NICE National Institute for Health and Care Excellence

NICE guidance

Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Guidance

1.1 Bevacizumab, sorafenib and temsirolimus are not recommended as first-line treatment options for people with advanced and/or metastatic renal cell carcinoma.

1.2 Sorafenib and sunitinib are not recommended as second-line treatment options for people with advanced and/or metastatic renal cell carcinoma.

1.3 People who are currently being treated with bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for advanced and/or metastatic renal cell carcinoma should have the option to continue their 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 regional 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 a UK marketing authorisation for treatment of people with advanced RCC. For those people receiving immunotherapies for the treatment of advanced RCC it is suggested that median overall survival is 11.4 months compared with a median overall survival of 7.6 months for 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 in whom first-line immunotherapy has failed, 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 a 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. The initial dose of bevacizumab should be delivered over 90 minutes and if the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes. IFN-α (Roferon-A, Roche Products) 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 for use in advanced and/or metastatic RCC 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. The manufacturer of bevacizumab (Roche) has agreed a patient access scheme with the Department of Health for advanced and/or metastatic RCC. 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 a UK marketing authorisation for the treatment of people with advanced RCC in whom IFN-α or interleukin-2-based therapy has failed or who are considered unsuitable for such therapy. Sorafenib has designated EU orphan drug status for RCC.

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 for use in people with advanced RCC as long as clinical benefit is observed or until unacceptable adverse events occur. The current price for a pack of 200-mg tablets (112 tablets per pack) is £2980.47 (excluding VAT). The average daily cost of sorafenib treatment is £106.45, with an average 6-week cycle costing £4471. The manufacturer of sorafenib (Bayer) has agreed a patient access scheme with the Department of Health for

advanced RCC. Costs of treatment cycles 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 a UK marketing authorisation for the treatment of people with advanced and/or metastatic RCC.

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 dose may be adjusted in steps of 12.5 mg according to tolerability (dose range 25–75 mg). 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. The manufacturer of sunitinib (Pfizer) has agreed a patient access scheme with the Department of Health for advanced and/or metastatic RCC. Costs of treatment cycles 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 a 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)
- serum 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 for RCC.

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. Treatment with temsirolimus should continue until there is no clinical benefit or until unacceptable toxicity occurs. The net-price for a 30-mg vial of temsirolimus is £620 (excluding VAT; BNF edition 57). Costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

The Appraisal Committee (appendix A) considered evidence from a number of sources (appendix B). The following sections are based on the evidence received for the appraisal of 'bevacizumab, sorafenib, sunitinib and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma'. However, the following sections do not relate specifically to the appraisal of sunitinib for the first-line treatment of advanced and/or metastatic RCC.

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 people suitable for immunotherapy (bevacizumab plus IFN-α compared with IFN-α)
- first-line treatment for people suitable for immunotherapy and with a poor prognosis (bevacizumab plus IFN-α and temsirolimus [as monotherapy] compared with IFN-α)
- first-line treatment for people unsuitable for immunotherapy (sorafenib compared with best supportive care)
- first-line treatment for people with a poor prognosis unsuitable for immunotherapy (sorafenib and temsirolimus [both as monotherapy] compared with best supportive care)
- second-line treatment for people in whom immunotherapy has failed (sorafenib and sunitinib [both as monotherapy] compared with best supportive care)
- second-line treatment for people in whom first-line treatment has failed and who are unsuitable for immunotherapy (sorafenib [as monotherapy] compared with best supportive care).

First-line treatment for people suitable for immunotherapy

4.1.2 One randomised controlled trial (RCT) of 649 people assessed the effect of bevacizumab plus IFN-α (n = 327) compared with IFN-α plus placebo (n = 322). In this study, the primary outcome was overall survival. The study was unblinded after a pre-planned interim analysis based on approximately 250 deaths, and participants in the IFN-α arm who had not progressed were offered bevacizumab plus IFN-α. IFN-α was given for a maximum of 1 year. The 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.

4.1.3 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 plus placebo arm. There was no statistically significant difference in overall survival between bevacizumab plus IFN-α compared with IFN-α plus placebo (hazard ratio [HR] 0.79, 95% confidence interval [CI] 0.62 to 1.02, p = 0.0670).

4.1.4 Progression-free survival was defined as the time between randomisation and first documented disease progression or death from any cause. There was a statistically significant difference in median progression-free survival for bevacizumab plus IFN-α (10.2 months) compared with IFN-α plus placebo (5.4 months); HR 0.63, 95% CI 0.52 to 0.75.

4.1.5 Tumour response rate was measured as a partial or complete reduction in tumour size. The overall tumour response rate in the bevacizumab plus IFN-α arm was 31% compared with 13% in the IFN-α plus placebo arm (p = 0.0001). Approximately half of all the trial participants achieved stable disease.

4.1.6 Adverse events were taken from the 'safety population' (that is, people were assigned to treatments in the analysis based on what they actually received, for example patients in the IFN-α plus 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. A total of 28% of participants discontinued treatment in

the bevacizumab plus IFN-α arm because of adverse events compared with 12% in the IFN-α plus placebo arm. Health-related quality of life was not measured in the study.

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

4.1.7 One RCT with 626 participants investigated the effectiveness of temsirolimus (n = 209), temsirolimus plus IFN-α (n = 210) and IFN-α alone (n = 207) 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.

4.1.8 In the temsirolimus study, there were statistically significant differences 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 0.61, 95% CI 0.41 to 0.91) 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 0.63 to 1.11) and those who had clear cell carcinoma (HR 0.85, 95% CI 0.64 to 1.08).

4.1.9 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 difference 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 investigators' assessment (HR 0.74, 95% CI 0.60 to 0.90; p = 0.0028). Compared with IFN-α, temsirolimus improved progression-free survival for those who had not undergone prior nephrectomy (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). Compared with IFN-α, temsirolimus improved progression-free survival for those who had non-clear-cell carcinoma (HR 0.36, 95% CI 0.22 to 0.59), and there was a non-statistically significant difference for those who had clear cell carcinoma (HR 0.84, 95% CI 0.67 to 1.05).

4.1.10 The temsirolimus study measured objective tumour response rate. The manufacturer of temsirolimus (Wyeth Pharmaceuticals) stated that no statistically significant differences were observed; the objective partial tumour response rate was 8.6% (18 participants) for those who received temsirolimus compared with 4.8% (10 participants) for those who received IFN-α. There was a statistically significant difference in the number of participants that achieved stable disease for at least 8 weeks with temsirolimus (131 participants, 62.7%) compared with IFN-α (80 participants, 38.6%).

4.1.11 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 participants in the temsirolimus arm discontinued treatment because of adverse events compared with 14% (n = 29) in the IFN-α alone arm. 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.

4.1.12 In the bevacizumab study (see section 4.1.2), 9% of participants receiving bevacizumab plus IFN-α and 8% of those receiving IFN-α plus placebo were defined as having a poor prognosis. Only progression-free survival was reported according to this subgroup. 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).

First-line treatment for people unsuitable for immunotherapy

4.1.13 The Assessment Group did not identify any full reports of RCTs assessing sorafenib as first-line treatment for people with advanced and/or metastatic RCC who were unsuitable for immunotherapy. One RCT was identified with a small population subgroup (17% of the total number of participants) that was unsuitable for immunotherapy. However, these participants did not receive sorafenib as a first-line treatment because the RCT only included people who had received at least one prior systemic therapy. Further details of the sorafenib RCT are given in section 4.1.15. The manufacturer of sorafenib (Bayer) submitted data on first-line treatment of people unsuitable for immunotherapy from two expanded access programmes conducted in Europe (318 participants unsuitable for immunotherapy) and North America (224 participants unsuitable for immunotherapy). Both were in effect single-arm studies and the results were reported only in abstract form. The expanded access studies reported median progression-free survival of 6.0 months and 8.1 months, respectively.

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

4.1.14 The Assessment Group did not identify any data on the clinical effectiveness of sorafenib 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 in whom immunotherapy has failed

4.1.15 One RCT with 903 participants investigated the effectiveness of sorafenib (n = 451) compared with placebo, which was considered equivalent to best supportive care (n = 452). The RCT included 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 favourable or intermediate MSKCC prognostic score. A total of 83% of participants had received previous immunotherapy and the remaining 17% of participants were unsuitable for immunotherapy so had received other first-line therapies. The primary outcome of the RCT was overall survival. The RCT was terminated early, on ethical grounds, after an independent review decided that sorafenib should be offered to participants who were receiving placebo.

4.1.16 For the whole trial population, at the time of the first interim analyses, the median 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 pre-specified O'Brien–Fleming threshold of less than or equal to 0.0005.

4.1.17 From the whole trial population of the sorafenib RCT, results were reported of a pre-planned interim analysis and an unplanned updated analysis (at the point of crossover) for progression-free survival. For the pre-planned analyses, both the independent and investigator assessments resulted in statistically significant differences in median progression-free survival. The independent assessment of median progression-free survival was 5.5 months in the sorafenib arm compared with 2.8 months in the placebo arm (HR 0.44, 95% CI 0.35 to 0.55). The investigator assessment of median progression-free survival was 5.9 months in the sorafenib arm compared with 2.8 months in the placebo arm ($p < 0.001$). The unplanned investigator assessment of median progression-free survival at the time of crossover was 5.5 months in the sorafenib arm compared with 2.8 months in the placebo arm (HR 0.51, 95% CI 0.43 to 0.60).

4.1.18 The sorafenib RCT measured tumour response rate. Out of the whole trial population, 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, and 333 (74%) participants receiving sorafenib and 239 (53%) receiving placebo achieved stable disease. This difference was statistically significant ($p < 0.001$).

4.1.19 Health-related quality of life was measured in the whole trial population of 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 statistically significant difference in mean FKSI-10 total score between groups over the first 32 weeks of treatment ($p = 0.83$ and $p = 0.98$, respectively). However, median time to health status deterioration, as defined by a four-point or more drop in FKSI-10 total score, was significantly greater for those receiving sorafenib compared with those receiving placebo ($p < 0.0001$). 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 people receiving sorafenib reported 'bothersome side effects of treatment' than those receiving placebo ($p <$

0.0001). Skin rashes, hypertension, diarrhoea and hand–foot syndrome were more common in the sorafenib arm.

4.1.20 One randomised discontinuation trial was also identified that compared sorafenib with best supportive care. The randomised discontinuation trial included 65 people with advanced and/or metastatic RCC. In most participants immunotherapy had failed. Most participants in this trial had an ECOG performance status of 0 or 1 and had undergone prior nephrectomy. The median progression-free survival in the sorafenib randomised discontinuation trial was significantly longer for 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). Overall survival, health-related quality of life and adverse events were not assessed in the randomised discontinuation trial.

4.1.21 Two single-arm phase II studies, of 63 and 106 participants, investigated the effectiveness of sunitinib as second-line treatment following prior nephrectomy and at least one course of cytokine-based therapy. 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.

4.1.22 The median overall survival in the smaller sunitinib study was 16.4 months (95% CI 10.8 to 'not reached') 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 suggests that sunitinib may be clinically effective

compared with best supportive care.

Second-line treatment for people unsuitable for immunotherapy

4.1.23 The Assessment Group did not identify any full reports of RCTs assessing sorafenib as a second-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 but had received other first-line treatments. This was a trial of sorafenib compared with placebo, which was assumed to be equivalent to best supportive care. Further details of the sorafenib RCT are given in section 4.1.15. The Assessment Group did not consider the results from 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.

Summary of clinical effectiveness

4.1.24 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 bevacizumab plus IFN-α appears to have significant benefits compared with IFN-α alone in terms of progression-free survival and tumour response. 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 differential effect on people who have non-clear-cell carcinoma and who have not undergone nephrectomy. The frequency of adverse events associated with bevacizumab and temsirolimus is comparable to that associated with IFN-α monotherapy, but the adverse event profiles differ between treatments.

4.1.25 The Assessment Group concluded that for second-line treatment for people in whom immunotherapy had failed, sorafenib demonstrated clinically and statistically significant benefits compared with best

supportive care in terms of progression-free survival and tumour response rate. Sorafenib was associated with more adverse events than best supportive care, particularly hand–foot skin reactions and hypertension. 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 drawn 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, progressive disease and death. The model compared bevacizumab plus IFN-α with IFN-α plus placebo as a first-line treatment for people suitable for immunotherapy. 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 plus placebo 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 plus placebo overall survival Gompertz curve. The treatment-specific (that is, different utility scores calculated for the different trial arms) utility data from an RCT of sunitinib compared with IFN-α 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 (that is, the amount of drug administered in a

clinical trial as a proportion of the amount that would have been administered if there had been no withdrawals of participants or dose reductions). The cost adjustment of bevacizumab was estimated as 62%; that of IFN-α was estimated 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 g 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 plus placebo produced a base-case incremental cost-effectiveness ratio (ICER) of £74,999 per quality-adjusted life year (QALY) gained. One-way sensitivity analyses consisted only of exploring the effects of using 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. The manufacturer of bevacizumab acknowledged that this sensitivity analysis may be implausible because the use of a log–logistic model resulted in a longer life expectancy (20 years) than would be expected for people with advanced and/or metastatic RCC.

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

4.2.4 The manufacturer of temsirolimus (Wyeth Pharmaceuticals) submitted a state-transition model with three health states: progression-free survival, post-progression 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. Patient-level data were taken from the temsirolimus trial described in section 4.1.7. 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 and post-progression. Drug costs were adjusted according to RCT data on dose intensity and estimated as 92% for temsirolimus and 56% for IFN-α. At the time of the original submission, the manufacturer used a price of

£515 (excluding VAT) for a 30-mg vial of temsirolimus (see section 4.2.18) and no wastage was assumed.

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

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

4.2.6 The manufacturer of temsirolimus (Wyeth Pharmaceuticals) submitted an indirect comparison of temsirolimus with best supportive care. The model described in section 4.2.4 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 in whom immunotherapy has failed or who are unsuitable for immunotherapy

4.2.7 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 in whom immunotherapy had failed or who were unsuitable for immunotherapy. Patient-level data were taken from the sorafenib RCT (see section 4.1.15). 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 a second-line treatment who were unsuitable for immunotherapy and in whom a non-immunotherapy-based first-line treatment had failed; 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 are 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%. The manufacturer used a price of £2504.60 (excluding VAT) for a pack of 200-mg tablets (112 per pack).

4.2.8 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 as demonstrated by Tornado diagrams reported in the manufacturer's 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.

4.2.9 The manufacturer of sorafenib submitted revised cost-effectiveness analyses for the whole trial population and for the 83% of the trial participants in whom immunotherapy had failed. The revised cost-effectiveness estimates also incorporated a patient access scheme in which the first pack of sorafenib is free to the NHS. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS. Details of the new price of sorafenib of £2980.47 for a pack of 112 200-mg tablets, which was agreed in the context of the Pharmaceutical Price Regulation Scheme (PPRS), were also provided. In the revised analyses, the progression-free and overall survival curves for both sorafenib and best supportive care were modelled by fitting independent Weibull distributions to each

separate curve (rather than exponential extrapolation as in the original submission). The manufacturer stated that this approach was justified because it was more consistent with the distributions used in the Assessment Group's economic model. The manufacturer also made further amendments to the cost and utility assumptions to more closely reflect the original model developed by the Assessment Group. The revised ICER (taking into account the patient access scheme and new price) for the whole trial population was £72,546 per QALY gained. The revised ICER (taking into account the patient access scheme and new price) for the subgroup of participants in whom immunotherapy had failed was £62,256 per QALY gained. No sensitivity analyses of the revised cost-effectiveness estimates were presented by the manufacturer of sorafenib.

4.2.10 In the original submission, the manufacturer of sorafenib (Bayer) also submitted a cost-effectiveness estimate of sorafenib as second-line treatment for people who were unsuitable for immunotherapy compared with best supportive care. Patient-level data were taken from a small population subgroup of 17% of participants in the sorafenib RCT (described in section 4.1.15). The cost-effectiveness estimates for this subgroup were marked as academic in confidence. Therefore they are not presented in this document.

4.2.11 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. Patient-level data on the effectiveness of sunitinib were taken from the smaller of the two single-arm phase II trials (see section 4.1.21). 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 independent data from different sources. 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/progressed disease and best supportive care/progressed disease = 0.683. The cost-effectiveness estimates also incorporated a

patient access scheme in which the first pack of sunitinib is free to the NHS. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden on the NHS.

4.2.12 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

4.2.13 The Assessment Group model was developed to estimate the cost 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 Markov model considered three treatment strategy questions: first-line treatment (bevacizumab plus IFN-α 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.

4.2.14 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). 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 was estimated using the ITT hazard ratios from the bevacizumab trial.

4.2.15 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 4.1.7). 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). 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.

4.2.16 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 as it was not clear whether the subgroups were defined a priori and the sample size calculations were based on the entire trial population. The cost effectiveness of sunitinib as a second-line treatment compared with best supportive care 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.

4.2.17 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 data submitted by the manufacturer of sunitinib and used in the appraisal of sunitinib as a first-line treatment for advanced and/or metastatic RCC. 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 came from the Pfizer submission.

4.2.18 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), and the agreed patient access scheme of the first pack of sorafenib being free to the NHS was applied. All other costs were inflated to 2007–8 values. Because temsirolimus had no BNF list price at the time of the submission, 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 in their original submission of £515 was included in the sensitivity analyses. The patient access scheme for bevacizumab, which was described by the manufacturer, was 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.

4.2.19 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. In particular, the Assessment Group highlighted a paucity of data surrounding accurate health-state utility values and best supportive care costs. 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

4.2.20 With discounting at 3.5% per annum, the comparison of bevacizumab plus IFN-α with IFN-α alone produced an ICER of £171,301 per QALY gained. 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 were particularly sensitive to variations in estimates of the hazard ratio for overall survival, with ICERs ranging from £90,693 (HR for overall survival = 0.58) to £868,881 (HR for overall survival = 0.97) per QALY gained for bevacizumab plus IFN-α compared with IFN-α alone.

4.2.21 With discounting at 3.5% per annum and using a vial price of £618, the comparison of temsirolimus with IFN-α produced an ICER of £94,385 per QALY gained. In the subgroup analyses for temsirolimus (clear cell, non-clear-cell carcinoma; nephrectomy, no nephrectomy; and only participants with a poor prognosis according to the Motzer criteria), 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) per QALY gained in the Assessment Group's initial analyses.

4.2.22 With discounting at 3.5% per annum and using the original price of £2504.60, the comparison of sorafenib with best supportive care produced an ICER of £102,498 per QALY gained for all patients. 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) per QALY gained.

Assessment Group's exploration of the manufacturer models using the Assessment Group's assumptions and exploration of the Assessment Group's model using the manufacturers' assumptions

4.2.23 All ICERs 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.

4.2.24 In relation to the economic model submitted by Roche Products (bevacizumab plus IFN-α compared with IFN-α plus placebo), the Assessment Group stated that it was essentially the assumptions about costs (especially drug-related costs) that were associated with different cost-effectiveness estimates. If the original 'dose cap' patient access scheme 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 original 'dose cap' patient access scheme was removed from the manufacturer's model, the ICER increased from £74,999 to £108,329 per QALY gained. 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 £74,999 to £117,000 per QALY gained.

4.2.25 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 the administration of IFN-α. If the Assessment Group's assumptions of lower costs of administration of IFN-α were incorporated into the Wyeth model (which used a vial price of £515), the Wyeth base case ICER increased from £55,814 to £102,000 per QALY gained. The ICERs for the different subgroups also increased: from £51,159 to £63,100 per QALY gained for the subgroup with non-clear-cell carcinoma; from

£57,731 to £121,300 per QALY gained for the subgroup with clear cell carcinoma; from £49,690 to £84,000 per QALY gained for the subgroup with no prior nephrectomy; and from £60,575 to £117,000 per QALY gained for the subgroup with prior nephrectomy.

Incorporation of Roche's suggested parameter changes and agreed patient access scheme into the Assessment Group's model by the Decision Support Unit

4.2.26 Following consultation on the draft guidance, the Assessment Group and the Decision Support Unit (DSU) were requested to explore the issues raised during the consultation.

4.2.27 The manufacturer of bevacizumab (Roche Products) requested that the following parameters were altered in the Assessment Group's economic model:

- The hazard ratio for overall survival should be reduced from 0.75 to 0.613. This is because 28% of the participants in the bevacizumab plus IFN-α arm and 18% of the participants in the IFN-α plus placebo arm of the trial received second-line treatments. The hazard ratio of 0.613 represents the effect of bevacizumab plus IFN-α compared with IFN-α plus placebo on overall survival when the participants who received any second-line treatments were censored from the analysis.
- The average cumulative dose of bevacizumab per participant should be based on the empirical trial data; that is, an average dose of 756.7 mg of bevacizumab per administration (the Assessment Group's base case assumed an average bevacizumab dose intensity of 88% over 12 months, which was based on the dosage implied by the trial protocol).
- The average number of bevacizumab administrations per participant should be based on empirical trial data; that is, an average duration of bevacizumab treatment of 7.36 months (the Assessment Group's base case assumed a treatment duration of 12 months, based on the interpretation of the trial protocol).
- The cost of bevacizumab administration should be reduced from £197 to £98 because of the reduced time needed to administer intravenous bevacizumab.

4.2.28 Applying these parameter changes to the Assessment Group's base case reduced the cost-effectiveness estimate of bevacizumab plus IFN-α compared with IFN-α plus placebo. Applying the revised hazard ratio for overall survival reduced the ICER from £171,301 per QALY gained to £101,340 per QALY gained. Using the empirical trial data on dosage of bevacizumab and number of administrations reduced the base-case ICER from £171,301 to £114,624 per QALY gained and reduced the revised ICER (with a hazard ratio for overall survival of 0.613) from £101,340 to £68,561 per QALY gained. Reducing the cost of bevacizumab administration further reduced the base-case ICER from £114,624 to £108,835 per QALY gained and the revised ICER (with a hazard ratio for overall survival of 0.613) from £68,561 to £65,213 per QALY gained.

4.2.29 The DSU highlighted concerns that the revised hazard ratio for overall survival as presented by Roche (0.613) was now lower than the hazard ratio for progression-free survival (0.63). The DSU performed additional analysis of the parameter changes that set the hazard ratio for overall survival equal to that of progression-free survival (that is, hazard ratios of 0.63 for both). This reduced the original Assessment Group base-case ICER from £171,301 to £107,489 per QALY gained.

4.2.30 Following consultation on the parameter changes made to the Assessment Group model by the DSU, the manufacturer of bevacizumab responded stating that the dose intensity should be revised to 92%. A revised cost of bevacizumab administration of £170 per dose was also suggested by the manufacturer of bevacizumab. The DSU was requested to calculate an updated cost-effectiveness estimate for bevacizumab plus IFN-α compared with IFN-α in the Assessment Group's model. The DSU was asked to use the following parameters: a corrected bevacizumab dose intensity of 92%; a bevacizumab administration cost of £170; and a hazard ratio for overall survival of 0.63 (equal to that of progression-free survival). Using these parameters in the Assessment Group's model resulted in an ICER of £82,732 per QALY gained for bevacizumab plus IFN-α compared with IFN-α.

4.2.31 Following further consultation, the manufacturer of bevacizumab (Roche) included details of an updated patient access scheme which had been

agreed with the Department of Health. The patient access scheme includes a rebate of the costs of bevacizumab after 10 g has been given to a patient in a 12-month period and a rebate of all costs of IFN-α when it is given with bevacizumab. The Department of Health considered that this patient access scheme does not constitute an excessive administrative burden to the NHS. The DSU was asked to provide a revised cost-effectiveness estimate using the Assessment Group model, incorporating the parameter changes requested by the manufacturer of bevacizumab (see section 4.2.27) and the costs with the patient access scheme. Applying the parameter changes and including the costs from the patient access scheme reduced the cost-effectiveness estimate of bevacizumab plus IFN-α compared with IFN-α plus placebo from £82,732 to £53,820 per QALY gained.

Validity check of Bayer's data by the Decision Support Unit

4.2.32 The manufacturer of sorafenib (Bayer) provided a late submission, which revised their original analysis of the whole trial population and the 83% of participants in whom first-line immunotherapy had failed. No revised analyses were provided of the 17% in whom other first-line (non-immunotherapy) treatments had failed. The revised analyses also included details of a patient access scheme in which the first pack of sorafenib is free to the NHS. The manufacturer also presented information about the new price of sorafenib in the context of the PPRS. The DSU was asked to appraise the approach used by the manufacturer and provide cost-effectiveness estimates using the Assessment Group model, incorporating costs with the scheme and the new increased price. In relation to the approach used by the manufacturer. The DSU acknowledged that the alternative modelling approach, utility values and costs had been changed by the manufacturer to reflect those used in the Assessment Group model and that a more complete dataset for the people in whom immunotherapy had failed was used in the revised analyses. The DSU also agreed with the manufacturer that the assumption of proportional hazards was not valid and this resulted in a large reduction in the ICERs. However, the DSU noted that the revised analysis resulted in ICERs for people in whom immunotherapy had failed which were lower than the total group ICERs and this was markedly different from the original (confidential) analyses presented by the

manufacturer of sorafenib, where the subgroup ICER was higher than the total group ICER. The DSU also highlighted that the follow-up of the participants randomised to receive sorafenib was much longer than that of the participants randomised to receive best supportive care. This was because participants were allowed to crossover from best supportive care to sorafenib treatment after the study was terminated early on ethical grounds. There were also no details about whether participants randomised to receive sorafenib received any subsequent treatments. Therefore the DSU stated that a more appropriate approach would have been to censor both arms at the same point. The DSU noted that this approach was presented in the main publication of the trial.

4.2.33 The DSU then calculated the respective cost-effectiveness estimates using the Assessment Group's economic model. The DSU accepted arguments presented by the manufacturer of sorafenib that the proportional hazards assumption did not hold and that independent curve modelling should be used. In order to address the concerns surrounding the censoring approach used by the manufacturer, the DSU censored both arms at the same point (that is, at the point of trial termination). The DSU then modelled the progression-free and overall survival curves for sorafenib and best supportive care using independent Weibull curves. The revised ICER for the whole trial population (including costs with the patient access scheme and new price) was £74,915 per QALY gained. The revised ICER (including costs with the patient access scheme and new price) for the subgroup of participants in whom immunotherapy had failed was £65,929 per QALY gained.

4.3 Consideration of the evidence

4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line), having considered evidence on the nature of the condition and the value placed on the benefits of bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) 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.

4.3.2 The Committee heard from clinical specialists and patient experts that there are limited treatment options for people with advanced and/or metastatic RCC. The Committee noted that the only current standard first-line treatment is immunotherapy and there are no current treatment options for people in whom immunotherapy has failed or who are considered unsuitable for immunotherapy. Moreover, there are no current standard second-line treatment options. The Committee heard from people with RCC and patient experts that immunotherapy is associated with limited effectiveness and high toxicity. The Committee also heard that RCC does not respond well to conventional chemotherapies and that bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) represent improvements in the treatment of advanced and/or metastatic RCC.

4.3.3 The Committee heard from people with RCC and patient experts that advanced and/or metastatic RCC is a relatively rare cancer and noted the views of both patient and clinical experts concerning the severity of the disease. The Committee also heard from clinical experts, the Assessment Group and manufacturers that there is a paucity of data on the utility values associated with living with advanced and/or metastatic RCC. The Committee noted that it may be difficult to fully capture the effects of bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) on health-related quality of life. The Committee acknowledged the comments that were received from people with RCC and the public, stating that some people with RCC had experienced significant improvements in their quality of life as a result of using the drugs.

4.3.4 The Committee was aware of the supplementary advice from NICE that should be taken into account when appraising treatments which may extend the life of people with a short life expectancy and which are licensed for indications that affect small numbers of people with incurable illnesses. For this advice to be applied, all the following criteria must be met:

- The treatment is indicated for patients with a short life expectancy, normally less than 24 months.

- There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment.
- No alternative treatment with comparable benefits is available through the NHS.
- The treatment is licensed or otherwise indicated for a small patient population.

In addition, when taking these into account the Committee must be persuaded that the estimates of the extension to life are robust and the assumptions used in the reference case economic modelling are plausible, objective and robust.

First-line treatment for people suitable for immunotherapy

4.3.5 The Committee reviewed the evidence of clinical effectiveness from the bevacizumab study. The Committee noted that bevacizumab plus IFN-α demonstrated a statistically significant gain in terms of progression-free survival compared with IFN-α plus placebo. The Committee was aware that the data presented 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, the Committee heard testimony from clinical specialists and people with RCC that IFN-α is associated with high toxicity, is poorly tolerated and is administered by subcutaneous injection. Therefore the Committee was mindful of the concerns highlighted by patient experts and clinical specialists associated with the combination of bevacizumab and IFN-α.

4.3.6 The Committee 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. These differences resulted in different estimates of cost effectiveness between the manufacturer and the Assessment Group of £75,000 and £171,000 per QALY gained, respectively. The Committee noted that when the original patient access scheme was applied to the Assessment Group cost-effectiveness estimate, the Assessment Group base-case ICER was reduced from £171,000 to £90,500 per QALY gained. The Committee

noted that the original patient access scheme was not agreed by the Department of Health and that the final agreed patient access scheme had an additional component which would further reduce these ICERs.

4.3.7 The Committee considered the parameter changes suggested by the manufacturer of bevacizumab for insertion into the Assessment Group's model (see section 4.2.27). Although the first suggestion to censor participants once second-line treatments were received was appropriate in principle, the Committee noted that its application produced some anomalous findings: there were more participants in the bevacizumab arm than the IFN-α arm that were censored. Although the Committee noted that, on average, the participants in the bevacizumab plus IFN-α arm had received treatment for almost twice as long as those in the IFN-α plus placebo arm, the Committee considered that the cause of the greater censoring was likely to be the withdrawal of more participants from bevacizumab plus IFN-α treatment than IFN-α plus placebo treatment because of the adverse effects of bevacizumab plus IFN-α. It also noted that the revised hazard ratio for overall survival was now lower than the original hazard ratio for progression-free survival. The Committee considered that a reduced hazard ratio for overall survival was plausible, but that it would not be expected to be lower than the hazard ratio for progression-free survival. The Committee then reviewed the bevacizumab dosages and quantity and cost of bevacizumab administrations applied in the economic model. The Committee accepted that it was plausible that in the trial participants may have stopped treatment before 12 months, but considered that the trial protocol and exact interpretation of treatment duration was unclear. The Committee also considered that lower costs of bevacizumab administration were plausible, although noted that the costs of administration were unlikely to be halved. The Committee noted and accepted the revised dose intensity estimate of 92% and bevacizumab administration cost of £170 as provided by the manufacturer of bevacizumab.

4.3.8 The Committee then discussed the fact that bevacizumab was licensed to be given to people with advanced and/or metastatic RCC in combination with IFN-α. It noted that the health-state utilities used in calculating the cost-effectiveness estimate of bevacizumab plus IFN-α compared with IFN-α plus placebo were obtained from an RCT of

sunitinib compared with IFN-α (see section 4.2.2), and that the health-state utilities were not treatment specific. The Committee was aware that the costs of adverse effects had been included in the economic model, although these were negligible. It considered that there would be disutility associated with the high toxicity, poor tolerance and issues with the administration of bevacizumab plus IFN-α, that had been highlighted by clinical specialists and patient experts, and that this disutility had not been incorporated into the cost-effectiveness estimate of bevacizumab plus IFN-α compared with IFN-α. Taking these concerns that had been highlighted into account the Committee agreed that the ICER was likely to be an underestimate and therefore the Committee concluded that the lowest plausible ICER estimate was £53,800 per QALY gained.

4.3.9 The Committee next discussed whether bevacizumab plus IFN-α for the treatment of advanced and/or metastatic RCC fulfilled the criteria for a life-extending, end-of-life treatment. The Committee noted from the clinical trials that life expectancy with IFN-α treatment alone was unlikely to be greater than 24 months and was potentially as low as 12 months. The Committee agreed that it was likely that bevacizumab plus IFN-α would increase overall survival by more than 3 months in comparison with IFN-α alone. It had heard that RCC does not respond well to IFN-α alone, but considered that bevacizumab plus IFN-α does represent a marked change in the treatment of advanced and/or metastatic RCC. The Committee was aware that the total number of people with advanced and/or metastatic RCC in England and Wales was approximately 4000. However, the Committee understood that it should take into account the cumulative population for each product in considering the strength of any case, for justifying decisions which employ, in whole or part, the supplementary criteria for appraising life-extending, end-of-life treatments. It noted that bevacizumab was licensed for a number of other indications involving much larger patient groups. The Committee noted that the manufacturer argued that the use of bevacizumab was restricted in the UK and that, in effect, the valid patient population for bevacizumab is small. However the Committee considered that this point did not override its view that bevacizumab is licensed for a relatively large population across its range of indications. In summary, the Committee was not persuaded that bevacizumab plus IFN-α meets all the criteria for a life-extending end-of-life treatment, given

the size of the patient populations (in RCC and other cancers) for whom it is licensed.

4.3.10 The Committee considered the lowest plausible cost-effectiveness estimate of bevacizumab plus IFN-α of £53,800 per QALY gained and 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.

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

4.3.11 The Committee reviewed the evidence of clinical effectiveness from the temsirolimus study. 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. It 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 discussed the available subgroup data, but had concerns as to whether the data were robust enough to distinguish particular subgroup responses. Some of the subgroups were very small, in particular one of the subgroups highlighted by the manufacturer, non-clear-cell carcinoma, was based on less than 20% (n=73) of the trial population. This subgroup was also defined imprecisely as 'non-clear-cell carcinoma and 'indeterminate histologies' in the trial. It was also unclear whether all of the subgroup analyses had been defined a priori. However, the Committee was persuaded that in general temsirolimus is a clinically effective first-line treatment for people with a poor prognosis, and was minded to consider the cost-effectiveness evidence, including the subgroups who might gain greater benefit.

4.3.12 Therefore the Committee considered the estimates of cost effectiveness of temsirolimus. It noted that the original 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. However, the Committee heard from clinical specialists 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. The Committee acknowledged consultation responses from the manufacturer that highlighted that the duration of temsirolimus treatment had been overestimated in the Assessment Group economic model by the use of hazard ratios for deriving survival curves. Therefore the Committee considered that the most appropriate ICERs were those calculated by the manufacturer, but with the Assessment Group's costs for IFN-α administration incorporated and the manufacturer's initial cost for the acquisition of temsirolimus. These resulted in a base-case ICER of £102,000 per QALY gained and subgroup ICERs ranging from £63,100 ('non-clear-cell carcinoma and indeterminate histologies') to £121,300 (clear-cell carcinoma) per QALY gained. However, The Committee noted the recently published price of £620 for a vial of temsirolimus and was aware that these ICER estimates were derived using an underestimate of the price of a vial of temsirolimus of £515. Therefore it concluded that the ICERs were underestimates and would all increase if the recently published price of temsirolimus was incorporated into the cost-effectiveness analyses.

4.3.13 The Committee next discussed whether temsirolimus for the treatment of advanced and/or metastatic RCC fulfilled the criteria for a life-extending, end-of-life treatment. The Committee noted from the clinical trials that life expectancy with IFN-α treatment alone was unlikely to be greater than 24 months and was potentially as low as 7 months for patients with a poor prognosis. The Committee considered that evidence from the temsirolimus trial suggested that temsirolimus increased survival by more than 3 months compared with IFN-α alone and it considered temsirolimus to be an improvement in treatment for advanced and/or metastatic RCC. It was aware that the total number of people with advanced and/or metastatic RCC in England and Wales was approximately 4000 and that temsirolimus was licensed for people with a poor prognosis and so had a very small patient population. The Committee agreed that the criterion for the robustness of evidence was convincing for the overall trial data, but not for the subgroup data. In summary, the Committee was satisfied that temsirolimus met the criteria for being a life-extending, end-of-life treatment for the whole trial population.

4.3.14 The Committee then considered the cost-effectiveness estimate of

temsirolimus of £102,000 per QALY gained (noting that this was an underestimate because of the underestimated price of temsirolimus), in light of the appraisal of a life-extending, end-of-life treatment. The Committee was aware that the patient population eligible for temsirolimus treatment was very small, but noted that NICE had not received direction from the Department of Health that 'ultra-orphan' conditions should be appraised differently from any other appraisal; including those that meet the end-of-life criteria. The Committee considered that the additional weight that would need to be assigned to the original QALY benefits in this patient group for the cost effectiveness of temsirolimus to fall within the current threshold range would be too great. The subgroup data were not considered to be robust enough to apply a consideration of additional weight that would need to be assigned to the original QALY benefits in these subgroups. 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.

4.3.15 Very few data were presented to the Committee on the clinical effectiveness of bevacizumab plus IFN-α compared with IFN-α plus placebo as a first-line treatment for people with a poor prognosis, suitable for immunotherapy. The Committee noted that only a small subgroup of the bevacizumab RCT (see section 4.1.2) had a poor prognosis and the data available confirmed no benefit in terms of progression-free survival. The Committee concluded that with such limited evidence, it could not consider bevacizumab plus IFN-α as a clinically effective first-line treatment for people with poor prognosis, suitable for immunotherapy with advanced and/or metastatic RCC.

First-line treatment for people unsuitable for immunotherapy

4.3.16 The only data presented to the Committee for the first-line treatment of people unsuitable for immunotherapy came from two single-arm studies of sorafenib which were presented in abstract form only. The Committee concluded that, with such weak evidence, it could not consider sorafenib as a clinically effective first-line treatment for people with advanced RCC who were unsuitable for immunotherapy.

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

4.3.17 The Committee reviewed the evidence of clinical and cost effectiveness for temsirolimus compared with best supportive care as presented by the manufacturer (Wyeth Pharmaceuticals). 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. The Committee concluded that temsirolimus had not been shown to be a clinically effective first-line treatment for people with advanced RCC and a poor prognosis and who were unsuitable for immunotherapy.

4.3.18 No data were presented to the Committee on the clinical or cost effectiveness of sorafenib compared with best supportive care as a first-line treatment for people with a poor prognosis who were unsuitable for immunotherapy. The Committee noted that the sorafenib RCT included only people with an ECOG performance status of 0 or 1 and therefore did not include people with a poor performance. The Committee concluded that, in the absence of evidence, sorafenib had not been shown to be a clinically effective first-line treatment for people with advanced RCC and a poor prognosis and who were unsuitable for immunotherapy.

Second-line treatment for people in whom immunotherapy has failed

4.3.19 The Committee reviewed the clinical effectiveness of sorafenib for people in whom immunotherapy has failed. The Committee noted that sorafenib demonstrated a clinically relevant and statistically significant advantage over best supportive care in terms of progression-free survival and tumour response for the 83% of the trial participants in whom immunotherapy had failed. The Committee was persuaded that sorafenib is a clinically effective therapy for second-line treatment of RCC for people in whom immunotherapy has failed.

4.3.20 The Committee then reviewed the cost-effectiveness estimates for the subgroup in whom immunotherapy had failed. The Committee noted that

the trial was not stratified according to prior treatments, but acknowledged responses from consultation that the subgroup was pre-specified, and considered that the subgroup represented most of the trial participants and was relatively large. The Committee noted comments from the DSU that the reduced ICERs, presented by the manufacturer of sorafenib in the revised analyses, were derived using appropriate modelling techniques, similar to that used by the Assessment Group. However, the Committee agreed that due to the concerns raised by the DSU about the change in direction of the subgroup ICER as presented by the manufacturer of sorafenib that the most reasonable subgroup estimate came from the DSU revised analysis using the Assessment Group's economic model. The Committee, noting instructions from the Department of Health that all of the cost-effectiveness estimates should include the first pack of sorafenib as free to the NHS and the new increased price of sorafenib, accepted that the most plausible ICER for sorafenib compared with best supportive care for people in whom immunotherapy had failed was £65,900 per QALY gained.

4.3.21 The Committee next discussed whether sorafenib for the treatment of advanced RCC fulfilled the criteria for consideration as a life-extending, end-of-life treatment. The Committee noted from the clinical trials that life expectancy with best supportive care alone was unlikely to be greater than 24 months and was potentially as low as 6 months. The Committee considered that even though the sorafenib trial was terminated early, this was done after a report of increased progression-free survival in the sorafenib arm. The Committee considered that it was likely that sorafenib would increase overall survival by more than 3 months in comparison with best supportive care. It also agreed that sorafenib provided an improvement in the treatment of advanced RCC. It was aware that the total number of people with advanced and/or metastatic RCC in England and Wales was approximately 4000. Therefore the Committee was satisfied that sorafenib meets the criteria for being a life-extending, end-of-life treatment and that the trial evidence presented for this consideration was robust.

4.3.22 The Committee then considered the most plausible cost effectiveness of sorafenib for people in whom immunotherapy had failed, of £65,900 per

QALY gained, in light of the appraisal of a life-extending, end-of-life treatment. It considered that the magnitude of additional weight that would need to be assigned to the original QALY benefits in this patient group for the cost effectiveness of the drug to fall within the current threshold range would be too great. Therefore the Committee concluded that sorafenib as a second-line treatment for people with advanced RCC in whom immunotherapy has failed would not be a cost-effective use of NHS resources.

4.3.23 The Committee then reviewed the clinical and cost effectiveness for sunitinib as a second-line treatment compared with best supportive care for people in whom immunotherapy had failed. The Committee was concerned that the data informing the comparisons came from two small single-arm trials. The Committee acknowledged that the 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 concluded that sunitinib could not be considered a clinically effective second-line treatment for people with advanced and/or metastatic RCC in whom immunotherapy had failed.

Second-line treatment for people in whom non-immunotherapy first-line treatment has failed and who are unsuitable for immunotherapy

4.3.24 The Committee reviewed the academic-in-confidence evidence on the clinical effectiveness of sorafenib compared with best supportive care for people unsuitable for immunotherapy as presented by the manufacturer (Bayer). The Committee noted that the subgroup constituted a small proportion (17%) of the sorafenib RCT, but that the overall trial population was relatively large. Following consultation, the Committee heard that the data informing the comparison came from a pre-planned subgroup from the sorafenib RCT, although it was unclear what prior therapies the subgroup had received. The Committee concluded that, although the data were limited, sorafenib could be considered as a clinically effective second-line treatment for those unsuitable for immunotherapy with advanced RCC.

4.3.25 The Committee then reviewed the estimates of cost effectiveness of

sorafenib as a second-line treatment for people unsuitable for immunotherapy. The Committee noted that the manufacturer of sorafenib (Bayer) had not provided revised ICERs for this subgroup. The Committee noted that, overall, the revised 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 revised manufacturer base-case ICER for the whole trial population of £72,500, per QALY gained and a DSU revised Assessment Group base-case ICER of £74,900 per QALY gained. The Committee noted that the subgroup ICER for the 83% of trial participants in whom immunotherapy had failed was lower than these ICERs for the whole trial population. The Committee therefore agreed that the most plausible subgroup ICER for the 17% of trial participants who were unsuitable for immunotherapy must be higher than the ICER for the whole trial population of £72,500 or £74,900 per QALY gained.

4.3.26 The Committee agreed that the criterion for the robustness of evidence for this subgroup was not convincing therefore the Committee did not discuss whether sorafenib for the second-line treatment of people with advanced RCC who are unsuitable for immunotherapy fulfilled the criteria for consideration as a life-extending, end-of-life treatment. This was because it was not clear what prior therapies the people in the subgroup had received and no cost-effectiveness estimates were provided. The Committee considered the most plausible ICERs that were higher than £72,500 and £74,900 per QALY gained and concluded that sorafenib as second-line treatment for people in whom non-immunotherapy first-line treatment has failed and who are unsuitable for immunotherapy with advanced RCC would not be a cost-effective use of NHS resources.

Second-line treatment for people in whom sunitinib has failed

4.3.27 The Committee noted the suggestion made by the manufacturer of sorafenib that consideration should be given to the sequencing of treatments (particularly sunitinib as a first-line treatment followed by sorafenib as second-line treatment). It also noted that the marketing authorisation of sorafenib was for people in whom immunotherapy had failed or who were unsuitable for immunotherapy. Therefore the

Committee considered that the use of sorafenib after sunitinib would be relevant only for people who had received sunitinib as a first-line treatment and were unsuitable for immunotherapy. The Committee noted that the evidence base for this treatment pathway was absent, because participants were excluded from the sorafenib RCT if they had received sunitinib as a first-line treatment and the sunitinib RCT only included people who were suitable for immunotherapy. In the absence of robust data, the Committee could not reach any conclusions on whether sorafenib could be considered a clinically effective second-line treatment for people with advanced RCC who had received sunitinib as a first-line treatment.

The Institute's duties under the equalities legislation

4.3.28 In carrying out its consideration of the evidence and reaching its conclusions, the Committee was aware of the Institute's duties under the equalities legislation and considered whether those duties required the Committee to alter or to add to its recommendations in any way. However, the Committee did not identify any way in which its guidance would have a particular impact on any of the groups whose interests are protected by the equalities legislation. It noted that in relation to first-line treatment for people who are unsuitable for immunotherapy and second-line treatment for people who are unsuitable for immunotherapy its recommendations are based on the view that there is limited or no evidence of clinical effectiveness for any patient group. For the other patient populations the Committee's conclusions are based on the view that the treatments are not cost effective for any patient group. The guidance does not recommend the availability of the treatments to some patients and not to others. The recommendations apply to all patients with renal cell carcinomas and all such patients are affected by the guidance in the same way.

5 Implementation

5.1 The Secretary of State and the Welsh Assembly Minister for Health and Social Services have issued directions to the NHS on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends use of a drug or treatment, or other technology, the NHS must provide funding and resources for it within 3 months of the guidance being published. If the Department of Health issues a variation to the 3-month funding direction, details will be available on the NICE website. The NHS is not required to fund treatments that are not recommended by NICE.

5.2 NICE has developed tools to help organisations put this guidance into practice (listed below).

- A costing statement explaining the resource impact of this guidance.
- Audit support for monitoring local practice.

6 Recommendations for further research

6.1 There are a number of ongoing trials which are actively recruiting participants and which are relevant to this appraisal. Some of these trials are investigating the optimum sequences of treatment. Full details of ongoing research can be found at the National Institute for Health Research Clinical Research Network, ClinicalTrials.gov and Current Controlled Trials.

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 temsirolimus and sorafenib as first-line treatments (both as monotherapy) compared with best supportive care in people who are unsuitable or have contraindications for immunotherapy and who have a poor or intermediate prognosis.
- RCTs of sunitinib as a second-line treatment in people in whom immunotherapy has failed.
- RCTs of sorafenib as a second-line treatment in whom first-line non-immunotherapy treatment (including sunitinib) has failed and who are unsuitable or have contraindications to immunotherapy.

7 Related NICE guidance

- Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma. NICE technology appraisal guidance 169 (2009).
- Percutaneous radiofrequency ablation of renal cancer. NICE interventional procedure guidance 91 (2004). [Replaced by NICE interventional procedure guidance 353 (2010)]
- Improving outcomes in urological cancers. NICE cancer service guidance (2002).

8 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 The guidance on this technology will be considered for review by June 2011.

Andrew Dillon
Chief Executive
August 2009

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.

Dr Kathryn Abel
Reader and Consultant Psychiatrist, Director of Centre for Women's Mental Health, University of Manchester

Professor David Barnett
Professor of Clinical Pharmacology, University of Leicester

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

Brian Buckley
Lay member

Mr Mark Campbell
Director of Standards, Bury Primary Care Trust

Professor Mike Campbell
Professor of Medical Statistics, University of Sheffield

Mr David Chandler
Lay member

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, Watford

Dr Rachel A Elliott
Lord Trent Professor of Medicines and Health, University of Nottingham

Mrs Eleanor Grey
Lay member

Dr Peter Jackson
Clinical Pharmacologist, University of Sheffield

Professor Peter Jones
Pro Vice Chancellor for Research and Enterprise, Keele University

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

Mrs Ruth Oliver-Williams
Head of Nursing, Quality Improvement Lead Surgical Services, Royal Derby Hospital, Derby

Dr Katherine Payne
Health Economics Research Fellow, University of Manchester

Dr Danielle Preedy
Lay member

Dr Martin J Price
Head of Outcomes Research, Janssen-Cilag, Buckinghamshire

Dr Philip Rutledge
Consultant in Medicines Management, NHS Lothian

Mr Miles Scott
Chief Executive, Bradford Teaching Hospitals NHS Foundation Trust

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

Professor Andrew Stevens
Chair of Appraisal Committee C

Dr Matt Stevenson
Technical Director School or Health and Related Research, University of Sheffield

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
Technical Lead

Joanna Richardson
Technical Adviser

Laura Malone
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, Hoyle M, Green C 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 Primary Care Trust
- 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 alfa)

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 were also 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
- Mr Bill Savage, nominated by the Rarer Cancers Forum – patient expert

Changes after publication

February 2014: minor maintenance

March 2012: minor maintenance

About this guidance

NICE technology appraisal guidance is about the use of new and existing medicines and treatments in the NHS in England and Wales.

This guidance was developed using the NICE multiple technology appraisal process.

We have produced a summary of this guidance for patients and carers. Tools to help you put the guidance into practice and information about the evidence it is based on are also available.

Your responsibility

This guidance represents the views of NICE and was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to avoid unlawful discrimination and to have regard to promoting equality of opportunity. Nothing in this guidance should be interpreted in a way which would be inconsistent with compliance with those duties.

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