (2002) 'Improving outcomes in urological cancers' recommends that all patients with large tumours who are fit to undergo surgery should be offered a radical nephrectomy. Patients with small tumours should be considered for nephron-sparing surgery. Surgery is often the only treatment needed for localised disease. Immunotherapy should be available for patients with metastatic disease. As there is no standard

treatment for patients with metastatic RCC who do not respond to first-line immunotherapy, their condition should be managed by either local cancer teams or specialist centres. Radiotherapy is recommended for selected symptomatic patients with non-resectable brain or osseous lesions who do not respond to other conservative treatments.

2 The technologies

Table 1. Summary description of technologies

Non-proprietary name	Bevacizumab	Sorafenib	Sunitinib	Temsirolimus
Proprietary name	Avastin	Nexavar	Sutent	Torisel
Manufacturer	Roche Pharmaceuticals	Bayer/Onyx	Pfizer	Wyeth
Dose	10 mg/kg given once every 2 weeks plus IFN-α 9MU 3 times weekly	400 mg twice daily	50 mg daily for 4 weeks, followed by 2-week rest period	25 mg once per week
Acquisition cost (BNF edition 55)	£924.40 per 400 mg bevacizumab plus £45,19 per 9MU, IFN-α.	£2,504.06 per 200 mg 112–tablet pack	£3,363 per 30-capsule 50-mg pack	Not currently listed in BNF[a]
Cost per day	£151.42 per day (combination of bevacizumab plus IFN-α) for an 80-kg patient, exclusive of administration costs	£89.45 per day	£74.74 per day	
a The Assessment Group have assumed £618 for 30mg based on imputation from Wyeth's submission, stating £515 for 25mg and vials only produced as 30mg. [redacted]				

Bevacizumab

Bevacizumab (table 1) is a recombinant humanised IgG1 antibody that inhibits tumour growth by blocking the formation of new tumour blood vessels induced by human vascular endothelial growth factor (VEGF). It has UK marketing

authorisation for first-line therapy in combination with IFN-α in patients with advanced and/or metastatic RCC. It has EU orphan drug status.

Bevacizumab is administered as an intravenous infusion. The recommended dosage for advanced and/or metastatic RCC is 10 mg/kg body weight once every 2 weeks. IFN-α is administered by subcutaneous injection three times per week, typically at a dose of 9–10 MIU and can be self-administered by patients.

Sorafenib

Sorafenib (table 1) is a multikinase inihibitor which inhibits the development of tumour blood vessels and tumour cell proliferation. It has a dual action, inhibiting the raf cascade, and VEGF/platelet-derived growth factor (PDGF) receptors on tumour cells, vascular endothelial cells and pericytes.

Sorafenib has UK marketing authorisation for the treatment of patients with advanced RCC whose condition has failed to respond to IFN-α or IL-2 therapy or who are considered unsuitable for such therapy. It has EU orphan drug status. It is taken orally. The recommended dosage is 400 mg twice daily, either 1 hour before or 2 hours after food.

Sunitinib

Sunitinib (table 1) is a multitargeted inhibitor of a group of closely related tyrosine kinase receptors. It inhibits VEGF/PDGF receptors on cancer cells, vascular endothelial cells and pericytes, inhibiting proliferation of tumour cells and development of tumour vasculature.

Sunitinib has UK marketing authorisation for the treatment of patients with advanced and/or metastatic RCC. It has EU orphan drug status. It is taken orally. The recommended dosage is 50 mg once daily for four consecutive weeks with a 2-week rest period (that is, a complete treatment cycle of 6 weeks). The dosage can be modified according to tolerability, but the total daily dose should not exceed 50 mg or decrease below 25 mg.

Temsirolimus

Temsirolimus (table 1) is a selective inhibitor of the mammalian target of rapamycin (mTOR), a serine threonine kinase that regulates a signalling cascade controlling growth factor-induced cell proliferation. Temsirolimus inhibits mTOR-dependent protein translation induced by growth factor stimulation. Tumour growth may also be affected indirectly by the inhibition of other factors such as VEGF.

Temsirolimus has UK marketing authorisation for the first-line treatment of patients with advanced RCC who have at least three of the six following prognostic risk factors:

- less than 1 year from time of initial RCC diagnosis to randomisation or initiation of treatment
- Karnofsky performance status of 60–70
- haemoglobin less than the lower limit of normal
- corrected calcium of greater than 10 mg/dl
- lactate dehydrogenase more than 1.5 times the upper limit of normal
- more than one metastatic organ site.

Temsirolimus has EU orphan drug status. Temsirolimus is administered by intravenous infusion. The recommended dosage is 25 mg over a 30- to 60-minute period once weekly. Pre-medication with intravenous antihistamine is recommended to minimise allergic reactions.

Table 2 Possible treatment options for renal cell carcinoma

	Bevacizumab plus IFN-α	**Sorafenib**	**Sunitinib**	**Temsirolimus**
First-line (suitable for immunotherapy)	√		√	
First-line (not suitable for immunotherapy)		√	√	
First-line, poor prognosis (suitable for immunotherapy)	√		√	√

First-line, poor prognosis (not suitable for immunotherapy)		√	√	√
Second-line (failed immunotherapy)		√	√	

3 The evidence

The Assessment Group reviewed the clinical effectiveness of the 4 technologies in accordance with their UK marketing authorisations (see table 2). Technologies were compared with current standard treatment; suitability for immunotherapy was defined in terms of contraindication to treatment and trial definitions of best supportive care were used (including placebo). Eight clinical trials reported in 13 publications were identified by the Assessment Group, which informed the following comparisons:

First-line treatment in patients suitable for immunotherapy:

- bevacizumab plus IFN-α compared with IFN-α alone
- sunitinib compared with IFN-α.

First-line treatment in patients with three out of six prognostic risk factors:

- bevacizumab plus IFN-α compared with IFN-α
- temsirolimus compared with IFN-α

Second-line treatment in patients who have failed immunotherapy:

- sorafenib compared with best supportive care
- sunitinib compared with best supportive care.

The Assessment Group conducted indirect comparisons where appropriate and meta-analyses are presented accordingly.

Table 3 Evidence identified by the Assessment Group for treatment options for renal cell carcinoma

	Bevacizumab plus IFN-α	Sorafenib	Sunitinib	Temsirolimus
First-line (suitable for immunotherapy)	AVOREN (Escudier et al 2007) CALGB (Rini et al 2008)		A6181034 (Motzer et al 2007)	
First-line (not suitable for immunotherapy)		X	X	
First-line, poor prognosis (suitable for immunotherapy)	AVOREN (Escudier et al 2007) (subgroup data presented separately)		X (Subgroup data from A16181034 not presented separately)	Global ARCC (Hudes et al 2007)
First-line, poor prognosis (not suitable for immunotherapy)		X	X	X
Second-line (failed immunotherapy)		TARGET (Escudier et al 2007) RDT (Ratain et al 2006)	2 single arm studies (Motzer et al 2006a,b)	

The Assessment Group was unable to identify any suitable data on clinical effectiveness in the following areas:

- For first-line treatment in patients unsuitable for treatment with immunotherapy, no suitable data on sunitinib or best supportive care were identified. Sub-group data from a trial for sorafenib were identified but was not considered further.

- In patients with poor prognosis, no data on sorafenib were identified and for sunitinib the sub-group data were not reported separately.

- No randomised clinical trials of sunitinib as second-line therapy were identified

- No randomised clinical trials of any of the interventions in comparison to IL-2

3.1 Clinical effectiveness

3.1.1 First-line treatment (patients suitable for immunotherapy)

Bevacizumab plus IFN-α

The Assessment Group identified one published RCT (AVOREN published by Escudier et al), that investigated the clinical effectiveness of bevacizumab plus IFN-α compared with IFN-α alone. The AVOREN trial was an international, double blind, placebo controlled phase III RCT, including 649 patients stratified by condition type, Karnofsky performance and Memorial Sloan-Kettering Cancer Centre (MSKCC) risk groups. Patients were required to have undergone nephrectomy or partial nephrectomy, but were otherwise untreated with systemic therapy. For further details of the patient characteristics in the trial see table 10, pages 49 in the assessment report.

The analysis was performed on an intention-to-treat (ITT) basis. The median duration of bevacizumab therapy was 9.7 months (range 0–24.4 months), and median duration of placebo treatment was 5.1 months (range 0–24 months) in the control group. The median duration of IFN-α treatment was 7.8 months (range 0–13.9 months) in the bevacizumab plus IFN-α arm and 4.6 months (range 0.2–12.6 months) in the control arm. The main results of this trial are presented in table 4.

Table 4 Main results from AVOREN study

Health Outcomes	Results (Bevacizumab plus IFN-α versus placebo plus IFN-α)
Median Overall Survival	Not reached (at time of data cut-off) versus 19.8 months HR 0.79 (95% CI 0.62-1.02) , p=0.0670 Analysis of overall survival, stratified according to baseline MSKCC for risk groups: Favourable prognosis sub-group HR 0.69 (95% CI 0.36 – 1.33) Intermediate prognosis sub-group HR 0.74 (95% CI 0.53 – 1.02) Poor prognosis sub-group HR 0.87 (95% CI 0.48 – 1.56)
Median Progression free survival	10.2 months versus 5.4 months HR 0.63 (95% CI 0.52-0.75), p<.0001 Favourable prognosis sub-group (MSKCC) 12.9 months versus 7.6 months HR 0.6, p=0.004 Intermediate prognosis sub-group (MSKCC) 10.2 months versus 4.5 months HR 0.55 p<0.0001 Poor prognosis sub-group (MSKCC) 2.1 months versus 2.2 months, HR 0.81, p=0.457
Tumour response	Overall: 31(96) versus 13(37) (p=0.0001) Complete: 1(4) versus 2(6) Partial: 30(92) versus 11(31)

rate % (n)	

Another RCT, CALGB by Rini et al, assessed the clinical effectiveness of bevacizumab plus IFN-α compared to IFN-α alone, but the results of this study were available in abstract format only. Median time to progression was 8.5 months in patients receiving bevacizumab plus IFN-α and 5.2 months in the group receiving IFN-α alone. The stratified estimate of the hazard ratio was 0.71 (95% CI 0.61 – 0.83, p<0.0001)

The AVOREN trial was conducted predominantly in patients with clear cell carcinoma, with risk factors suggestive of a favourable or intermediate prognosis, who had undergone a previous nephrectomy. The Assessment Group stated that it is not clear whether the results can be extrapolated to other groups of patients with RCC.

The mean numbers of patients with grade 3 or worse adverse effects (AE) were 1.3 and 0.9 in the intervention and control group respectively in the AVOREN trial. For further details on AEs of bevacizumab plus IFN-α, see table 17, pages 61-62 in the assessment report. Twenty eight percent of the patients in the intervention group and 12% in the control group had to discontinue due to AEs. proteinuria, hypertension and gastrointestinal perforation were the most common reasons. Adverse event related deaths were reported in 2% patients who received bevacizumab and 2% patients who were in the control group. Three of the deaths in patients who received bevacizumab (two bleeding events and one gastrointestinal perforation) were believed to be possibly related to bevacizumab.

Health related quality of life was not reported in this trial.

Sunitinib

The Assessment Group identified one RCT A16181034 published by Motzer et al 2007 which assessed the efficacy of first-line treatment with sunitinib compared with IFN-α in the treatment of metastatic RCC in 750 patients. This trial was an international multicentre phase III RCT. Patients were stratified

according to levels of lactate dehydrogenase, ECOG performance status and previous nephrectomy. For further details of patient characteristics in the trial see table 10, page 49 in the assessment report.

The median duration of treatment was 6 months (range 1–15 months) in the sunitinib group and 4 months (range 1–13 months) in the IFN-α group. The main results of this trial are presented in table 5.

Table 5 Main results from the Motzer et al 2007 study

Health Outcomes	Results (Sunitinib versus IFN-α)
Median Overall Survival	Not reached in either group (at the time of analysis), HR 0.65 (95% CI 0.45-0.94), p=0.02 (the comparison did not meet the pre-specified level of significance for the interim analysis).
Median Progression free survival	Interim pre-specified analysis 11 months versus 5 months HR 0.42 (95% CI 0.32-0.54), p<0.001 based on investigator assessment. 11 months versus 5 months: Hazard Ratio 0.42 (95% CI 0.32-0.54) based on independent radiographic assessment. Unplanned updated analysis 10.8 months versus 4.1months HR 0.52 (95% CI 0.43-0.62) based on investigator assessment 11 months versus 5.1 months HR 0.54 (95% CI 0.44-0.66) based on independent radiographic assessment
Tumour response rate % (n)	Overall: 31(103) versus 6(20) p<.001 Complete: 0 versus 0 Partial: 31(103) versus 6(20)

The majority of patients in the study had clear cell carcinoma and had a favorable or intermediate prognosis and had undergone previous nephrectomy. The Assessment Group stated that it is not clear whether the results can be extrapolated to other groups of patients with RCC.

This study also allowed for a small subgroup analysis between people who had undergone surgical resection of the primary tumour compared with those who have not. A small proportion of patients who had not had a previous nephrectomy were included; 9% in the sunitinib arm and 11% in the IFN-α one. The results suggest that sunitinib is relatively more effective than IFN-α in patients who have undergone a previous nephrectomy than those who have not, HR= 0.38 (95% CI 0.3-0.53) However, the results for the no nephrectomy group were not statistically significant. In addition, the 95% CI for people who

have undergone surgery overlaps with the 95% CI for people who have not undergone surgery, suggesting that this distinction might not be appropriate.

The most commonly reported grade 3 and 4 AEs associated with sunitinib were elevated lipase (16%), lymphopenia (12%), neuropenia (12%), hypertension (8%), fatigue (7%) and thrombocytopenia (8%). It has been suggested that 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.

In relation to health related quality of life, the overall results were all significantly better for patients in the sunitinib group than in the IFN-α group ($p<0.001$).

Indirect comparison between bevacizumab plus IFN-α and sunitinib

The Assessment Group and the manufacturer of sunitinib (Pfizer) concluded that the two studies (AVOREN and Motzer et al, 2007) were suitable for an adjusted indirect comparison between bevacizumab plus IFN-α and sunitinib. Table 15, page 56 of the assessment report shows the summary of study and patient characteristics for the indirect comparison.

The results of the adjusted indirect analysis are presented in table 6. Progression-free survival may be superior with sunitinib compared with bevacizumab plus IFN-α. A similar result was seen for overall survival, but the estimated effect is more marginal and as the confidence intervals cross unity, the result would not be considered statistically significant.

Table 6 Indirect comparison between sunitinib and bevacizumab plus IFN-α

Indirect comparison	HR[a] for OS[b] (95% CI)	HR for PFS[c] (95% CI)
Assessment Group	0.82 (0.53 to 1.28)	0.67 (0.50 to 0.89)
Pfizer	Not reported (Not reported)	0.66 (0.49 to 0.90); (using data from Motzer et al. 2007) 0.80 (0.62 to 1.04) (using updated data from the Motzer

		et al ASCO 2007 study)
[a] HR, hazard ratio; [b] OS, overall survival; [c] PFS, progression-free survival.		

The manufacturer of bevacizumab has contrasted the outcomes of the AVOREN study with those from Motzer 2007 (study A6181034 in manufacturer's submission) which compared sunitinib with IFN-α. However, no meta-analysis was undertaken for adjustment of the results. The Assessment Group state that in general the manufacturer of bevacizumab has concluded that the efficacy of bevacizumab plus IFN-α is comparable to the efficacy of sunitinib as monotherapy in the first-line treatment of metastatic RCC. However, sunitinib monotherapy appeared to be associated with more treatment-related adverse events than bevacizumab plus IFN-α, with the latter combination being better tolerated, with fewer and less severe adverse events.

3.1.2 First-line treatment (suitable for immunotherapy) for patients with at least three of six prognostic factors

Temsirolimus

The Assessment Group identified only one RCT (Global ARCC) by Hudes et al that examined the clinical effectiveness of temsirolimus as monotherapy and in combination with IFN-α. This trial is an international, multicentre, three-way parallel group, randomised phase III trial in which 626 people with previously untreated metastatic RCC and poor prognosis received either temsirolimus alone or in combination with IFN-α. The comparator therapy was IFN-α. Patients were stratified according to the geographic location of the centre and whether they had undergone previous nephrectomy. The key patient characteristics of this trial are reported in table 19, pages 69 of the assessment report.

Median treatment duration of temsirolimus was 3.92 months (range 0.23–29.08 months) in the temsirolimus monotherapy group and 3.46 months (range 0.23–31.85 months) in the group receiving combination treatment. For IFN-α, the respective figures were 1.85 months (range 0.23–28.62 months) in

the IFN-α group and 2.77 months (range 0.23–31.85 months) in the combination group. The main results of this trial are presented in table 7.

Table 7 Main results of the Global ARCC trial

Health Outcomes		Results (Temsirolimus (plus IFN-α) versus IFN-α)
Median Overall Survival	**Interim analysis**	10.9 (95% CI 8.6 – 12.7 montths) months versus 7.3 (95% CI 6.1 – 8.8 months) HR 0.73 (95% CI 0.58 – 0.92), p=0.008
	Final analysis	10.9 (95% CI 8.6 to 12.7 months) months versus 7.3 (95% CI 6.1 – 8.8 months) HR 0.78 (95% CI 0.63 – 0.97), p=0.0252
Median Progression free survival	**Interim analysis**	Site investigators assessment: 3.8 (95% CI 3.6 – 5.2) months versus 1.9 (95% CI 1.9 – 2.2) months, (HR - Not reported) Independent blinded review: 5.5 months (95% CI 3.9 – 7.0 months) months versus 3.1 months (95% CI 2.2 – 3.8 months), (HR – not reported)
	Final analysis	Site investigators assessment: 3.8 (95% CI not reported) months versus 1.9 (95% CI 1.9 – 2.2) months HR 0.74 (95% CI 0.6 – 0.9, p=0.0028) Independent assessment: 5.6 months (95% CI 3.9 – 7.2 months) months versus 3.2 months (95% CI 2.2 – 4.0 months) HR 0.74 (95% CI 0.6 – 0.91, p=0.0042)
(Objective) tumour response rate %		8.6% (95% CI 4.8 to 12.4%) versus 4.8% (95% CI 1.9% – 7.8%)

Results from a subgroup analysis from the Hudes et al trial on people with clear cell RCC compared with those with non-clear cell RCC, and people who have undergone surgical resection of the primary tumour compared with those who have not, suggested that temsirolimus was more effective than IFN-α in all these subgroups (table 8).

Table 8 Subgroup analyses in people with poor prognosis receiving temsirolimus

Comparison	Temsirolimus versus IFN-α	
	HR[a] for OS[b] (95% CI)	**HR[a] for PFS[c] (95% CI)**
Clear cell	0.85 (0.64 to 1.06)	0.84 (0.67 to 1.05)
Non clear cell	0.55 (0.33 to 0.90)	0.36 (0.22 to 0.59)
Prior nephrectomy	0.84 (0.65 to 1.12)	0.72 (0.55 to 0.93)
No prior nephrectomy	0.62 (0.42 to 0.93)	0.62 (0.43 to 0.88)

[a] HR, hazard ratio; [b] OS, Overall Survival ; [c]PFS, progression-free survival.

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 of temsirolimus were anaemia (20%), fatigue/asthenia (11%), hyperglycaemia (11%) and dyspnoea (9%).

Health related quality of life outcomes were not reported in the full-text paper. Summary of EQ-5D scores for people with poor prognosis treated with temsirolimus versus IFN-A, as reported in a subsequent conference abstract in 2007, were i) 0.689 at baseline, ii) 0.587 on progression, iii) 0.585 during a grade 3 or 4 adverse event, and iv) 0.689 during stable disease (obtained at weeks 12 and 32 of treatment).

Comparison of temsirolimus with bevacizumab plus IFN A, sunitinib and sorafenib for poor prognostic patients (suitable for immunotherapy)

In the bevacizumab study by Escudier et al, 9% of patients who received bevacizumab plus IFN-α and 7% of the patients receiving IFN-α had three or more MSKCC risk factors for poor prognosis. Median progression-free survival in this patient group was not significantly different in the intervention and control groups, with 2.2 months for those receiving bevacizumab plus IFN-α and 2.1 months for those treated with IFN-α (HR = 0.81, 95% CI 0.46 to 1.42).

In the paper by Motzer et al (2007) six percent of the patients receiving sunitinib and 7% of patients on IFN-α had three or more MSKCC risk factors and were therefore classified as having poor prognosis however data were not presented separately for this subgroup.

In order to determine whether an indirect comparison of bevacizumab plus IFN-α, sunitinib and temsirolimus was valid, the Assessment Group examined the internal validity and similarity of the three trials, see table 23 on page 75 of

the assessment report. Participants in all three trials were similar in age and gender distribution, and were all undergoing first-line treatment for RCC. However, there were some important differences between the patient populations in terms of disease status, definitions of poor prognosis (if the MSKCC were applied to the patients in the temsirolimus trial, 25% of the temsirolimus patients would have been classed as intermediate and not poor prognosis), dose of IFN-α used, dose intensity of IFN-α received, and the treatment duration and response to IFN-α in the comparator arms. Therefore, they concluded that there were sufficient differences between trials to render an indirect comparison between interventions inappropriate.

3.1.3 First line treatment (patients unsuitable for immunotherapy)

Sorafenib

The Assessment Group was unable to locate any full published reports of RCTs of sorafenib and sunitinib as first-line treatment in people with advanced and/or metastatic RCC who are unsuitable for immunotherapy. The manufacturer of sorafenib, in its submission to NICE, has presented data for two subgroups of patients. One of these consists of patients who are unsuitable for immunotherapy. The analyses were presented as commercial in confidence. Results showed that

[redacted] However, the Assessment Group raised serious concerns with regards to the quality of these analyses (see page 85 in the assessment report), and decided not to consider these data further.

3.1.4 Second-line treatment

Sunitinib

The Assessment Group identified two similar open-label, single-arm trials of sunitinib as second-line therapy in patients with metastatic clear cell RCC whose condition has failed to respond to treatment with cytokine-based immunotherapy both by Motzer et al. The key features of the patient characteristics of these trials can be found in table 29 on pages 87–88 of the

assessment report. Both trials were carried out in multiple centres in the USA. The sample sizes of the trials were 63 and 106, respectively.

As the Assessment Group state due to a lack of comparators, interpretation of the following results from these trials is difficult. The main results are presented in table 9.

Table 9 Main results of Motzer et al (2006 a,b)

Study		Sunitinib
Motzer et al. 2006a	**Median overall survival**	16.4 months (95% CI 10.8 to not yet attained)
	Median progression free survival	8.7 months (95% CI 5.5 to 10.7)
	Tumour response n (%)	***Complete response*** - 0 ***Partial response*** - 25 (40) ***Stable response*** - 17 (27) ***Progressive disease*** - 21 (33) patients had either progressive disease, stable disease for less than three months or were not assessable
Motzer et al. 2006b	**Median overall survival**	23.9 months (95% CI 14.1 to 30.7)
	Median progression free survival	8.8 months (95% CI 7.8 to 13.5)
	Tumour response n (%)	***Complete response*** - 0 ***Partial response*** - 36 (34) ***Stable response*** - 30 (29) ***Progressive disease*** - 39 (29) patients had either progressive disease, stable disease for less than three months or were not assessable

No sub-group data were reported.

Health-related quality of life was assessed using the EQ–5D and the FACIT–fatigue tool. Mean and median baseline scores for the study population were 40.4 and 44, respectively, which is similar to scores for a population with cancer but without anaemia (40 and 42, respectively). 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.

Sorafenib

The Assessment Group identified two trials (TARGET and RDT) that investigated the efficacy of sorafenib as a second-line treatment in patients with advanced and/or metastatic RCC whose condition failed to respond to treatment with cytokine-based immunotherapy. The key features of the trials are presented in table 29 on pages 87–88 of the assessment report. The TARGET study was an international, multicentre, double blind and placebo-controlled phase III RCT of 903 patients with histologically confirmed metastatic clear cell RCC, who had progressed after one systemic treatment within the previous 8 months. Patients were stratified at baseline according to demographic factors and disease status. The median duration of treatment was 23 weeks in the sorafenib group and 12 weeks in the placebo group.

The RDT trial was an international, multicentre, retrospective, phase II randomised discontinuation trial of sorafenib versus placebo in 202 patients with metastatic clear cell RCC. Patients had been previously treated with cytokine-based therapy, radiotherapy or nephrectomy. Patients were stratified at baseline according to demographic factors and disease status.

Table 10 Main results of the TARGET trial

Health Outcomes	Results (sorafenib versus placebo)
Median Overall Survival (interim analysis)	Not reached versus 14.7 months HR 0.72 (95% CI 0.54 to 0.94) , p=0.02
Median Progression free survival	1st planned interim analysis 5.5 months versus 2.8 months HR 0.44 (95% CI 0.35 to 0.55) , p<0.001 assessment by independent radiologists 5.9 months versus 2.8 months p<0.001 (HR not reported) assessment by investigators Unplanned analysis prior to crossover 5.5 months versus 2.8 months HR 0.51 (95% CI 0.43 to 0.6), p<0.001assessment by investigators 5.5 months versus 2.8 months HR 0.51 (95% CI 0.43 to 0.6), p<0.001 assessment by investigators
Tumour response n (%)	**Complete response** - 1(<1) versus 0 (p<0.001) **Partial response** - 43 (10) versus 8 (2) (p<0.001) **Stable disease** - 333 (74) versus 239 (53) **Progressive disease** - 56 (12) versus 167 (37)

Results of the RDT trial showed that at 12 weeks post randomisation there was a statistically significant (p=0.0077) difference in the proportion of patient in whom disease progression was evident between groups (50% of patients treated with sorafenib versus 82% treated with placebo). Median progression free survival from the date of randomisation was also significantly longer in the sorafenib group (24 weeks versus 6 weeks, p=.0087). In this trial the most common grade 3 or 4 AE was hypertension (31% of patients). Nine patients discontinued treatment, as a result of unacceptable toxicity. There were no adverse event related deaths.

In relation to an indirect comparison of sorafenib versus sunitinib versus best supportive care, the Assessment Group concluded that although they 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, it was not possible to consider an indirect comparison of sorafenib, sunitinib and best supportive care.

From the data reported in these trials, 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). In a systematic review identified by the Assessment Group, 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%). In a different systematic review and meta-analysis identified by the Assessment Group, 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.

Health-related quality of life was assessed using two disease-specific tools (FACT–G and FKSI). There was no significant difference between the placebo and sorafenib groups in mean FACT–G physical well-being score or any numerical or statistical difference in mean FKSI–10 total score between

groups over the first 30 weeks of treatment. However, there were 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.

The Assessment Group concluded that according to the limited data available, second-line therapy with sorafenib appears to have clinically relevant and statistically significant advantages over treatment with placebo. However, given the specified patients' disease status in these trials, it is unclear whether results can be extrapolated to other patient groups.

3.1.5 Summary of clinical effectiveness

First-line treatment

From the limited clinical data available, treatment with the combination of bevacizumab plus IFN-α and sunitinib as monotherapy appears to have clinically relevant and statistically significant advantages over treatment with IFN-α alone in terms of progression-free survival and tumour response. Although promising, data on overall survival from these trials are premature. The results from the indirect comparison of bevacizumab plus IFN-α and sunitinib as monotherapy suggested that, in terms of progression-free survival, sunitinib may be superior to bevacizumab plus IFN-α.

Treatment with temsirolimus appears to have clinically relevant and statistically significant advantages over treatment with IFN-α in people with poor prognosis, in terms of overall survival, progression-free survival and tumour response. Data on patients with and without clear cell carcinoma and prior nephrectomy suggest that temsirolimus is more effective than IFN-α in all these subgroups. Whether the results are sufficiently different from each other to suggest that people in these subgroups respond differently to temsirolimus is not clear.

Second-line treatment

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. The results from the two single-arm phase II trials investigating sunitinib as second-line therapy were difficult to interpret or extrapolate. The Assessment Group has suggested that using the placebo arm of the sorafenib trial as an informal comparator suggests that sunitinib may be efficacious in this population.

3.2 Cost effectiveness

The Assessment Group's literature search did not yield any published cost-effectiveness studies of bevacizumab, sorafenib, sunitinib and temsirolimus, which met the inclusion criteria of the protocol. Six study abstracts were found; three of which compared sunitinib with best supportive care and three which compared sorafenib with best supportive care. None of the abstracts gave sufficient detail for critical appraisal of the study methods.

The four manufacturers submitted cost-effectiveness models. The Assessment Group developed their own economic model and critiqued the de novo models submitted by the manufacturers.

3.2.1 Manufacturer submissions

All of the models aimed to consider the cost effectiveness of the technologies from an NHS perspective. All were Markov models, and had three health states: progression-free survival (PFS), progressive disease (PD) and death. Parameter uncertainty was addressed using probabilistic sensitivity analysis (PSA) and a range of one-way sensitivity analyses in all models. All costs and benefits were discounted at a rate of 3.5% per annum.

Pfizer model – sunitinib

The Pfizer economic evaluation compared the use of sunitinib with IFN-α in a first-line treatment model and sunitinib with best supportive care in a second-line treatment model. Cost-effectiveness estimates of bevacizumab plus IFN-α compared with IFN-α alone (first-line treatment) and sorafenib compared with best supportive care (second-line treatment) are also presented, but for comparative purposes only (see appendix 6, page 235 and page 239 in the assessment report for further details). In all their analyses, a pricing strategy

of the first cycle of sunitinib being free of charge to the NHS has been applied, but it should be noted that this has not been confirmed by the Department of Health as being standard practice in England and Wales.

In the first-line treatment model (sunitinib versus IFN-α), patient-level data from a phase III trial (Motzer 2007) were incorporated. In this trial, patients were not able to switch treatments and following progression patients received best supportive care. The trial had a 2-year follow-up period. Survival modelling techniques were used to extrapolate trial data beyond the follow-up period. Weibull survival curves were fitted to the trial data to model progression free survival and overall survival for baseline disease progression (IFN-α alone) for 10 years in the base-case analysis. The manufacturer stated that the survival curve does not fit the empirical data well after 6 months. Relative measures of treatment effectiveness (hazard ratios) for sunitinib were then used to extrapolate progression free survival and overall survival curves for sunitinib treatment.

Two base-case analyses were presented: using pre-planned interim analysis data (13 months) and unplanned updated analysis data (25 months). The unplanned analysis was included for completeness and contained crossover between treatment arms. The health state utilities used are taken from EQ–5D data collected in the Motzer 2007 RCT, but not reported in the published results, with different utility values assigned according to treatment and health state: sunitinib/PFS = 0.77; IFN-α /PFS = 0.79; sunitinib/PD = 0.72; IFN-α /PD = 0.69. The resource use data cover costs for drug acquisition, drug administration costs, medical management, an allowance for the mean cost of differences in expected adverse events, and costs associated with ongoing best supportive care. Drug costs are adjusted according to RCT data on dose intensity; the first-line drug cost for sunitinib is weighted by 86.4%.

The comparison of sunitinib with IFN-α produced an incremental cost-effectiveness ratio (ICER) of £28,546 per quality-adjusted life year (QALY) gained in the first base case and £33,241 per incremental QALY gained in the second base case. The one-way sensitivity analyses demonstrated that, for both base cases, the ICERs were most sensitive to the extrapolation method

and choice of utility value for progressed disease, increasing the ICERs to between £31,207 and £40,536 (first base case) and £36,019 to £43,797 (second base case) when using the lower and upper confidence limits of each parameter. Further details of the sensitivity analyses can be found on table 35, page 111 of the assessment report. The PSA showed that at a willingness to pay threshold of £30,000 per QALY, sunitinib has a 54% (first base case) and 36% (second base case) probability of being cost effective compared with IFN-α as first-line treatment.

In the second-line treatment model, comparing sunitinib with best supportive care, effectiveness and utility data for sunitinib were incorporated from a phase II, single-arm study. 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. For sunitinib, the data are from a phase II single arm trial (Motzer 2006). For best supportive care, the submission used a pooled analysis of data from review (Motzer 2004) and Medicare data. In the sunitinib treatment arm, patients took sunitinib until progression and then switched to best supportive care. In the comparator arm, patients received best supportive care throughout. The health state utilities used are taken from EQ–5D data collected in the phase II trial (Motzer 2006), with different utility values assigned according to treatment and health state: sunitinib/PFS = 0.803; best supportive care/PFS = 0.758; sunitinib/PD and best supportive care/PD = 0.683.

The comparison of sunitinib with best supportive care produced an ICER of £37,519 per QALY gained in the base case. The one-way sensitivity analyses demonstrated that the ICER was most sensitive to health state utility values assigned to PFS and PD health states and the extrapolation choice of the OS and PFS curve and data source (see appendix 6, page 238 in the assessment report for further details). The PSA showed that at a willingness to pay threshold of £30,000 per QALY, sunitinib has a 36% probability of being cost effective compared with best supportive care as second-line treatment.

Roche model – bevacizumab

The Roche economic evaluation compared the use of bevacizumab plus IFN-α with IFN-α alone as a first-line treatment. In all analyses, a 'dose-cap' scheme was applied (whereby bevacizumab is free to the NHS once 10,000 mg has been purchased for an individual patient within a year of treatment initiation). However, it should be noted that this pricing strategy has not been confirmed by the Department of Health as standard practice in England and Wales.

In the model, patient-level data from the phase III RCT (Escudier et al) were incorporated. The model assumed that patients received bevacizumab plus IFN-α or IFN-α alone until disease progression, although IFN-α use was limited to 1 year in both treatment arms, as in the RCT. Following disease progression, patients received best supportive care and were able to take second-line treatments, such as sunitinib and sorafenib.

Survival modelling techniques were used to extrapolate trial data beyond the follow-up period. Gompertz survival curves were chosen as best fits to the progression free survival and overall survival curves for IFN-α treatment and the progression free survival curve for bevacizumab plus IFN-α treatment. These curves were used to extrapolate the trial results to a lifetime horizon. Median overall survival for the bevacizumab plus IFN-α arm had not been reached in the trial, so the stratified overall survival hazard ratio for bevacizumab plus IFN-α from the safety population was applied to the baseline IFN-α survival data to estimate the overall survival for bevacizumab plus IFN-α.

The health state utilities used are taken from EQ–5D data collected in the Motzer 2007 RCT that compared sunitinib with IFN-α. The model used a utility value of 0.78 for PFS, and 0.705 for PD. These values were applied independent of treatment (values were derived by averaging the treatment-specific data reported in the Motzer 2007 RCT). The resource use data cover costs for drug acquisition, drug administration, medical management, adverse events, and costs associated with best supportive care of progressive disease. The costs of drug acquisition and administration are reduced according to the dose intensity data reported in the RCT. No drug wastage

was assumed. The dose intensity data are estimated as 62% for bevacizumab, 80% for IFN-α when used with bevacizumab and 63% for IFN-α alone.

The comparison of bevacizumab plus IFN-α with IFN-α alone produced an ICER of £74,999 per QALY gained in the base case. One-way sensitivity analyses are only used to explore the effects of alternative mathematical survival curves used in the extrapolation of trial results (see pages 120-1 of the assessment report for further details). The PSA reported that at a willingness to pay threshold of £30,000 per QALY, bevacizumab plus IFN-α has a 0% probability of being cost effective compared with IFN-α alone as a first-line treatment.

Wyeth model – temsirolimus

The Wyeth economic evaluation compared the use of temsirolimus with IFN-α as a first-line treatment for patients with at least three of six poor prognostic factors (see section 2, page 6 of the overview). An indirect comparison of temsirolimus with best supportive care was also presented using data from an RCT of IFN-α compared to best supportive care. In all analyses, the cost of temsirolimus was assumed to be £515 per 25 mg.

In the model, the progression-free survival health state is subdivided into three categories (sub-states) of complete/partial response, stable disease and progressive disease. The model uses survival analysis, employing clinical effectiveness data from a single RCT (Hudes et al) to model survival and disease progression over time. The approach uses Weibull regression models, applied to progression-free survival and overall survival data, to calculate the time-dependent state transition probabilities.

At the start of the model, patients are distributed across health states based on the RCT data. Modelling assumes that patients receive temsirolimus and IFN-α until disease progression, which is consistent with the RCT. In the post-progression health state, patients receive best supportive care and second-line drugs. Health state utilities were derived from the EQ–5D questionnaire collected during the RCT. The model used a utility of 0.658 for

complete/partial response, 0.600 for stable disease and 0.446 for progressive disease. Resource use data cover costs for drug acquisition, drug administration, medical management, adverse events, and best supportive care and second-line drugs in the post-progression health state. The costs of temsirolimus and IFN-α and the cost of administration of temsirolimus are reduced according to dose intensity data from the temsirolimus RCT. The dose intensities were estimated as 92% for temsirolimus and 56% for IFN-α. No drug wastage is assumed. Each drug administration of temsirolimus and IFN-α is assumed to cost the equivalent of one outpatient appointment.

The comparison of temsirolimus with IFN-α produced an ICER of £55,814 per QALY gained in the base case. The one-way sensitivity analyses demonstrated that the ICER was most sensitive to the drug-related treatment costs/assumptions (see appendix 6 pages 246–8 of the assessment report for further details). The PSA showed that at a willingness to pay threshold of £30,000 per QALY, temsirolimus has a 0% probability of being cost effective compared with IFN-α alone as a first-line treatment.

In subgroup analyses, the ICER for the patient subgroup with clear cell carcinoma was £57,731 per QALY, £51,159 for patients with non-clear cell carcinoma, £60,575 for patients with prior nephrectomy and £49,690 for patients without prior nephrectomy.

Bayer model – sorafenib

The Bayer economic evaluation compared the use of sorafenib with best supportive care as treatment according to the licensed indication of sorafenib. Analysis was presented according to the following subgroups: patients on second-line therapy, patients unsuitable for cytokines and a combination of the two subgroups. The cost-effectiveness of sorafenib compared with sunitinib as second-line treatment is also reported.

In the model, patient-level data from an RCT (Escudier et al) were applied to model survival and disease progression over time. For progression-free survival the trial data were used directly for both the sorafenib and best supportive care treatment arms. However, due to a short follow-up period, the

data for overall survival were immature and were extrapolated, using an exponential function, over time.

Modelling assumes patients receive sorafenib until disease progression, and that all patients start in the progression-free state as in the RCT. Following disease progression, patients receive best supportive care. The health state utilities used are 0.737 for PFS and 0.548 for the PD health state, both 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 costs for best supportive care after disease progression. There are no drug administration costs. Modelling assumes a dose intensity of 100% for sorafenib.

The comparison of sorafenib with best supportive care produced an ICER of £90,630 per QALY gained for the combined patient group in the base case. The subgroup analyses produce ICERs of [redacted] per QALY gained for patients receiving second-line therapy with sorafenib and [redacted] for those unsuitable for cytokine therapy. The PSA showed that at a willingness to pay threshold of £30,000 per QALY, sorafenib has a 0% probability of being cost effective compared with best supportive care.

For the indirect comparison of sorafenib versus sunitinib, the ICER was [redacted] per QALY gained. This analysis was presented for descriptive purposes only owing to the poor quality of the data (see page 128 and appendix 6, page 250 in the assessment report for further details).

3.2.2 The economic model from the Assessment Group

The Assessment Group developed estimates of the cost effectiveness of sunitinib, sorafenib, bevacizumab plus IFN-α and temsirolimus against relevant comparators within the licensed indications for each drug, and according to the scope. The Markov model considered three treatment strategy questions: first-line treatment; first-line treatment of patients with a poor prognosis and second-line treatment using similar model structures but with different model parameter data. The Assessment Group have not conducted a cost-effectiveness analysis for the treatment of patients who are

unsuitable for immunotherapy because they state that the clinical data are inadequate. The model used three distinct health states (progression-free survival, progressive disease and death), with all patients assumed to start in progression-free survival. A 10-year time horizon, 6-week model cycle and a half-cycle correction were applied to the model.

Effectiveness data

The model used survival analysis to consider progression of RCC over time. In this approach, the baseline progression of disease is modelled for each question using data from clinical trials, with treatment effect modelled using measures of relative treatment effect as reported in the relevant RCTs.

First-line treatment (patients suitable for immunotherapy): cost effectiveness of bevacizumab plus IFN-α and sunitinib compared with IFN-α alone.

Baseline disease progression (IFN-α alone) was taken from the RCT (Escudier et al) that compared bevacizumab plus IFN-α with IFN-α alone. Data for progression-free survival and overall survival for patients receiving IFN-α were read directly from reported Kaplan–Meier curves, and Weibull curves were then fitted for use in the model. The disease progression for bevacizumab plus IFN-α and sunitinib were estimated using the relevant relative treatment effect measures (hazard ratios):

Table 11: Treatment effect of bevacizumab plus IFN-α and sunitinib

	Hazard ratio for progression-free survival (95% CI)	Hazard ratio for overall survival (95% CI)
Bevacizumab plus IFN-α compared with IFN-α	0.63 (0.52 to 0.75)	0.75 (0.58 to 0.97)
Sunitinib compared with IFN-α	0.42 (0.33 to 0.52)	0.60 (0.45 to 0.94)
Sunitinib compared with bevacizumab plus IFN-α	0.67 (0.50 to 0.89)	0.82 (0.53 to 1.28)

The model also allows an indirect comparison of bevacizumab plus IFN-α, sunitinib and IFN-α alone, which was justified by the interchangeability of the key features of the relevant RCTs.

First-line treatment (patients suitable for immunotherapy with poor prognosis): cost effectiveness of temsirolimus compared with IFN-α

Baseline disease progression (IFN-α alone) for progression-free survival and overall survival was estimated by fitting Weibull curves to empirical Kaplan–Meier data from the RCT reported by Hudes et al. To model disease progression for those treated with temsirolimus, relative measures of clinical effectiveness (hazard ratios) of 0.74 (95% CI 0.60 to 0.91) for progression-free survival and 0.73 (95% CI 0.58 to 0.92) for overall survival were then applied.

No indirect comparisons were performed owing to the very small numbers of patients with poor prognosis receiving the other three technologies and major differences between the relevant RCTs. Data for temsirolimus were available for the following five subgroups: clear cell/non-clear cell carcinoma; prior nephrectomy/no prior nephrectomy and those patients having a poor prognosis according to the Motzer score (approximately 75% of patients in the Hudes RCT). Hazard ratios for these subgroups ranged from 0.36 to 0.84 for progression-free survival and 0.55 to 0.85 for overall survival.

Second-line treatment: cost effectiveness of sorafenib compared with best supportive care and sunitinib compared with best supportive care

Baseline disease progression was modelled by fitting Weibull curves to the empirical progression-free survival and overall survival curves from the best supportive care arm of the RCT by Escudier et al, which compared sorafenib with best supportive care. Disease progression for patients receiving sorafenib was estimated by applying the following hazard ratios from the RCT: 0.51 (95% CI 0.43 to 0.60) for progression-free survival and 0.72 (95% CI 0.54 to 0.94) for overall survival.

No subgroup analyses were presented in the Assessment Group model.

The cost effectiveness of sunitinib compared with best supportive care as a second-line treatment was not evaluated in the Assessment Group model because the data came from two single-arm trials and were considered inadequate by the Assessment Group.

Health state utilities

The health state utilities used in the Assessment Group model are derived from trial data and UK EQ–5D tariffs. In the model, patients are assumed to be similar at baseline in terms of health state value, and therefore treatment-specific health state values are not applied.

Table 12: Health state utilities

Question	Treatments	Health state	Base case (s.e.)[a]	Source
First-line (not poor prognosis)	IFN-α, sunitinib, bevacizumab plus IFN-α	Progression-free survival	0.78 (0.01)	Pfizer submission
		Progressive disease	0.70 (0.02)	
First-line (poor prognosis)	IFN-α, temsirolimus	Progression-free survival	0.60 (0.06[b])	Wyeth submission
		Progressive disease	0.45 (0.04[b])	
First-line (unsuitable for IFN-α) and second-line	Sorafenib, best supportive care	Progression-free survival	0.76 (0.03)	Pfizer submission
		Progressive disease	0.68 (0.04)	

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

Resource data

Additional costs associated with each of the drugs, drug administration costs and medical management costs when in progression-free survival (outpatient

monitoring, scans, tests, treatment of adverse events) were included in the model. Drug costs, except for sorafenib, were modified according to dose intensities reported in the RCTs. Current list prices taken from the 'British national formulary' (BNF edition 55) are used for drug pricing. All other costs are inflated to 2007–08 values. As temsirolimus had no BNF list price, the price of a 30-mg vial was imputed from the price of a 25-mg dose of temsirolimus as submitted by the manufacturer, and calculated as £618. The pricing strategies for bevacizumab and sunitinib, described by the manufacturers, were included in sensitivity analyses only.

Drug-related administration costs were estimated per cycle for IFN-α, bevacizumab plus IFN-α and temsirolimus as £112, £590 and £1179, respectively. It was assumed that 75% of IFN-α monotherapy was self-administered. There were no administration costs for best supportive care, sunitinib (oral) and sorafenib (oral). The cost of administering drugs was not adjusted according to dose intensity data.

When patients are in the progression-free survival health state and on drug treatment, additional resource uses associated with outpatient monitoring, scans and tests were used in the model. While in progression-free survival, medical management cost per cycle was £81 for best supportive care and £223 for all other drug treatments. In the progressive disease state cost for each cycle was £435 for all treatments. Costs associated with grade 3 or 4 vomiting, diarrhea and hypertension were also included.

Results

First-line treatment (patients suitable for immunotherapy)

In the comparison of sunitinib with bevacizumab plus IFN-α, sunitinib presents with additional benefits at lower cost and therefore dominates bevacizumab plus IFN-α.

Table 13: First-line treatments for patients suitable for immunotherapy base case results

	IFN-α monotherapy	Sunitinib	Bevacizumab plus IFN-α	Sunitinib versus IFN-α	Bevacizumab plus IFN-α versus IFN-α
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 administration costs	£491	£0	£5,554	-£491	£5,063
Cost of medical management[a]	£1,198	£2,832	£1,887	£1,635	£689
Cost of best supportive care in progressive disease	£3,798	£2,779	£3,766	-£1,019	-£31
Total costs	£8,438	£39,623	£53,873	£31,185	£45,435
ICERs					
Cost per life year gained				£58,647	£133,952
Cost/QALY				**£71,462**	**£171,301**

[a] Refers to monitoring, blood tests, CT scans and adverse events combined.

The deterministic sensitivity analyses demonstrated that estimates of treatment effectiveness, drug pricing (including dose intensity data) and health state utility input parameters were the key drivers affecting the ICERs. The ICERs for both drugs were particularly sensitive to variations in estimates of the hazard ratio for overall survival, with ICERs ranging from £39,759 (HR for overall survival = 0.45) to £263,363 (HR for overall survival = 0.94) for sunitinib compared with IFN-α and £90,693 (HR for overall survival = 0.58) to £868,881 (HR for overall survival = 0.97) for bevacizumab plus IFN-α compared with IFN-α alone (see pages 159–64 of the assessment report for further details).

According to PSA, at a willingness to pay threshold of £30,000, sunitinib and bevacizumab plus IFN-α have a 0% probability of being cost effective compared with IFN-α alone as first-line treatments.

First-line treatment (patients suitable for immunotherapy with poor prognosis)

Table 14: First-line treatment of patients suitable for immunotherapy with poor prognosis base case results

	IFN-α	Temsirolimus	Temsirolimus versus IFN-α
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 administration cost	£367	£6,215	£5,848
Cost of medical management	£729	£1,176	£447
Cost of best supportive care in progressive disease	£2,599	£3,422	£822
Total costs	£6,519	£28,791	£22,272
ICERs			
Cost per life year gained			£49,571
Cost/QALY			**£94,385**

In the subgroup analyses for temsirolimus (clear cell versus non-clear cell carcinoma, nephrectomy versus no nephrectomy and Motzer poor prognosis), the ICERs ranged from £74,184 to £154,334 per QALY gained. The only subgroup that demonstrated a lower ICER than the base case analysis was the subgroup with no prior nephrectomy, at £74,184 per QALY gained.

The deterministic sensitivity analyses demonstrated that estimates of treatment effectiveness, cost of acquisition and administration of temsirolimus, and health state utility input parameters were the key drivers affecting the

ICERs. The ICERs was particularly sensitive to variations in estimates of the hazard ratio for overall survival, with ICERs ranging from £56,452 (HR for overall survival = 0.58) to £253,443 (HR for overall survival = 0.92). See pages 172–74 of the assessment report for further details.

According to PSA, at a willingness to pay threshold of £30,000, temsirolimus has a 0% probability of being cost effective compared with IFN-α alone as first-line treatment for patients with poor prognosis.

Second-line treatment

Table 15: Second-line treatment base case results

	Best supportive care	Sorafenib	Sorafenib versus best supportive care
Life years	1.30	1.60	0.30
QALYs	0.91	1.15	0.23
Time on treatment (months)	NA	8.7	NA
Drug cost	£0	£23,058	£23,058
Drug administration cost	£0	£0	£0
Cost of medical management	£248	£1,380	£1,132
Cost of best supportive care in progressive disease	£3,549	£3,360	-£189
Total costs	£3,797	£27,797	£24,001
ICERs			
Cost per life year gained			£78,960
Cost/QALY			**£102,498**

The deterministic sensitivity analyses demonstrated that estimates of treatment effectiveness cost of sorafenib (dose intensity assumption) were the key drivers affecting the ICERs. The health state utility parameters affected the ICER marginally. The ICERs was particularly sensitive to variations in estimates of the hazard ratio for overall survival, with ICERs ranging from £55,585 (HR for overall survival = 0.54) to £368,830 (HR for overall

survival = 0.94). See pages 179–81 of the assessment report for further details.

According to PSA, at a willingness to pay threshold of £30,000, sorafenib has a 0% probability of being cost effective as a second-line treatment compared with best supportive care.

3.2.3 Comparison of the manufacturer and Assessment Group models

In all cases, the ICERs per QALYs gained are higher in the Assessment Group model than the manufacturer models. This is owing to a number of key differences in the model structures and data inputs.

Key differences

Pfizer and Assessment Group models

One of the main differences between the Pfizer (sunitinib compared with IFN-α) and the Assessment Group model is the choice of data used to model the baseline progression for IFN-α alone. The Assessment Group chose data on progression with IFN-α alone from the RCT reported by Escudier et al. The Pfizer base case analysis uses data from the RCT reported by Motzer et al (2007) which has a shorter follow-up period (25 months versus 13 months). When the Assessment Group model uses the same baseline progression as the Pfizer model (but with an adjusted fit to the empirical survival data), the ICER does decrease from £71,462 to £61,868 per QALY gained. Incorporating the Pfizer pricing strategy (first cycle of sunitinib free of charge to the NHS) reduces the Assessment Group's ICER from £71,462 to £57,737 per QALY gained.

Roche and Assessment Group models

A number of differences in structural assumptions and data inputs were highlighted by the Assessment Group in relation to the economic model submitted by Roche (bevacizumab plus IFN-α compared with IFN-α). Owing to similarities in the structure of the models in terms of disease progression and health state utilities, it is essentially the assumptions over costs (especially drug-related costs) that result in different cost-effectiveness

estimates. If the Assessment Group model applies the 'dose cap' pricing scheme that Roche uses, then the ICER in the Assessment Group model is reduced from £171,301 to £90,584 per QALY gained. Similarly, if the 'dose cap' pricing strategy is removed from the Roche model, then the ICER increases from £74,978 to £108,329.

Another important difference between the Roche and Assessment Group models is the use of data on dose intensity. Dose intensity data are used to adjust the cost of bevacizumab and IFN-α. Unpublished dose intensities of 62% and 63% are used for bevacizumab and IFN-α monotherapy in the Roche model, compared with 88% for bevacizumab and 86% for IFN-α monotherapy in the Assessment Group model, taken from Escudier (2007a). Incorporating the Assessment Group's higher dose intensity estimates into the Roche economic model, the ICER is increased from £74,948 to £117,000.

Wyeth and Assessment Group model

There are a number of differences in the health outcomes predicted in these two models. The Assessment Group model estimated greater mean survival and QALYs for both treatment arms and a higher incremental benefit from temsirolimus compared with IFN-α. However, different assumptions on resource use and costs resulted in a much higher mean incremental cost of temsirolimus compared with IFN-α (£22,272) than in 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-α. In the Assessment Group model, each 30-mg vial of temsirolimus was assumed to be £618 as there was no BNF list price available. This price was calculated from the £515 price of a 25-mg dose of temsirolimus used by Wyeth, assuming a price per milligram and no sharing of the 30-mg vials. Incorporating the Assessment Group's estimate of the cost of temsirolimus into the Wyeth model, the cost per QALY for temsirolimus compared with IFN-α increased from £55,814 to £74,819. Incorporating the Wyeth cost of temsirolimus into the Assessment Group model decreased the ICER from £94,385 to £81,687.

The costs for the administration of IFN-α are high in the Wyeth model compared with the assumptions made by the Assessment Group. In the Wyeth model, it is assumed that IFN-α will be administered in a hospital setting three times per week. The Assessment Group assumed that IFN-α is administered at home on all occasions; by patients or carers in 75% of cases and by district nurse in 25% of cases. These assumptions were based on information provided by clinical experts on current practice. If the Assessment Group's assumptions of lower costs of administration of IFN-α are incorporated into the Wyeth model, the ICER increases from £55,814 to £102,000.

Bayer and Assessment Group models

The Assessment Group and the Bayer model use the same RCT data to predict disease progression, although different approaches to model disease progression were used. The different approaches led to the Assessment Group model predicting a greater level of mortality over time, resulting in the Assessment Group model predicting lower survival and lower incremental life years gained for sorafenib. There were also differences in the health state utilities used in the models and, although fewer patients survive in the Assessment Group model, those that do have a greater utility gain than those in the Bayer model. Incorporating the Assessment Group's utility health state values into the Bayer model results in a reduction in the ICER from £90,630 to £80,135 per QALY gained for sorafenib compared with best supportive care.

Table 16: Comparisons of manufacturer and Assessment Group results

Comparison	Manufacturer base case cost per QALY	Assessment Group base case cost per QALY
First-line treatment in patients suitable for immunotherapy		
Sunitinib versus IFN-α	£28,546 Assessment Group adjustment: manufacturer model using Assessment Group fit of survival data for progression-free survival = £48,052	£71,462 Assessment Group model with first cycle of sunitinib free of charge to the NHS (Pfizer strategy), and using data from sunitinib RCT (Motzer 2007) for baseline

		progression = £57,737
Bevacizumab plus IFN-α versus IFN-α	£74,978 Assessment Group adjustment: manufacturer model without 'dose cap' pricing assumption = £108,329	£171,301 Assessment Group model with 'dose cap' pricing = £90,584
First-line treatment in patients with poor prognosis		
Temsirolimus versus IFN-α	£55,814 Assessment Group adjustment: applying Assessment Group assumptions on cost of administration for IFN-α to Wyeth model = £102,000 Applying Assessment Group assumptions on cost for administration of IFN-α, and cost for temsirolimus (vial price) = £121,175	£94,385
Second-line treatment		
Sorafenib versus best supportive care	£90,630 Assessment Group adjustment: applying Assessment Group assumptions on health state utility values to Bayer model = £80,135.	£102,498

4 Issues for consideration

The scope of the appraisal identified three groups for which the Assessment Group stated they had inadequate data. These were patients receiving first-line treatment with sorafenib (that is, those who are unsuitable for immunotherapy); patients receiving second-line treatment with sunitinib and patients unsuitable for immunotherapy with poor prognosis (that is temsirolimus indirectly compared to best supportive care). Data for these groups were presented by the manufacturers as a small subgroup analysis, two single-arm trials and an indirect comparison, respectively. Does the Committee consider that analysis should be conducted for these groups of patients or that the effectiveness and cost-effectiveness results would be generalisble to these groups of patients?

The majority of the patients included in the trials had clear cell, metastatic RCC, had undergone previous nephrectomy and were of favourable or intermediate prognosis, with good performance status. The Assessment Group has expressed a concern over the generalisability of the trials to the wider patient population.

In the assessment report, unsuitability for treatment with immunotherapy is defined as having clinical contraindications to therapy (for example, autoimmune disease or a history of depression). Patients defined as having an intermediate or poor prognosis are considered 'suitable' for treatment with immunotherapy. There is variation in practice around the UK. In some centres, patients with intermediate or poor prognosis would not be offered immunotherapy. Does the Committee consider that the definition of unsuitability for immunotherapy used in the assessment report is reasonable?

The trials included in the submissions and the assessment report have relatively short follow-up periods and the data are generally premature. In the cost-effectiveness analyses, trial data for baseline disease progression were extended by fitting survival curves. The manufacturers and the Assessment Group have used different survival curves.

- For first-line treatment for patients suitable for immunotherapy, Pfizer have used a survival curve to predict PFS with IFN that fits the trial data well up to 6 months. This gives an ICER of £28,546. The Assessment Group have removed early outliers and fitted the same survival curve. This gives an ICER of £48,052. What does the Committee consider the most appropriate approach?

The Assessment Group state that estimates of relative treatment effectiveness for each technology are particularly uncertain with wide ranges. In all comparisons, the estimates of cost effectiveness are most sensitive to variations in the hazard ratios for overall survival.

Pfizer, in their comments on the assessment report, submitted additional evidence on the clinical effectiveness of sunitinib for first-line treatment. With

regards to overall survival estimates, the manufacturer presents two analyses, one including censored data at the time of patients cross-over and another one with no censored data. Although, the overall survival HRs were very similar in both analyses, they were higher than those presented in their original submission. As these data are different to the original submission, they will also affect the results of the indirect comparison between sunitinib and bevacizumab.

The Assessment Group have used investigator-assessed data from the Escudier AVOREN trial (bevacizumab plus IFN-α compared with IFN-α) in order to estimate the cost effectiveness of sunitinib compared with IFN-α. In this trial, patients were given IFN-α for a maximum of one year in both arms and after disease progression were eligible to receive second-line treatments such as sunitinib and sorafenib. Concern has been expressed that the design of the Escudier AVOREN trial does not reflect standard NHS practice and no independent assessment was conducted.

The Assessment Group noted that the ICER for first-line sunitinib might have been underestimated as a result of some other issues, such as the length of interferon prescription, the price of interferon and PSA approaches use of different distributions in the PSA to the ones drawn by clinical data, mix-up of standard errors. A detailed discussion of these issues is provided in pages 107–14 of the assessment report.

In the Pfizer submission, the overall survival and progression free survival curves for sunitinib for second-line treatment were taken from a small single arm trial. Data on best supportive care were taken from another trial. Does the Committee consider this a valid approach?

The Assessment Group assumed that IFN-α is predominantly administered at home. Consultees have commented that this assumption is incorrect and that between 0-50% of patients would self-administer IFN-α, The use of this different assumption in the model would decrease the incremental costs between treatments that have IFN-α as a comparator, and thus reduce the cost effectiveness estimates.

No consistent definition of best supportive care for RCC or trials of best supportive care were identified. The Assessment Group estimated resource use and costs of best supportive care following consultation with clinical experts, but recognised that the definition of best supportive care is likely to vary widely in practice. Consultees have commented that no palliative care costs or costs of death to the NHS have been included in the Assessment Group's model. Does the Committee consider the approach and assumptions made about best supportive care to be reasonable?

The Assessment Group have not used the pricing strategies as presented by the manufacturers for bevacizumab and sunitinib in their base-case, in line with the NICE reference case. The Department of Health have also not confirmed that these schemes are available nationally. The price of temsirolimus has been imputed from the manufacturer submission as no current BNF list price was available.

There was a lack of evidence on health utility values for all technologies and health states. The Assessment Group had to use trial data calculated by the manufacturer and reported in their submissions. For bevacizumab, sunitinib and temsirolimus there was a lack of transparency as to how these utility values were derived. For sorafenib, the utility estimates were derived from 5 clinicians. Concern has been expressed by consultees that, due to this lack of evidence and uncertainty around utility values, the Assessment Group should have considered a wider range of utility estimates in sensitivity analyses.

5 Authors

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Appendix A: Sources of evidence considered in the preparation of the overview

A The assessment report for this appraisal was prepared by Peninsula Technology Assessment Group:

Thompson Coon J, Hoyle M, Green C, et al. Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma: a systematic review and economic evaluation*,* May 2008.

B Submissions from the following organisations:

I Manufacturer/sponsors:

- Bayer
- Roche
- Pfizer
- Wyeth

II Professional/specialist and patient/carer groups:

- Cancer Backup
- Kidney Cancer UK
- James Whale Kidney Cancer Fund
- Kidney Research
- National Kidney Confederation
- Royal College of Physicians