NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Appraisal consultation document

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

The Department of Health has asked the National Institute for Health and Clinical Excellence (NICE or the Institute) to conduct a multiple technology appraisal of bevacizumab, sorafenib, sunitinib and temsirolimus and provide guidance on their use to the NHS in England and Wales. The Appraisal Committee has had its first meeting to consider both the evidence submitted and the views put forward by non-manufacturer consultees and commentators, and by the clinical specialist and patient expert representatives nominated for this appraisal by non-manufacturer consultees and commentators. The Committee has developed preliminary recommendations on the use of bevacizumab, sorafenib, sunitinib and temsirolimus.

This document has been prepared for consultation with the formal consultees. It summarises the evidence and views that have been considered and sets out the preliminary recommendations developed by the Committee. The Institute is now inviting comments from the formal consultees in the appraisal process (the consultees for this appraisal are listed on the NICE website, www.nice.org.uk). This document should be read in conjunction with the evidence base for this appraisal (the evaluation report), which is available from www.nice.org.uk

Note that this document does not constitute the Institute's formal guidance on bevacizumab, sorafenib, sunitinib and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma. The recommendations made in section 1 are preliminary and may change after consultation.

The process the Institute will follow after the consultation period is summarised below. For further details, see the 'Guide to the technology appraisal process' (this document is available on the Institute's website, www.nice.org.uk).

- The Appraisal Committee will meet again to consider the original evidence and this appraisal consultation document in the light of the views of the formal consultees.
- At that meeting, the Committee will also consider comments made on the document by people who are not formal consultees in the appraisal process.

- After considering feedback from the consultation process, the Committee will prepare the final appraisal determination (FAD) and submit it to the Institute.
- Subject to any appeal by consultees, the FAD may be used as the basis for the Institute's guidance on the use of the appraised technology in the NHS in England and Wales.

The key dates for this appraisal are:

Closing date for comments: 29th August 2008

Second Appraisal Committee meeting: 10th September 2008

Details of membership of the Appraisal Committee are given in appendix A, and a list of the sources of evidence used in the preparation of this document is given in appendix B.

Note that this document does not constitute the Institute's formal guidance on bevacizumab, sorafenib, sunitinib and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma. The recommendations made in section 1 are preliminary and may change after consultation.

1 Appraisal Committee's preliminary recommendations

Proposals were submitted by two of the manufacturers in this appraisal relating to drug acquisition costs. However, these proposals have not been considered by the Department of Health. In order for the Committee to consider any currently proposed, revised or new strategies from manufacturers, all arrangements need to have first been agreed by the Department of Health.

1.1 Bevacizumab, sorafenib, sunitinib and temsirolimus are not recommended as treatment options for advanced and/or metastatic renal cell carcinoma.

1.2 People currently receiving bevacizumab, sorafenib, sunitinib and temsirolimus should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

2 Clinical need and practice

2.1 Renal cell carcinoma (RCC) is a type of kidney cancer that usually originates in the lining of the tubules of the kidney and contains many blood vessels. RCC accounts for 90% of kidney cancers and approximately 3% of all adult cancers. In England and Wales, kidney cancer is the 8th most common cancer in men and the 14th most common in women. In 2004, there were 5745 cases of newly diagnosed kidney cancer registered in England and Wales. The

incidence of kidney cancer begins to rise after the age of 40 and is highest in people older than 65. In England and Wales the estimated overall 5-year survival rate for RCC is 44%, but there are large differences according to the stage of disease at the time of diagnosis. The worldwide incidence of kidney cancer among both men and women has been rising steadily since the 1970s.

2.2 The American Joint Committee on Cancer (AJCC) tumour node metastases (TNM) system is used to grade RCC into stages I to IV. Advanced RCC, in which the tumour is either locally advanced and/or has spread to regional lymph nodes, is generally defined as stage III. Metastatic RCC, in which the tumour has spread beyond the lymph nodes to other parts of the body, is generally defined as stage IV.

2.3 In 2006, of people presenting with RCC in England and Wales for whom staging information was available, an estimated 26% and 17% had stage III and stage IV disease, respectively. About half of those who have curative resection for earlier stages of the disease also go on to develop advanced and/or metastatic disease. The prognosis following a diagnosis of advanced and/or metastatic RCC is poor. The 5-year survival rate for metastatic RCC is approximately 10%.

2.4 There are currently no treatments that reliably cure advanced and/or metastatic RCC. The primary objectives of medical intervention are relief of physical symptoms and maintenance of function. Metastatic RCC is largely resistant to chemotherapy, radiotherapy and hormonal therapy. People with advanced and/or metastatic RCC are usually treated with either interferon alfa-2a (IFN-α) or interleukin-2 immunotherapy or a combination of IFN-α and interleukin-2. IFN-α (Roferon-A, Roche Products) is the most commonly used immunotherapy in England and Wales and has UK

marketing authorisation for treatment for people with advanced RCC. For those people receiving immunotherapies for the treatment of advanced RCC it is suggested that, on average, median survival is increased by 3.8 months compared with those receiving control treatments. Commonly experienced adverse effects of IFN-α include flu-like symptoms, tiredness and depression. There is no standard treatment for people with advanced and/or metastatic RCC whose condition does not respond to first-line immunotherapy, or for people who are unsuitable for immunotherapy.

3 The technologies

3.1 Bevacizumab

3.1.1 Bevacizumab (Avastin, Roche Products) is a recombinant humanised monoclonal IgG1 antibody that inhibits the formation of blood vessels (angiogenesis inhibitor). It targets the biological activity of human vascular endothelial growth factor (VEGF), which stimulates new blood vessel formation in the tumour. Bevacizumab in combination with IFN-α has UK marketing authorisation for first-line treatment of people with advanced and/or metastatic RCC.

3.1.2 Bevacizumab is contraindicated in pregnant women, people with untreated central nervous system metastases, and people who have hypersensitivity to the active substance or to any of the excipients, to products derived from Chinese hamster ovary cell cultures or to other recombinant human or humanised antibodies. The summary of product characteristics (SPC) lists the following conditions that may be associated with bevacizumab treatment: gastrointestinal perforation, fistulae, wound healing complications, hypertension, proteinuria, arterial thromboembolism, haemorrhage, congestive heart failure and neutropenia. For full details of side effects and contraindications, see the SPC.

3.1.3 Bevacizumab is administered as an intravenous infusion. The recommended dosage for advanced and/or metastatic RCC is 10 mg/kg body weight once every 14 days. IFN-α (Roferon-A, Roche) is administered by subcutaneous injection three times per week at a dose of 3 MIU for 1 week, 9 MIU for the following week and 18 MIU thereafter; if 18 MIU is not tolerated then the dose should be reduced to 9 MIU. Bevacizumab treatment is licensed until there is underlying disease progression. The price for a 400-mg vial of bevacizumab is £924.40 and the price of IFN-α is £45.19 for 9 MIU (excluding VAT; 'British national formulary' [BNF] edition 55). Assuming an average weight of 76.5 kg and no wastage, the average daily cost of bevacizumab plus IFN-α is £151.42. Over a 6-week cycle, the average total cost of drug acquisition is £5982 per patient for the first cycle and £6117 for subsequent 6-week cycles. These figures assume a typical dose of IFN-α of 9-10 MIU. Costs may vary in different settings because of negotiated procurement discounts.

3.2 Sorafenib

3.2.1 Sorafenib (Nexavar, Bayer) is a multikinase inhibitor that 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 people with advanced RCC whose condition has failed to respond to IFN-α or interleukin-2 based therapy or who are considered unsuitable for such therapy. Sorafenib has designated EU orphan drug status.

3.2.2 Sorafenib is contraindicated in people who have hypersensitivity to the active substance or to any of the excipients. The SPC lists the following conditions that may be associated with sorafenib treatment: dermatological toxicities, hypertension, haemorrhage,

cardiac ischaemia and/or infarction, hepatic impairment and wound healing complications. For full details of side effects and contraindications, see the SPC.

3.2.3 Sorafenib is administered orally. The recommended dosage for advanced RCC is 400 mg twice daily. Sorafenib treatment is licensed as long as clinical benefit is observed or until unacceptable adverse events occur. The price for a pack of 200-mg tablets (112 tablets per pack) is £2504.60 (excluding VAT; BNF edition 55). The average daily cost of sorafenib treatment is £89.45, with an average 6-week cycle costing £3757. Costs may vary in different settings because of negotiated procurement discounts.

3.3 Sunitinib

3.3.1 Sunitinib (Sutent, Pfizer) is an inhibitor of a group of closely related tyrosine kinase receptors. It inhibits VEGF/PDGF receptors on cancer cells, vascular endothelial cells and pericytes, inhibiting the proliferation of tumour cells and the development of tumour blood vessels. Sunitinib has UK marketing authorisation for the treatment of people with advanced and/or metastatic RCC. Sunitinib has designated EU orphan drug status.

3.3.2 Sunitinib is contraindicated in people who have hypersensitivity to sunitinib malate or to any of the excipients. The SPC lists the following conditions that may be associated with sunitinib treatment: skin and tissue problems, gastrointestinal events, haemorrhage, hypertension, haematological problems, venous thromboembolic events, pulmonary embolism and hypothyroidism. For full details of side effects and contraindications, see the SPC.

3.3.3 Sunitinib is administered 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 price for a pack of 50-mg capsules (30 capsules per pack) is £3363.00

(excluding VAT; BNF edition 55). The average daily cost of sunitinib is £74.74, with an average 6-week cycle costing £3139. Costs may vary in different settings because of negotiated procurement discounts.

3.4 Temsirolimus

3.4.1 Temsirolimus (Torisel, Wyeth Pharmaceuticals) 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 people 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 greater than 10 mg/100 ml (or 2.5 mmol/litre)
- lactate dehydrogenase more than 1.5 times the upper limit of normal
- more than one metastatic organ site.

Temsirolimus has designated EU orphan drug status.

3.4.2 Temsirolimus is contraindicated in people who have hypersensitivity to temsirolimus, its metabolites (including sirolimus), polysorbate 80 or to any of the excipients. The SPC lists the following conditions that may be associated with temsirolimus treatment: intracerebral bleeding, renal failure, hyperglycaemia,

infections, interstitial lung disease, hyperlipaemia and wound healing complications. Pre-medication with intravenous antihistamine is also recommended to minimise allergic reactions. For full details of side effects and contraindications, see the SPC.

3.4.3 Temsirolimus is administered by intravenous infusion. The recommended dosage is 25 mg over a 30- to 60-minute period once a week. The net-price for a 30-mg vial of temsirolimus is not currently listed in the BNF (see sections 4.2.7 and 4.2.19 for further details).

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B).

4.1 Clinical effectiveness

4.1.1 The Assessment Group and manufacturers identified evidence on the clinical effectiveness of bevacizumab plus IFN-α, sorafenib, sunitinib and temsirolimus against relevant comparators within the licensed indications for each drug, and according to the appraisal scope. The following potential treatment strategies were investigated:

- first-line treatment for those suitable for immunotherapy (bevacizumab plus IFN-α and sunitinib as monotherapy compared with IFN-α)
- first-line treatment of those with a poor prognosis who were suitable for immunotherapy (bevacizumab plus IFN- α, sunitinib and temsirolimus [both as monotherapy] compared with IFN-α);
- first-line treatment of those unsuitable for immunotherapy (sorafenib and sunitinib [both as monotherapy] compared with best supportive care)

- first-line treatment of those with a poor prognosis who were unsuitable for immunotherapy (sorafenib, sunitinib and temsirolimus [all as monotherapy] compared with best supportive care)
- second-line treatment for those whose condition has failed to respond to immunotherapy (sorafenib and sunitinib [both as monotherapy] compared with best supportive care).

First-line treatment for people suitable for immunotherapy

4.1.2 Two randomised controlled trials (RCTs) have investigated the clinical effectiveness of first-line treatments of advanced and/or metastatic RCC for those suitable for immunotherapy. One RCT of 649 people assessed the effect of bevacizumab plus IFN-α compared with IFN-α plus placebo. Another RCT of 750 people assessed the effect of sunitinib compared with IFN-α alone. For the bevacizumab study, the primary outcome was overall survival and for the sunitinib study the primary outcome was progression-free survival. An interim analysis was planned in the bevacizumab study, based on approximately 250 deaths, after which the study was unblinded and participants in the IFN-α arm who had not progressed were offered bevacizumab plus IFN-α. Three interim analyses were scheduled in the sunitinib study. After the second analysis the study was unblinded and participants in the IFN-α group with progressive disease were allowed to cross over into the sunitinib group. However, as the Assessment Group highlighted, it is not clear why participants with progressive disease were offered further treatment. The protocol stated that all treatment would be stopped when there was evidence of disease progression. The bevacizumab study included predominantly people with clear cell RCC who had risk factors suggestive of a favourable or intermediate prognosis. All participants had undergone a previous nephrectomy. The sunitinib study was conducted in participants with a good performance status (Eastern Cooperative Oncology

Group [ECOG] status 0 or 1) with clear cell RCC. Most had undergone prior nephrectomy.

4.1.3 In the bevacizumab study, median overall survival had not been reached in the bevacizumab plus IFN-α treatment arm at the time of data analysis and was 19.8 months in the IFN-α alone arm. There was no statistically significant difference in overall survival between bevacizumab plus IFN-α compared with IFN-α alone (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.62 to 1.02, p = 0.0670). In the sunitinib study, median overall survival had not been reached in either treatment arm at the time of data analysis. The comparison of sunitinib with IFN-α did not reach the pre-specified level of statistical significance (HR 0.65, 95% CI 0.45 to 0.94, p = 0.02).

4.1.4 In both studies, progression-free survival was defined as the time between randomisation and first documented disease progression or death from any cause. In the bevacizumab study, the median progression-free survival was 10.2 months in the bevacizumab plus IFN-α arm and 5.4 months in the IFN-α alone arm (HR 0.63, 95% CI 0.52 to 0.75). In the sunitinib study, pre-planned interim results (at 13 months) and unplanned updated results (at 25 months) were presented, but the latter contained crossover between treatment arms. For the pre-planned interim analyses, independent assessment showed median progression-free survival of 11 months in the sunitinib arm and 5 months in the IFN-α arm (HR 0.42, 95% CI 0.32 to 0.54). For the unplanned updated analyses, the independent assessment showed median progression-free survival of 11 months in the sunitinib arm and 5.1 months in the IFN-α arm (HR 0.54, 95% CI 0.44 to 0.66; p < 0.000001). In the sunitinib study, a few participants were included who had not had a prior nephrectomy: 9% in the sunitinib arm and 11% in the IFN-α arm. The subgroup analyses suggested that sunitinib significantly

improved progression-free survival for those who had undergone prior nephrectomy compared with IFN-α (HR 0.38, 95% CI 0.30 to 0.53). There was no significant improvement in progression-free survival for those who had not undergone prior nephrectomy (HR 0.58, 95% CI 0.24 to 1.03).

4.1.5 Both studies measured tumour response rate as a partial or complete reduction in tumour size. In both studies, the differences in tumour response rate reached statistical significance. In the bevacizumab study, the overall tumour response rate in the bevacizumab plus IFN-α arm was 31% compared with 13% in the IFN-α alone arm ($p = 0.0001$). In the sunitinib study, the partial tumour response rate in the sunitinib arm was 31% compared with 6% in the IFN-α arm ($p < 0.001$). No patient in the sunitinib study had a complete tumour response.

4.1.6 In both studies, adverse events were taken from the 'safety populations' (that is, people were assigned to treatments in the analysis based on what they actually received, for example patients in the placebo arm receiving one or more doses of bevacizumab were assigned to the bevacizumab arm). No significant differences between the treatment and control arms were reported. However, the adverse event profiles associated with the drugs differed slightly and there are emerging concerns about the frequency of cardiovascular events associated with sunitinib. In the bevacizumab study, 28% of participants discontinued treatment in the bevacizumab plus IFN-α arm because of adverse events compared with 12% in the IFN-α alone arm. In the sunitinib study, 8% of participants receiving sunitinib discontinued treatment because of adverse events compared with 13% in the IFN-α arm. In the sunitinib study, overall results for health-related quality of life (total score and all subscales using the functional assessment of cancer therapy – general [FACT-G] and functional assessment of

cancer therapy – kidney symptom index [FKSI] tools) were significantly better in the sunitinib arm compared with the IFN-α arm. Health-related quality of life was not measured in the bevacizumab study.

4.1.7 The Assessment Group and the manufacturer of sunitinib (Pfizer) judged that an indirect comparison between the two studies to compare sunitinib with bevacizumab plus IFN-α was appropriate. The Assessment Group highlighted that the results of indirect comparisons may not be as robust or as reliable as direct comparisons obtained from head-to-head randomised controlled trials. Therefore it stressed that the results of such an indirect comparison should be treated with caution. The Assessment Group's indirect comparison showed no statistically significant difference in terms of overall survival (HR 0.82, 95% CI 0.53 to 1.28). Both the Assessment Group's and Pfizer's indirect comparison using the pre-planned interim analyses showed that sunitinib was statistically significantly better than bevacizumab plus IFN-α in terms of progression-free survival (HR 0.67, 95% CI 0.50 to 0.89 and HR 0.66, 95% CI 0.49 to 0.90, respectively; p = 0.004). Pfizer's indirect comparison using the unplanned updated analyses showed no statistically significant difference between sunitinib and bevacizumab plus IFN-α (HR 0.80, 95% CI 0.62 to 1.04).

First-line treatment for people unsuitable for immunotherapy

4.1.8 The Assessment Group did not identify any full reports of RCTs assessing sorafenib or sunitinib as first-line treatment for people with advanced and/or metastatic RCC who were unsuitable for immunotherapy. The manufacturer of sorafenib (Bayer) submitted data from an RCT with a small population subgroup (17% of the total number of participants) who were unsuitable for immunotherapy. This was a trial of sorafenib as a first-line treatment compared with placebo, which was assumed to be

equivalent to best supportive care. Further details of the sorafenib RCT are given in section 4.1.16 The Assessment Group did not consider this subgroup because it was unclear whether the subgroups were defined at the start of the study and the size of the subgroup was small. The results of the trial for this subgroup were marked as academic in confidence. Therefore they are not presented in this document.

First-line treatment for people suitable for immunotherapy with at least three of six factors indicating poor prognosis

4.1.9 One RCT with 626 participants investigated the effectiveness of temsirolimus, temsirolimus plus IFN-α and IFN-α alone as first-line treatments of RCC in people who were suitable for immunotherapy and had at least three of six factors indicating poor prognosis. The combination of temsirolimus plus IFN-α does not have a UK marketing authorisation and so data from this group were not considered. The primary outcome in this temsirolimus study was overall survival. Approximately 80% of participants had a Karnofsky performance status of 70 or less and clear cell carcinoma. Approximately 66% of participants had undergone prior nephrectomy. Interim and final analyses were presented.

4.1.10 According to the Memorial Sloan-Kettering Cancer Center (MSKCC) risk classification, 31% of participants in the temsirolimus arm and 24% in the IFN-α alone arm had an intermediate rather than a poor prognosis. According to a slightly different classification to that used in the temsirolimus study (the MSKCC classification does not include metastasis to other organs), 9% of participants receiving bevacizumab plus IFN-α and 8% of those receiving IFN-α plus placebo in the bevacizumab study were defined as having a poor prognosis. In the sunitinib study, 6% of participants receiving sunitinib and 7% of participants receiving IFN-α were classified as

having a similar poor prognosis. However, the sunitinib study did not report outcome data for this subgroup separately.

4.1.11 In the temsirolimus study, there was a statistically significant improvement in median overall survival with temsirolimus (10.9 months) compared with IFN-α (7.3 months), in both the interim (HR 0.73, 95% CI 0.58 to 0.92; p = 0.008) and final analyses (HR 0.78, 95% CI 0.63 to 0.97; p = 0.0252). Some participants had not undergone prior nephrectomy and some had non-clear cell carcinoma. Subgroup analyses suggested that temsirolimus compared with IFN-α significantly improved overall survival for those who had not undergone prior nephrectomy (HR 0.62, 95% CI 0.42 to 0.93) and for those with non-clear cell carcinoma (HR 0.55, 95% CI 0.33 to 0.90). No significant improvements in overall survival were observed for those who had undergone prior nephrectomy (HR 0.84, 95% CI 0.65 to 1.12) and those who had clear cell carcinoma (HR 0.85, 95% CI 0.64 to 1.06). Data on overall survival were not presented separately for participants with poor prognosis in the bevacizumab study.

4.1.12 In the interim analyses, median progression-free survival was assessed by both site investigators and blinded independent assessment. For those receiving temsirolimus, the median progression-free survival was 3.8 months and 5.5 months as assessed by site investigators and blinded independent assessment, respectively. For those receiving IFN-α, the median progression-free survival was 1.9 months and 3.1 months, respectively. No statistical analysis was reported for the interim analyses. In the final analyses, the median progression-free survival was 3.8 months and 5.6 months as assessed by site investigators and blinded independent assessment, respectively. For those receiving IFN-α median progression-free survival was 1.9 months and 3.2 months, respectively. There was a statistically

significant improvement in median progression-free survival with temsirolimus compared with IFN-α according to the independent assessment (HR 0.74, 95% CI 0.60 to 0.91; p = 0.0042), and the investigator's assessment (HR 0.74, 95% CI 0.60 to 0.90; p = 0.0028). Temsirolimus improved progression-free survival for those who had not undergone prior nephrectomy compared with IFN-α (HR 0.62, 95% CI 0.43 to 0.88) and for those who had undergone prior nephrectomy (HR 0.72, 95% CI 0.55 to 0.93) Temsirolimus improved progression-free survival for those who had non-clear cell carcinoma compared with IFN-α (HR 0.36, 95% CI 0.22 to 0.59), and for those who had clear cell carcinoma (HR 0.84 95% CI 0.67 to 1.05). In the bevacizumab study there was no statistically significant difference in median progression-free survival between bevacizumab plus IFN-α (2.2 months) and IFN-α alone (2.1 months) for participants with at least three MSKCC risk factors for poor prognosis (HR 0.81, 95% CI 0.46 to 1.42).

4.1.13 The temsirolimus study measured objective tumour response rate. There were no statistically significant differences observed; the objective tumour response rate was 8.6% for those who received temsirolimus compared with 4.8% for those who received IFN-α. Data on tumour response rate were not presented separately for the subgroup of participants with poor prognosis in the bevacizumab study.

4.1.14 In the temsirolimus study, time without symptoms and toxicity (TWiST) and quality-adjusted survival and toxicity (Q-TWiST) were reported as pre-defined endpoints. The reported results included some participants from the third treatment arm (temsirolimus plus IFN-α). Participants receiving temsirolimus had a significantly longer time in both TWiST and Q-TWiST health states (6.5 months and 7.0 months, respectively) compared with participants receiving IFN-α alone (4.7 months and 5.7 months, respectively). In the

temsirolimus study, 67% of participants receiving temsirolimus and 78% of those receiving IFN-α alone reported a grade 3 or 4 adverse event ($p = 0.02$). Anaemia was the most commonly reported grade 3 or 4 adverse event in the temsirolimus arm (20%) and asthenia (loss of strength) in the IFN-α alone arm (26%). A total of 7% (n = 15) of patients in the temsirolimus arm discontinued treatment because of adverse events compared with 14% (n = 29) in the IFN-α alone arm.

First-line treatment for people with poor prognosis unsuitable for immunotherapy

4.1.15 The Assessment Group did not identify any full reports of RCTs assessing sorafenib or sunitinib or temsirolimus as first-line treatment for people with advanced and/or metastatic RCC who had a poor prognosis and were unsuitable for immunotherapy. In order to inform a cost-effectiveness estimate for this population, the manufacturer of temsirolimus (Wyeth Pharmaceuticals) performed an indirect comparison of temsirolimus with best supportive care. Data were taken from the temsirolimus RCT and an RCT that compared IFN-α with medroxyprogresterone (MPA). No further details on clinical effectiveness were presented.

Second-line treatment for people whose condition has failed to respond to immunotherapy

4.1.16 One RCT and one randomised discontinuation trial have investigated the effectiveness of sorafenib compared with placebo, which was considered equivalent to best supportive care. The RCT included 903 people who had experienced disease progression after one systemic treatment within the previous 8 months. All participants in the RCT had clear cell carcinoma with an ECOG performance status of 0 or 1 and a low or intermediate MSKCC prognostic score. A total of 83% of participants had received previous immunotherapy. The randomised discontinuation trial included 65 people with advanced and/or metastatic RCC, most of

whom had not responded to treatment with immunotherapy. Most participants in this trial had an ECOG performance status of 0 or 1 and had undergone prior nephrectomy. The primary outcome of the RCT was overall survival and the primary outcome of the randomised discontinuation trial was the percentage of randomly assigned participants without progression at 24 weeks. The RCT was terminated early after an independent review decided that sorafenib should be offered to participants who were receiving placebo.

4.1.17 Two single-arm phase II studies have investigated the effectiveness of sunitinib as a second-line treatment for metastatic RCC. One study included 63 participants with metastatic RCC whose condition had failed to respond to at least one course of cytokine-based therapy, and who had an ECOG performance status of 0 to 1. The other study was of 106 people with clear cell carcinoma with a previous nephrectomy. A total of 57% of the pooled population had an ECOG performance status of 0. In both studies sunitinib was given until disease progression, and dose reductions were allowed if adverse effects were observed. In both studies, the primary outcome was objective tumour response.

4.1.18 The median actuarial overall survival in the sorafenib RCT had not been reached in the sorafenib arm, and was 14.7 months in the placebo arm (HR 0.72, 95% CI 0.54 to 0.94; p = 0.02). The difference was not considered statistically significant because it did not reach the O'Brien–Fleming threshold of 0.0005. Overall survival was not assessed in the sorafenib randomised discontinuation trial.

4.1.19 From the sorafenib RCT, results were reported of a pre-planned interim analysis and an unplanned updated analysis (before crossover occurred) for progression-free survival. For both analyses, both the independent and investigator assessments

resulted in median progression-free survival of 5.5 months in the sorafenib arm and 2.8 months in the placebo arm (HR 0.44, 95% CI 0.35 to 0.55 for pre-planned analyses and HR 0.51, 95% CI 0.43 to 0.60 for the unplanned updated analyses). The median progression-free survival in the sorafenib randomised discontinuation trial was significantly longer in participants receiving sorafenib (24 weeks) compared with those receiving placebo (6 weeks); $p = 0.0087$. At 24 weeks, a greater proportion of participants who had received sorafenib had no evidence of disease progression compared with those who had received placebo (50% and 18%, respectively; $p = 0.0077$).

4.1.20 The sorafenib RCT measured tumour response rate. One participant who received sorafenib achieved a complete tumour response compared with none who received placebo. A total of 43 (10%) participants receiving sorafenib and 8 (2%) receiving placebo achieved a partial response. This difference was statistically significant ($p < 0.001$).

4.1.21 Health-related quality of life was measured in the sorafenib RCT using the FACT-G and FKSI indices. There was no significant difference between the placebo and sorafenib groups in mean FACT-G physical well-being score nor was there any numerical 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). On the following items of the FKSI-15 index, those people who had received sorafenib scored significantly better than those who had received placebo: coughing ($p < 0.0001$); fever ($p = 0.0015$); worry about their disease ($p = 0.0004$); ability to enjoy life ($p = 0.0119$). However, a significantly greater number of adverse events were experienced by those receiving sorafenib than by those receiving placebo ($p < 0.0001$). Skin rashes, hypertension, gastrointestinal effects and hand-foot syndrome were more

common in the sorafenib arm. Health-related quality of life and adverse events were not recorded in the sorafenib randomised discontinuation trial.

4.1.22 The median overall survival in the smaller sunitinib study was 16.4 months (95% CI 10.8 to 'not yet attained') and 23.9 months (95% CI 14.1 to 30.7) in the larger sunitinib study. The median progression-free survival in the smaller sunitinib study was 8.7 months (95% CI 5.5 to 10.7) and 8.8 months (95% CI 7.8 to 13.5) in the larger sunitinib study. No participants achieved a complete tumour response in either of the sunitinib studies. A total of 40% in the smaller sunitinib study and 33% in the larger sunitinib study achieved partial tumour responses. Approximately equal proportions of the remaining participants in both studies experienced stable disease or progressive disease. Informal analysis comparing the pooled sunitinib studies with the best supportive care arm of the sorafenib RCT suggest that sunitinib may be clinically effective compared with best supportive care.

Summary of clinical effectiveness

4.1.23 The Assessment Group concluded from a summary of the data on the clinical effectiveness of first-line treatments for people who are suitable for immunotherapy, that both bevacizumab plus IFN-α and sunitinib as monotherapy appear to have significant benefits compared with IFN-α alone in terms of progression-free survival and tumour response. Although promising, data on overall survival are in general immature. For people with poor prognosis, temsirolimus appears to have significant benefits compared with IFN-α in terms of overall survival, progression-free survival and tumour response rate. There is some evidence to suggest that temsirolimus may have a greater effect on people who have non-clear cell carcinoma and who have not undergone nephrectomy. The frequency of adverse events associated with the first-line

treatments is comparable to that associated with IFN-α monotherapy, but the adverse event profiles differ between treatments.

4.1.24 The Assessment Group concluded, for second line treatments, that sorafenib appears to have clinically statistically significant benefits compared with best supportive care in terms of overall survival, progression-free survival and tumour response rate. Sorafenib was associated with slightly more adverse events than best supportive care; particularly hand-foot skin reactions and hypertension. The Assessment Group highlighted that the key sorafenib trial was terminated early to allow participants on placebo to cross over to receive sorafenib treatment. The Assessment Group also stated that although an informal comparison suggests that sunitinib may be beneficial compared with best supportive care, no definitive conclusions could be made because of the absence of any comparator in the studies.

4.2 Cost effectiveness

4.2.1 No published studies of the cost effectiveness of bevacizumab, sorafenib, sunitinib or temsirolimus were identified. The manufacturers of each of the drugs submitted cost-effectiveness models and the Assessment Group developed a model for each treatment question.

Manufacturers' models

First-line treatment for people suitable for immunotherapy

4.2.2 The manufacturer of bevacizumab (Roche Products) submitted a simple state-transition model with three health states: progression-free survival, progressed disease and death. The model compared bevacizumab plus IFN-α with IFN-α alone as a first-line treatment for people suitable for immunotherapy from the perspective of the NHS. Patient-level data were taken from the bevacizumab trial (see

section 4.1.2) and IFN-α use was limited to 1 year in both treatment arms as in the trial. Gompertz survival curves were fitted to the overall and progression-free survival data from the IFN-α arm in the trial and the progression-free survival curve for the bevacizumab plus IFN-α arm. Because median overall survival was not reached in the bevacizumab plus IFN-α arm, the hazard ratio from the stratified 'safety population' was applied to the baseline IFN-α overall survival Gompertz curve. The treatment-specific utility data from the sunitinib trial were averaged and the following values assigned: progression-free survival = 0.78 and progressive disease = 0.705. Drug costs were adjusted according to RCT data on dose intensity; the cost of bevacizumab was estimated as 62%, and that of IFN-α as 80% and 63% when used with bevacizumab and as monotherapy, respectively. A 'dose cap' pricing strategy was applied with bevacizumab being free to the NHS once 10,000 mg has been purchased for a patient within a year of initiation of treatment.

4.2.3 With discounting at 3.5% per annum, the comparison of bevacizumab plus IFN-α with IFN-α alone produced a base case ICER of £74,999 per QALY gained. One-way sensitivity analyses were only used to explore the effects of an alternative log–logistic survival curve in the extrapolation of trial results. The use of this model reduced the ICER to £39,978 per QALY gained.

4.2.4 The manufacturer of sunitinib (Pfizer) submitted a simple state-transition model with three health states: progression-free survival (PFS), progressed disease (PD) and death. The model compared sunitinib with IFN-α as a first-line treatment for people suitable for immunotherapy from the perspective of the NHS. Patient-level data were taken from the sunitinib trial described in section 4.1.2. Weibull survival curves were fitted to the overall and progression-free survival data from the IFN-α arm in the trial. Hazard ratios for

sunitinib were then used to extrapolate overall and progression-free survival for sunitinib treatment. Two base cases were presented using the pre-planned interim analyses and the unplanned updated analyses. The following treatment and health-state specific utility data from the sunitinib trial were applied: sunitinib/PFS = 0.77; IFN-α/PFS = 0.79; sunitinib/PD = 0.72; IFN-α/PD = 0.69. Drug costs were adjusted according to RCT data on dose intensity; the first-line drug cost for sunitinib was weighted by 86.4%. A pricing strategy with the first cycle of sunitinib being free of charge to the NHS was applied.

4.2.5 With discounting at 3.5% per annum, 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. 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, with ICERs ranging from £25,908 to £40,536 (first base case) and £29,949 to £43,797 (second base case). Both results were based on extrapolations of immature data and the results have been superseded by a late submission from the manufacturer reporting new base case ICERs of approximately £72,000 (see sections 4.3.1 to 4.3.3 for further details).

First-line treatment for people suitable for immunotherapy

4.2.6 The manufacturer of sorafenib (Bayer) submitted a cost effectiveness estimate of sorafenib compared with best supportive care as a first-line treatment for people who were unsuitable for immunotherapy. Patient-level data were taken from a small population subgroup from an RCT (as detailed in section 4.1.16). The cost effectiveness estimates for this subgroup were marked as

academic in confidence. Therefore they are not presented in this document.

First-line treatment for people with poor prognosis suitable for immunotherapy

4.2.7 The manufacturer of temsirolimus (Wyeth Pharmaceuticals) submitted a state-transition model with three health states: progression-free survival, progressed disease and death. The progression-free survival state was then subdivided into stable disease, complete/partial response and progressive disease. The model compared temsirolimus with IFN-α as a first-line treatment for people with at least three of six risk factors for poor prognosis, who were suitable for immunotherapy, from the perspective of the NHS. Patient-level data were taken from the temsirolimus trial described in section 4.1.9. Weibull regression models were applied to progression-free survival and overall survival data to calculate the time-dependent state transition probabilities. The following health state utility values, derived from the temsirolimus trial, were applied: 0.658 for complete/partial response, 0.600 for stable disease and 0.446 for progressive disease. Drug costs were adjusted according to RCT data on dose intensity and estimated as 92% for temsirolimus and 56% for IFN-α. The cost of a 30-mg vial of temsirolimus was £515 (see section 4.2.19) and no wastage was assumed.

4.2.8 With discounting at 3.5% per annum, 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 and when these were explored the ICERs ranged from £39,977 to £65,542. In subgroup analyses, the ICER for the subgroup with clear cell carcinoma was £57,731 per QALY, £51,159 for the subgroup with non-clear cell carcinoma, £60,575

for those with prior nephrectomy and £49,690 for those without prior nephrectomy.

First-line treatment for people with poor prognosis unsuitable for immunotherapy

4.2.9 The manufacturer of temsirolimus (Wyeth Pharmaceuticals) submitted an indirect comparison of temsirolimus with best supportive care. The model described in section 4.2.7 was used. Data were taken from the temsirolimus RCT and an RCT that compared IFN-α with medroxyprogresterone (MPA). With discounting at 3.5% per annum, the indirect comparison of temsirolimus with best supportive care produced an ICER of £81,201 per QALY gained. No sensitivity analyses were conducted.

Second-line treatments for people whose condition has failed to respond to immunotherapy

4.2.10 The manufacturer of sorafenib (Bayer) submitted a simple state-transition model with three health states: progression-free survival, progressed disease and death. The model compared sorafenib with best supportive care for people whose condition had failed to respond to immunotherapy or who were unsuitable for immunotherapy, from the perspective of the NHS. Patient-level data were taken from the sorafenib RCT (see section 4.1.16). For progression-free survival the trial data were used directly for both the sorafenib and placebo arms. However, because of a short follow-up period, the data for overall survival were immature and were extrapolated over time by using an exponential function. Analysis was presented according to the following subgroups: people receiving sorafenib as second-line treatment after failure of immunotherapy; people receiving sorafenib as first-line treatment because they were unsuitable for immunotherapy; and a combination of the two subgroups. An exploratory analysis comparing sorafenib with sunitinib as second-line treatments was also presented. However, because the subgroup data and indirect

comparison were marked as academic in confidence, only the data for the whole population will be presented in this document. The following health state utility values, taken from an unpublished survey of physicians, were applied: 0.737 for progression-free survival and 0.548 for progressed disease. The model assumed a sorafenib dose intensity of 100%.

4.2.11 With discounting at 3.5% per annum, the comparison of sorafenib with best supportive care produced an ICER of £90,630 per QALY gained for the combined group in the base case. The one-way sensitivity analyses did not produce an ICER lower than £60,000 per QALY gained, although the precise range of ICERs is not reported numerically in the manufacturer submission. The ICERs were most sensitive to health utility values for progression-free survival and progressed disease and the resource associated with the number of inpatient days required when receiving sorafenib and best supportive care.

4.2.12 The manufacturer of sunitinib (Pfizer) submitted a simple state-transition model with three health states: progression-free survival, progressed disease and death. The model compared sunitinib with best supportive care as second-line therapies, from the perspective of the NHS. Patient-level data on the effectiveness of sunitinib were taken from the smaller of the two single-arm phase II trials (see section 4.1.17). Data for best supportive care were taken from a pooled analysis of a review and Medicare data. Survival analysis was used to model disease progression, survival and treatment effect, with Weibull survival curves used to extrapolate the different, independent, sources of data. The health state utilities used were taken from EQ–5D data collected in the single-arm phase II trial with different utility values assigned according to treatment and health state: sunitinib/progression-free survival = 0.803; best supportive care/progression-free survival = 0.758;

sunitinib/progressive disease and best supportive care/progressed disease = 0.683.

4.2.13 With discounting at 3.5% per annum, 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 time spent in progression and the data source for best supportive care. The ICERs ranged from £27,935 to £206,962 per QALY gained when these parameters were explored.

Assessment Group model

Model structure and inputs

4.2.14 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 appraisal scope, from the perspective of the NHS. The Markov model considered three treatment strategy questions: first-line treatment (bevacizumab plus IFN-α and sunitinib as monotherapy compared with IFN-α); first-line treatment of people with a poor prognosis (temsirolimus compared with IFN-α) and second-line treatment (sorafenib compared with best supportive care) using similar model structures but with different model parameter data for each question. The model used three distinct health states: progression-free survival, progressive disease and death.

4.2.15 For first-line treatment of people suitable for immunotherapy, baseline disease progression (IFN-α alone) was taken from the bevacizumab study (see section 4.1.2). The Assessment Group stated that this data source was chosen as the overall survival Kaplan-Meier curve from the sunitinib RCT had not been published and that these data were immature. Data for progression-free survival and overall survival for people 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 as monotherapy were estimated using the hazard ratios from the bevacizumab study and the pre-planned interim analyses from the sunitinib study.

4.2.16 For first-line treatment of people with at least three of six factors indicating poor prognosis and who are suitable for immunotherapy, baseline disease progression (IFN-α alone) for progression-free survival and overall survival were estimated by fitting Weibull curves to empirical data from the temsirolimus study (see section 4.1.9). The disease progression for temsirolimus was estimated by applying the hazard ratios for progression-free and overall survival from the temsirolimus study. The following subgroup analyses were also performed: clear cell and non-clear cell carcinoma; prior nephrectomy and no prior nephrectomy; a poor prognosis according to the MSKCC score (approximately 75% of participants in the temsirolimus study) and no poor prognosis according to MSKCC score. The cost effectiveness of bevacizumab plus IFN-α for people with a poor prognosis was not estimated because of the small number of participants with a poor prognosis in the bevacizumab study.

4.2.17 For second-line treatment, 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 sorafenib RCT. Disease progression for participants receiving sorafenib was estimated by applying the hazard ratios from the sorafenib RCT. 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.

4.2.18 The health state utilities used in the Assessment Group model were derived from trial data in the manufacturer submissions and UK EQ–5D tariffs. Participants were assumed to be similar at baseline in terms of health state value. Therefore treatment-specific health state values were not applied. People who receive first-line treatments were assumed to have a utility of 0.78 when in the PFS state and 0.70 when in the PD state; these assumptions came from the Pfizer submission. People with a poor prognosis who can receive first-line treatments were assumed to have a utility of 0.60 when in the PFS state and 0.45 when in the PD state; these assumptions came from the Wyeth submission. People who were receiving second-line treatments were assumed to have a utility of 0.76 when in the PFS state and 0.68 when in the PD state; these assumptions also came from the Pfizer submission.

4.2.19 In the Assessment Group model, drug acquisition costs (except for sorafenib) were modified according to dose intensities reported in the relevant RCTs. Current list prices were taken from the BNF (edition 55). All other costs were inflated to 2007–8 values. Because temsirolimus had no BNF list price, the price of a 30-mg vial was inferred from the price of a 25-mg dose of temsirolimus as submitted by the manufacturer, and calculated as £618. However, the price stated by the manufacturer of £515 is included in the sensitivity analyses. The pricing strategies for bevacizumab and sunitinib, which were described by the manufacturers, were included in sensitivity analyses only. It was assumed that 100% of IFN-α monotherapy was administered at home, with 75% being self-administered. Additional resource uses associated with outpatient monitoring, scans and tests were used in the model for people in the PFS health state on drug treatment. In the PFS state,

the medical management cost per cycle was £81 for best supportive care and £223 for all other drug treatments. In the PD state, the cost for each cycle was £435 for all treatments.

4.2.20 A number of one-way and multi-way sensitivity analyses were performed to test the sensitivity of the cost-effectiveness analyses. The key sensitivity analyses investigated the assumptions that were made on clinical effectiveness, drug acquisition and administration costs, best supportive care and management costs and health-state utility values. The Assessment Group performed sensitivity analyses on their own model by varying their own assumptions and also by incorporating the manufacturers' parameters. The Assessment Group also performed sensitivity analyses on the manufacturers' models by incorporating the Assessment Group's parameters and assumptions.

Results from the Assessment Group model

4.2.21 With discounting at 3.5% per annum, the comparison of bevacizumab plus IFN-α with IFN-α alone produced an ICER of £171,301 and the comparison of sunitinib with IFN-α produced an ICER of £71,462. 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. For the indirect comparison of sunitinib with bevacizumab plus IFN-α, sunitinib presents with additional benefits at a lower cost and therefore dominates bevacizumab plus IFN-α.

4.2.22 With discounting at 3.5% per annum, the comparison of temsirolimus with IFN-α produced an ICER of £94,385. In the subgroup analyses for temsirolimus (clear cell, non-clear cell carcinoma; nephrectomy, 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 ICER 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).

4.2.23 With discounting at 3.5% per annum, the comparison of sorafenib with best supportive care produced an ICER of £102,498. The deterministic sensitivity analyses demonstrated that estimates of treatment effectiveness and cost of sorafenib (dose intensity assumption) were the key drivers affecting the ICERs. The health state utility parameters affected the ICER marginally. The ICER 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).

Results using Assessment Group and manufacturers' models inputting each others assumptions

4.2.24 When comparing the manufacturers' and Assessment Group's estimates of cost effectiveness, the ICERs for each comparison were higher when using the Assessment Group model than the manufacturers' models. In general, the model structures used by the Assessment Group and the manufacturers were similar.

However, there were some differences in assumptions and data inputs that have been highlighted by the Assessment Group.

4.2.25 In relation to the economic model submitted by Roche Products (bevacizumab plus IFN-α compared with IFN-α alone), the Assessment Group stated that it was essentially the assumptions over costs (especially drug-related costs) that were associated with different cost-effectiveness estimates. If the 'dose cap' pricing strategy detailed by the manufacturer was applied in the Assessment Group model, the ICER in the Assessment Group model was reduced from £171,301 to £90,584 per QALY gained. Similarly, if the 'dose cap' pricing strategy was removed from the manufacturer's model, the ICER increased from £74,978 to £108,329. Another important difference between the manufacturer's and Assessment Group models is the use of data on dose intensity. Incorporating the Assessment Group's higher dose intensity estimates into the manufacturer economic model further increased the ICER from £74,948 to £117,000.

4.2.26 In relation to the economic model submitted by Pfizer (sunitinib compared with IFN-α), the Assessment Group stated that a key difference was the choice of data used to model the baseline progression for IFN-α. The Assessment Group chose baseline disease progression from the bevacizumab trial. The manufacturer's base case analysis used baseline disease progression data from the sunitinib RCT. The Assessment Group was concerned about the extrapolation of the baseline disease progression undertaken by the manufacturer of sunitinib. It noted that the progression-free survival analysis was heavily influenced by the first few data points, which distorted the overall fit of the survival curve. The Assessment Group adjusted the baseline disease progression used by the manufacturer by smoothing out the early outliers in the regression. Applying the Assessment

Group's adjustment to the manufacturer's model resulted in an increase in the ICER from £28,546 to £48,052. When the Assessment Group used the same baseline progression data from the sunitinib RCT in their model, again with the adjusted fit, their ICER decreased from £71,462 to £61,868 per QALY gained. If the pricing strategy (first cycle of sunitinib free of charge to the NHS) was incorporated, the Assessment Group's base case ICER was reduced from £71,462 to £65,362 per QALY gained. If both the sunitinib trial baseline disease progression data (with an adjusted fit) and the pricing strategy were incorporated into a multi-way sensitivity analysis, the Assessment Group's ICER decreased from £71,462 to £57,737.

4.2.27 In relation to the economic model submitted by Wyeth Pharmaceuticals (temsirolimus compared with IFN-α), the Assessment Group stated that the key differences were the assumptions made on resource use and costs, particularly costs associated with the acquisition of temsirolimus and administration of IFN-α. Incorporating the Wyeth cost of temsirolimus into the Assessment Group's model decreased the ICER from £94,385 to £81,687. If the Assessment Group's assumptions of lower costs of administration of IFN-α were incorporated into the Wyeth model, the Wyeth ICER increased from £55,814 to £102,000.

4.3 Updated data from Pfizer

4.3.1 The manufacturer of sunitinib submitted updated analyses of the clinical and cost effectiveness of sunitinib compared with IFN-α as a first-line treatment for people suitable for immunotherapy. The updated data are after a maximum of 36 months of follow-up of the sunitinib RCT (see section 4.1.2). A number of estimates were provided, including a final intention-to-treat (ITT) analysis of the whole trial population, a final ITT analysis censored for those who crossed over from the IFN-α treatment arm to the sunitinib arm

(n = 25) and an analysis of those who did not go on to receive any other post-study treatment (193 in the sunitinib arm and 162 in the IFN-α arm). No characteristics of those who did not go on to receive any other post-study treatment were provided.

4.3.2 The median overall survival in the final ITT population was no longer significantly different for those who received sunitinib (26.4 months) compared with those who received IFN-α (21.8 months, HR 0.821, 95% CI 0.673 to 1.001, p = 0.0510). The median overall survival in the final ITT population that was censored for crossover did show a statistically significant benefit for those who received sunitinib (26.4 months) compared with those who received IFN-α (20.0 months, HR 0.808, 95% CI 0.661 to 0.987, p = 0.0362). The median overall survival was statistically significantly higher in those who received sunitinib and did not receive any post-study treatment (28.1 months) than those who received IFN-α (14.1 months, HR 0.647, 95% CI 0.483 to 0.870, p = 0.0033).

4.3.3 The updated estimate of cost effectiveness for the final ITT population gave an ICER of £72,003. For the final ITT population censored for crossover, the ICER was £71,760. For the population that did not receive any post-study treatments, the ICER was £41,472. The manufacturer adjusted and smoothed the modelled baseline progression-free survival curve to better fit the empirical data in the group that did not receive any post-study treatments. This adjustment was not reported in detail but appears to be similar to the original adjustments made to the sunitinib trial data by the Assessment Group. It resulted in an ICER of £35,245. Further similar adjustment and smoothing of the modelled baseline overall survival curve resulted in an ICER of £30,904 for sunitinib compared with IFN-α as first-line treatments.

4.4 Consideration of the evidence

4.4.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of bevacizumab, sorafenib, sunitinib and temsirolimus, having considered evidence on the nature of the condition and the value placed on the benefits of bevacizumab, sorafenib, sunitinib and temsirolimus by people with advanced and/or metastatic RCC, those who represent them, and clinical specialists. It was also mindful of the need to take account of the effective use of NHS resources.

4.4.2 The Committee heard from clinical specialists and patient experts that there are limited treatment options for people with advanced and/or metastatic RCC; the only current standard treatment is immunotherapy and there are no current treatment options for people whose condition had failed to respond to immunotherapy or who were considered unsuitable for immunotherapy.

First-line treatment for people suitable for immunotherapy

4.4.3 The Committee reviewed the evidence of clinical effectiveness from the bevacizumab study. The Committee noted that bevacizumab plus IFN-α demonstrated a significant gain in terms of progression-free survival compared with IFN-α alone. The Committee was aware that the data on overall survival were immature because median overall survival had not been reached. The Committee was persuaded that bevacizumab plus IFN-α is a clinically effective first-line treatment. However, it was mindful of the adverse effects associated with the combination of bevacizumab and immunotherapy.

4.4.4 The Committee then considered the estimates of cost effectiveness of bevacizumab plus IFN-α. It noted that the models from the manufacturer and the Assessment Group were similar in terms of structure and data sources; the models differed chiefly in the drug

acquisition costs. The Committee noted that these differences resulted in different estimates of cost effectiveness between the manufacturer and the Assessment Group. However, the Committee considered that neither model individually (£75,000 and £171,000 per QALY gained respectively), or with alternative assumptions applied, resulted in a cost-effectiveness estimate for bevacizumab plus IFN-α that was compatible with the best use of NHS resources. Therefore the Committee concluded that bevacizumab plus IFN-α as a first-line treatment for people with advanced and/or metastatic RCC would not be a cost-effective use of NHS resources.

4.4.5 The Committee reviewed the evidence of clinical effectiveness from the sunitinib study and also considered the updated clinical data provided by the manufacturer (Pfizer). The Committee noted that in the original study, sunitinib demonstrated a statistically significant gain in terms of progression-free survival compared with IFN-α. The Committee was aware that the data in the original sunitinib study on overall survival were immature, but considered the updated information on the final ITT population from Pfizer as a valid estimate of overall survival. The Committee, in considering whether the post-hoc subgroup with no post-study treatment could represent a valid estimate of clinical effectiveness, was concerned that no data on the selection or baseline characteristics of this subgroup had been presented. The Committee was persuaded that overall sunitinib is a clinically effective first-line treatment, but that no reliable inferences could be made about the post-hoc subgroup.

4.4.6 The Committee then considered the estimates of cost effectiveness of sunitinib provided by the manufacturer and the Assessment Group. The Committee noted that the adjustments made to the survival curves by the Assessment Group and their different costing assumptions resulted in a larger ICER than that originally

presented by the manufacturer (£71,500 per QALY gained compared with £28,500 per QALY gained, respectively). However, the Assessment Group's estimate was not larger than the updated baseline estimates of cost effectiveness provided by the manufacturer, despite the manufacturer's assumption of a free initial dose of sunitinib. The Committee did not consider that the estimate of cost effectiveness derived from the post-hoc subgroup that received no post-study treatments in the sunitinib trial could be considered a robust basis for decision-making as the estimates had not been critiqued by the Assessment Group and no details about the post-hoc subgroup were provided. Therefore the Committee concluded that sunitinib as first-line treatment for people with advanced and/or metastatic RCC would not be a cost-effective use of NHS resources.

First-line treatment for people unsuitable for immunotherapy

4.4.7 The Committee reviewed the academic-in-confidence evidence on the clinical and cost effectiveness of sorafenib compared with best supportive care as presented by the manufacturer (Bayer). The Committee was concerned that the data informing the comparisons came from a small subgroup from the sorafenib RCT. The Committee concluded that, although the data were limited, sorafenib as a first-line treatment for those unsuitable for immunotherapy with advanced and/or metastatic RCC would not be a cost-effective use of NHS resources.

4.4.8 No data were presented to the Committee on the clinical or cost effectiveness of sunitinib compared with best supportive care as a first-line treatment for people unsuitable for immunotherapy. In the absence of robust data, the Committee considered that it was unlikely that the parameters would differ greatly from those previously observed and would be unlikely to result in a cost-effectiveness estimate that would be compatible with the best use

of NHS resources. The Committee concluded that sunitinib as a first-line treatment for people unsuitable for immunotherapy with advanced and/or metastatic RCC would not be a cost-effective use of NHS resources.

First-line treatment for people suitable for immunotherapy with three of six factors indicating poor prognosis

4.4.9 The Committee reviewed the evidence of clinical effectiveness from the temsirolimus study. The Committee noted that temsirolimus demonstrated a statistically significant gain in terms of overall survival, progression-free survival and tumour response rate compared with IFN-α. The Committee was aware that subgroup data were available, but it was not sufficiently clear whether there was any significant difference in response between these subgroups. The Committee was mindful that the criteria used for defining poor prognosis in the temsirolimus trial were different from those commonly used in clinical practice. The Committee was persuaded that temsirolimus is a clinically effective first-line treatment for people with a poor prognosis.

4.4.10 The Committee then considered the estimates of cost effectiveness of temsirolimus. It noted that the models from the manufacturer and the Assessment Group were similar in terms of structure and data sources; the models differed chiefly in the acquisition cost of temsirolimus and costs associated with the administration of IFN-α. The Committee noted that these differences were associated with different estimates of cost effectiveness by the manufacturer and the Assessment Group. However, the Committee heard from clinical specialists that it is likely that most people would be able to self-administer IFN-α at home and that the proportion needing help with administration assumed by the Assessment Group was considered reasonable. Therefore neither the Assessment Group's base case ICER associated with a cost per QALY of £75,000, nor

the manufacturer's ICER incorporating the Assessment Group's IFN-α administration assumption of (£102,000) resulted in a cost-effectiveness estimate for temsirolimus that was compatible with the best use of NHS resources.

4.4.11 The Committee then considered the estimates presented by the Assessment Group with the lower price of temsirolimus acquisition as assumed by the manufacturer. However, irrespective of the lower price of temsirolimus, the costs per QALY gained using the Assessment Group model of £81,700 still remained well above the levels considered compatible with the best use of NHS resources. Therefore the Committee concluded that temsirolimus as a first-line treatment for people with advanced RCC and a poor prognosis would not be a cost-effective use of NHS resources.

4.4.12 Very few data were presented to the Committee on the clinical or cost effectiveness of bevacizumab plus IFN-α compared with IFN-α alone and sunitinib compared with IFN-α as first-line treatments for people with a poor prognosis, suitable for immunotherapy. In the absence of robust data, the Committee considered that it was unlikely that the parameters would differ greatly from those previously observed and would be unlikely to result in a cost-effectiveness estimate that would be compatible with the best use of NHS resources. The Committee concluded that bevacizumab and sunitinib as first-line treatments for people with poor prognosis, suitable for immunotherapy with advanced and/or metastatic RCC would not be a cost-effective use of NHS resources.

First-line treatment for people unsuitable for immunotherapy with three of six factors indicating poor prognosis

4.4.13 The Committee reviewed the evidence of clinical and cost effectiveness for temsirolimus compared with best supportive care as presented by the manufacturer (Wyeth). The Committee was aware that the data informing the comparisons came from an

indirect comparison. Limited information on the trial used in the comparison was presented and the Committee heard that the best supportive care in the trial was unlikely to be offered as current clinical practice and therefore the manufacturer cost-effectiveness estimate of £81,200 was likely to be an under-estimate. The Committee concluded that temsirolimus as a first-line treatment for patients with a poor prognosis, unsuitable for immunotherapy with advanced RCC would not be a cost-effective use of NHS resources.

4.4.14 No data were presented to the Committee on the clinical or cost effectiveness of sorafenib compared with best supportive care and sunitinib compared with best supportive care as first-line treatments for people with a poor prognosis and unsuitable for immunotherapy. In the absence of robust data, the Committee considered that it was unlikely that the parameters would differ greatly from those previously observed and would be unlikely to result in a cost-effectiveness estimate that would be compatible with the best use of NHS resources. The Committee concluded that sorafenib and sunitinib as first-line treatments for people with poor prognosis, suitable for immunotherapy with advanced and/or metastatic RCC would not be a cost-effective use of NHS resources.

Second-line treatment for people whose condition has failed to respond to immunotherapy

4.4.15 The Committee reviewed the clinical effectiveness of sorafenib and was aware that the sorafenib RCT was terminated early and people in the control arm were permitted to cross over and receive sorafenib. The Committee was mindful that this would introduce a confounding factor to the results, but that in clinical practice people are likely to receive additional therapies. The Committee noted that sorafenib demonstrated a clinically relevant and statistically significant advantage over best supportive care in terms of overall

survival, progression-free survival and tumour response. The Committee was persuaded that sorafenib is a clinically effective therapy for second-line treatment of RCC.

4.4.16 The Committee then reviewed the clinical and cost effectiveness for sunitinib as a second-line treatment compared with best supportive care. The Committee was concerned that the data informing the comparisons came from two small single-arm trials. The Committee acknowledged that the informal comparison with best supportive care suggested that sunitinib may be clinically effective compared with best supportive care. However, in the absence of further robust data, the Committee considered that it was unlikely that the parameters would differ greatly from those previously observed and would be unlikely to result in a cost-effectiveness estimate that would be compatible with the best use of NHS resources. Therefore the Committee concluded that sunitinib as a second-line treatment for advanced and/or metastatic RCC would not be a cost-effective use of NHS resources.

4.4.17 The Committee then reviewed the estimates of cost effectiveness of sorafenib. It noted that the models submitted by the manufacturer and the Assessment Group were generally similar in terms of structure, data sources and assumptions. The resulting estimates of cost effectiveness were broadly similar with a manufacturer base case ICER of £91,000 and Assessment Group base case ICER of £102,000. The Committee noted that neither estimate was compatible with the best use of NHS resources. Therefore the Committee concluded that sorafenib as a second-line treatment of people with advanced RCC would not be a cost-effective use of NHS resources.

4.4.18 Having concluded that bevacizumab, sorafenib, sunitinib and temsirolimus were not cost effective, within their licensed

indications for the treatment of RCC, the Committee considered the pricing strategies for bevacizumab and sunitinib proposed by the manufacturers, which include a 'dose cap' scheme and a free first cycle of drug treatment, respectively. The Committee was aware that these pricing strategies had not been considered by the Department of Health to establish whether the proposed discounts are nationally available and how long they will be in place. Sensitivity analyses of the Assessment Group's model taking these pricing strategies into account reduced the ICERs for bevacizumab plus IFN-α to £91,000 per QALY gained and for sunitinib to £57,700 per QALY gained, the latter without taking into account the late data on survival from Pfizer. Therefore, the costs per QALY gained still remained above the levels considered compatible with the best use of NHS resources. The Committee concluded that the use of bevacizumab plus IFN-α and sunitinib as first-line treatments for advanced and/or metastatic RCC, irrespective of the proposed pricing strategies, would still not be a cost-effective use of NHS resources. The Committee suggested that any revised or new pricing strategies, put forward to the Department of Health by the manufacturers, which could result in the use of these drugs being a cost-effective use of NHS resources, would be considered.

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

5.2 'Healthcare standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.

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

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

6 Proposed recommendations for further research

6.1 There are a number of ongoing trials, actively recruiting participants, relevant to this appraisal. A number of these trials are investigating the optimum sequences of treatment. Full details of ongoing research can be found at www.ukcrn.org.uk, www.clinicaltrials.gov and www.controlled-trials.com.

6.2 The Assessment Group considered that the following well-conducted RCTs reporting health-related utility values in accordance with the NICE methods guide could be of value.

- RCTs to investigate the effectiveness of bevacizumab plus IFN-α, sorafenib, sunitinib and best supportive care in patients who are unsuitable or contraindicated for immunotherapy who have a poor or intermediate prognosis.
- RCTs of sunitinib and sorafenib as second-line treatments after failure of immunotherapy.

7 Related NICE guidance

- Percutaneous radiofrequency ablation of renal cancer. NICE interventional procedure guidance 91 (2004). Available from www.nice.org.uk/IPG091
- Improving outcomes in urological cancer. NICE cancer service guidance (2002). Available from www.nice.org.uk/CSGUC

8 Proposed date for review of guidance

8.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider whether the technology should be reviewed. This decision will be taken in the light of information gathered by the Institute, and in consultation with consultees and commentators.

8.2 It is proposed that the guidance on this technology is considered for review in July 2011. The Institute would particularly welcome comment on this proposed date.

Andrew Stevens
Chair, Appraisal Committee
July 2008

Appendix A: Appraisal Committee members, and NICE project team

A Appraisal Committee members

The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets three times a month except in December, when there are no meetings. The Committee membership is split into three branches, each with a chair and vice-chair. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Professor David Barnett
Professor of Clinical Pharmacology, University of Leicester

Dr David W Black
Director of Public Health, Derbyshire County Primary Care Trust

Mr David Chandler
Chief Executive, Psoriasis and Psoriatic Arthritis Alliance

Mr Peter Clarke
Consultant Medical Oncologist, Clatterbridge Centre for Oncology, Merseyside

Dr Christine Davey
Senior Researcher, North Yorkshire Alliance R & D Unit

Dr Mike Davies

Consultant Physician, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips

Public Affairs Manager, Medtronic

Dr Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Mrs Eleanor Grey

Lay member

Dr Dyfrig Hughes

Reader in Pharmacoeconomics, Centre for Economics and Policy in Health, Bangor University.

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Professor Peter Jones

Pro Vice Chancellor for Research & Enterprise, Keele University

Ms Rachel Lewis

Nurse Advisor to the Department of Health

Dr Damien Longson

Consultant in Liaison Psychiatry, North Manchester General Hospital

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Richard Alexander Nakielny

Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

Dr Katherine Payne

Health Economics Research Fellow, University of Manchester

Dr Danielle Preedy

Senior Programme Manager, National Collaborating Centre for Efficacy and Mechanism Evaluation

Dr Martin J Price

Head of Outcomes Research, Janssen-Cilag

Dr Philip Rutledge

Consultant in Medicines Management, NHS Lothian

Dr Surinder Sethi

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

Professor Andrew Stevens

Chair of Appraisal Committee C

Dr Cathryn Thomas

Senior Lecturer, Department of Primary Care and General Practice, University of Birmingham

Dr William Turner

Consultant Urologist, Addenbrooke's Hospital, Cambridge

B NICE project team

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

Rebecca Trowman and George Vamvakas

Technical Leads

Joanna Richardson

Technical Adviser

Chris Feinmann

Project Manager

Appendix B: Sources of evidence considered by the Committee

A The assessment report for this appraisal was prepared by Peninsula Technology Assessment Group, University of Exeter.

- Thompson Coon J et al, Bevacizumab, sorafenib tosylate, sunitinib and temsirolimus for renal cell carcinoma, May 2008.

B The following organisations accepted the invitation to participate in this appraisal. They were invited to comment on the draft scope, assessment report and the appraisal consultation document (ACD). Organisations listed in I and II were also invited to make written submissions and have the opportunity to appeal against the final appraisal determination.

I Manufacturer/sponsor:

- Bayer (sorafenib)
- Pfizer (sunitinib)
- Roche Products (bevacizumab)
- Wyeth Pharmaceuticals (temsirolimus)

II Professional/specialist and patient/carer groups:

- British Uro-oncology Group
- Cancer Network Pharmacists Forum
- Cancer Research UK
- Cancerbackup
- James Whale Fund for Kidney Cancer
- Kidney Cancer UK
- Kidney Research UK
- National Kidney Federation
- Rarer Cancers Forum
- Royal College of Nursing
- Royal College of Pathologists
- Royal College of Physicians, Medical Oncology Joint Special Committee
- South Asian Health Foundation

III Other consultees

- Cambridgeshire PCT
- Department of Health
- Welsh Assembly Government

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

- Department of Health, Social Services and Public Safety for Northern Ireland
- MRC Clinical Trials Unit
- National Collaborating Centre for Cancer
- National Coordinating Centre for Health Technology Assessment
- NHS Quality Improvement Scotland
- Novartis Pharmaceuticals (interleukin-2)
- Peninsula Technology Assessment Group, University of Exeter
- Roche Products (interferon alpha)

C The following individuals were selected from clinical specialist and patient advocate nominations from the non-manufacturer/sponsor consultees and commentators. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on bevacizumab, sorafenib, sunitinib and temsirolimus by attending the initial Committee discussion and/or providing written evidence to the Committee. They are invited to comment on the ACD.

- Dr David Chao, Consultant Medical Oncologist nominated by Royal College of Physicians – clinical specialist
- Dr Pat Hanlon, nominated by Kidney Cancer UK – patient expert
- Mrs Kate Spall, Chair of and nominated by the Pamela Northcott Fund – patient expert
- Mr Bill Savage, nominated by the Rarer Cancers Forum – patient expert