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NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Final appraisal determination

Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma

1 Guidance

This guidance has been developed on the understanding that there are no further treatment options available after first-line treatment for advanced and/or metastatic renal cell carcinoma.

- 1.1 Sunitinib is recommended as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- 1.2 When using ECOG performance status score, clinicians should be mindful of the need to secure equality of access to treatments for people with disabilities. Clinicians should bear in mind that people with disabilities may have difficulties with activities of daily living that are unrelated to the prognosis of renal cell carcinoma. In such cases clinicians should make appropriate judgements of performance status taking these considerations into account.
- 1.3 People who are currently being treated with sunitinib for advanced and/or metastatic renal cell carcinoma but who do not meet the criteria in 1.1 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 whose condition does not respond to first-line immunotherapy, or for people who are unsuitable for immunotherapy.

3 The technology

3.1 Sunitinib

3.1.1 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.

3.1.2 Sunitinib is contraindicated in people who have hypersensitivity to sunitinib malate or to any of the excipients. The summary of

product characteristics (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.

- 3.1.3 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, in which the first treatment cycle 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. Costs of subsequent treatment cycles 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, they only relate to sunitinib for the first-line treatment of advanced and/or metastatic RCC.

4.1 Clinical effectiveness

4.1.1 The Assessment Group and manufacturer identified evidence on the clinical effectiveness of sunitinib as a first-line treatment within its licensed indications against relevant comparators. The following potential treatment strategies were investigated:

- first-line treatment for people suitable for immunotherapy (sunitinib compared with IFN- α)
- first-line treatment for people suitable for immunotherapy who have a poor prognosis (sunitinib compared with IFN- α)
- first-line treatment for people unsuitable for immunotherapy (sunitinib compared with best supportive care)
- first-line treatment for people with a poor prognosis unsuitable for immunotherapy (sunitinib compared with best supportive care).

First-line treatment for people suitable for immunotherapy

4.1.2 One randomised controlled trial (RCT) of 750 people assessed the effect of sunitinib (n = 375) compared with IFN- α alone (n = 375). The primary outcome was progression-free survival. Three interim analyses were scheduled and after the second analysis the study was unblinded and participants in the IFN- α group with progressive disease were allowed to cross over into the sunitinib group. This is at variance with the study protocol which stated that all treatment would be stopped when there was evidence of disease progression. The study was conducted in participants with a good performance status (ECOG status 0 or 1) with clear cell RCC. Most had undergone prior nephrectomy.

4.1.3 Median overall survival had not been reached in either treatment arm at the time of the interim data analyses. The manufacturer of sunitinib (Pfizer) submitted updated data on the final intention-to-

treat (ITT) population. The median final overall survival was 26.4 months in the sunitinib arm and 21.8 months in the IFN- α arm (HR 0.821, 95% CI 0.673 to 1.001, $p = 0.051$). There were 25 participants in the IFN- α arm who, during the course of the study, crossed over to receive sunitinib treatment after disease progression. Censoring the data for these 25 participants (that is, the data for these 25 people were only included up to the point at which they crossed over) gave a median overall survival of 26.4 months in the sunitinib arm and 20.0 months in the IFN- α arm (HR 0.808, 95% CI 0.661 to 0.987, $p = 0.0362$).

- 4.1.4 The manufacturer of sunitinib also provided post hoc data pertaining to a group of participants who did not receive any systemic post-study treatments. In this analysis, the median overall survival was 28.1 months for the 193 participants in the sunitinib arm and 14.1 months for the 162 participants in the IFN- α arm (HR 0.647, 95% CI 0.483 to 0.870, $p = 0.0033$).
- 4.1.5 Progression-free survival was defined as the time between randomisation and first documented disease progression or death from any cause. Pre-planned interim results (at 13 months) and unplanned updated results (at 25 months) were presented, but the latter contained crossover between treatment arms. Again, the manufacturer submitted final results based on the ITT population and the median final progression-free survival was 48 weeks (11 months) in the sunitinib arm and 22.3 weeks (5.1 months) in the IFN- α arm (HR 0.488, 95% CI 0.406 to 0.586, $p < 0.000001$). Analysis of the group of participants who received no systemic post-study treatments gave median progression-free survival of 50.1 weeks (11.5 months) in the sunitinib arm and 22.3 weeks (5.1 months) in the IFN- α arm (HR 0.52, 95% CI 0.39, 0.70).

- 4.1.6 A few participants were included who had not had a prior nephrectomy: 9% in the sunitinib arm and 11% in the IFN- α arm. The subgroup analyses, based only on the interim study results, suggested that sunitinib significantly improved progression-free survival for those who had undergone prior nephrectomy compared with IFN- α (HR 0.38, 95% CI 0.30 to 0.53). The improvement in progression-free survival for those who had not undergone prior nephrectomy was less and the difference between groups not statistically significant (HR 0.58, 95% CI 0.24 to 1.03).
- 4.1.7 Tumour response rate was measured as a partial or complete reduction in tumour size. Results for the interim analyses only showed that the partial tumour response rate in the sunitinib arm was 31% compared with 6% in the IFN- α arm ($p < 0.001$). No participant had a complete tumour response.
- 4.1.8 Adverse events were taken from the 'safety population' (that is, people were assigned to treatments in the analysis based on what they actually received). Results for the period up to the interim analyses only showed no significant differences between the treatment and control arms. However, the Assessment Group stated that there are emerging concerns in the published literature about the frequency of cardiovascular events associated with sunitinib. In the trial, the most commonly reported 'any grade' adverse events for participants receiving sunitinib were hypertension, fatigue, diarrhoea and hand-foot syndrome. For the participants receiving IFN- α , these were fatigue and asthenia. A total of 8% of participants receiving sunitinib discontinued treatment because of adverse events compared with 13% in the IFN- α arm. At the time of the interim analyses, overall results for health-related quality of life (total score and all subscales using the functional assessment of cancer therapy – general [FACT-G] and functional

assessment of cancer therapy – kidney symptom index [FKSI] tools) were significantly better in the sunitinib arm compared with the IFN- α arm.

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

4.1.9 In the RCT described above (see section 4.1.2), 6.1% of participants receiving sunitinib and 6.7% of participants receiving IFN- α were classified as having a poor prognosis according to the Memorial Sloan-Kettering Cancer Centre risk classification. However, outcome data were not reported separately for this subgroup.

First-line treatment for people unsuitable for immunotherapy

4.1.10 The Assessment Group did not identify any full reports of RCTs assessing sunitinib as first-line treatment for people with advanced and/or metastatic RCC who were unsuitable for immunotherapy.

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

4.1.11 The Assessment Group did not identify any data on the clinical effectiveness of sunitinib as first-line treatment for people with advanced and/or metastatic RCC who had a poor prognosis and were unsuitable for immunotherapy.

Summary of clinical effectiveness

4.1.12 The Assessment Group concluded that for people who are suitable for immunotherapy sunitinib appears to offer benefits compared with IFN- α alone in terms of overall survival, progression-free survival and tumour response. For people with a poor prognosis and people who are unsuitable for immunotherapy, limited evidence was identified and thus no conclusions about the clinical effectiveness of sunitinib as a first-line treatment in these groups

could be made. The frequency of adverse events associated with sunitinib is comparable to that associated with IFN- α monotherapy.

4.2 Cost effectiveness

4.2.1 No published studies of the cost effectiveness of sunitinib were identified. The manufacturer of sunitinib submitted a cost-effectiveness model and the Assessment Group developed a model to estimate the cost effectiveness of sunitinib..

Manufacturer's model

4.2.2 The manufacturer of sunitinib (Pfizer) submitted a simple state-transition model with three health states: progression-free survival (PFS), progressed disease (PD) and death. The model compared sunitinib with IFN- α as a first-line treatment for people suitable for immunotherapy. Patient-level data were taken from the sunitinib trial described in section 4.1.2. Weibull survival curves were fitted to the overall and progression-free survival data from the IFN- α arm in the trial. Hazard ratios for sunitinib were then used to extrapolate overall and progression-free survival for sunitinib treatment. The following treatment and health-state specific utility data from the sunitinib trial were applied: sunitinib/PFS = 0.77; IFN- α /PFS = 0.79; sunitinib/PD = 0.72; IFN- α /PD = 0.69. Drug costs were adjusted according to RCT data on dose intensity; the first-line drug cost for sunitinib was weighted by 86.4%. A pricing strategy with the first cycle of sunitinib being free of charge to the NHS was applied.

4.2.3 The original base cases submitted by the manufacturer of sunitinib used the interim effectiveness data which were superseded by the final ITT results. With discounting at 3.5% per annum, the comparison of sunitinib with IFN- α produced an ICER of £72,003 per QALY gained using the final ITT population and £71,760 per QALY gained using the final ITT population censored for crossover.

One-way sensitivity analyses applied to the original base case demonstrated that the ICERs were most sensitive to the extrapolation method and choice of utility value for progressed disease.

- 4.2.4 The manufacturer of sunitinib also submitted cost-effectiveness analyses using the data from the group of participants who received no systemic post-study treatments. The progression-free and overall survival curves for IFN- α were modelled using Weibull curves and the hazard ratios for sunitinib were then applied, as in the ITT analyses. Without any curve adjustments, the ICER for sunitinib compared with IFN- α was £41,472 per QALY gained. However, the manufacturer stated that the modelled IFN- α progression-free survival curve did not fit the observed progression-free survival data well, and adjusted the curve using fewer data points. Application of the trial hazard ratio to this curve then resulted in a progression-free survival curve that did not fit the empirical data from the sunitinib arm of the trial well. Therefore, the progression-free survival curve for sunitinib was also fitted independently. These adjustments resulted in an ICER of £35,245 per QALY gained for sunitinib compared with IFN- α .
- 4.2.5 The manufacturer of sunitinib then adjusted the overall survival curve for the IFN- α arm using the same principles as for adjustments for the progression-free survival curve. However, unlike the curve fitting for progression-free survival, for overall survival the trial hazard ratio was applied to the fitted IFN- α curve to derive an overall survival curve for the sunitinib arm. These adjustments resulted in an extrapolated mean overall survival of 46.6 months for participants in the sunitinib arm and 27.5 months for participants in the IFN- α arm. These adjustments were associated with an ICER of £29,440 per QALY gained for sunitinib

compared with IFN- α . Probabilistic sensitivity analyses of the final cost-effectiveness estimate demonstrated that at a willingness to pay threshold of £30,000 per QALY gained, sunitinib has a 51% probability of being a cost-effective treatment compared with IFN- α .

Assessment Group model

Model structure and inputs

4.2.6 The Assessment Group model was developed in order to estimate the cost effectiveness of sunitinib, sorafenib, temsirolimus and bevacizumab plus IFN- α , against relevant comparators and according to the licensed indication of each drug. The Markov model used three distinct health states: progression-free survival, progressive disease and death. Baseline disease progression (IFN- α alone) in the original Assessment Group model was taken from a study comparing bevacizumab plus IFN- α with IFN- α alone. The Assessment Group stated that this data source was chosen for the IFN- α ITT population cost-effectiveness analyses because at the time of the original analysis the overall survival Kaplan–Meier curve from the sunitinib RCT had not been published and that these data were therefore immature. Data for progression-free survival and overall survival for people receiving IFN- α were read directly from reported Kaplan–Meier curves, and Weibull curves were then fitted for use in the model. The disease progression was estimated using the hazard ratios from the sunitinib trial.

4.2.7 The health-state utilities used in the Assessment Group model were derived from trial data in the manufacturer submission 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 manufacturer (Pfizer) submission.

- 4.2.8 In the Assessment Group model, drug acquisition costs were modified according to dose intensities reported in the sunitinib RCT. Current list prices were taken from the BNF (edition 55), and the agreed patient access scheme of the first cycle of sunitinib being free to the NHS was applied. All other costs were inflated to 2007–8 values. 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 £223 for sunitinib treatment. In the PD state, the cost for best supportive care was £435 per cycle.
- 4.2.9 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 manufacturer's parameters. The Assessment Group also performed sensitivity analyses on the manufacturer's model by incorporating the Assessment Group parameters and assumptions.

Results from the Assessment Group model

- 4.2.10 The original Assessment Group base case comparing sunitinib with IFN- α was superseded by analyses using the final ITT results. The

comparison of sunitinib with IFN- α resulted in an ICER of £104,715 per QALY gained. The deterministic sensitivity analyses on the interim data 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. The Assessment Group also undertook cost-effectiveness analyses using the data from the 'no post-study treatment' group in the sunitinib trial once these had been submitted by the manufacturer. Using a similar approach to the manufacturer, the empirical progression-free and overall survival data from the IFN- α 'no post-study treatment' arm were modelled using a Weibull curve. The hazard ratio for overall survival for sunitinib of 0.647 from the 'no post-study treatment' group and the hazard ratio for progression-free survival for sunitinib of 0.488 from the ITT population were then applied to derive survival curves for sunitinib treatment. For the 'no post-study treatment' group, the cost-effectiveness analysis resulted in an ICER of £62,365 per QALY gained for sunitinib compared with IFN- α . Both of the ICERs calculated by the Assessment Group included the agreed patient access scheme of the first cycle of sunitinib being free to the NHS.

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

4.2.11 The manufacturer of sunitinib provided a late submission, which included details of the final ITT analysis and details of the 'no post-study treatment' group. The manufacturer also presented additional cost-effectiveness estimates based on the 'no post-study treatment' group. The Decision Support Unit (DSU) was asked to explore these data and the approach used in the manufacturer's model. In relation to the 'no-post study treatment' group, the DSU firstly noted that over half of the trial population did receive further treatments

and were therefore excluded from the 'no post-study treatment' group analyses. The DSU highlighted that the wholesale exclusion of participants based on whether or not they had received further treatments could be considered as inappropriate. This is because the reason for exclusion from the analyses is most likely to be disease progression, which is linked to a number of outcomes (including survival). The DSU noted that a more appropriate strategy would have been to censor, rather than exclude, the participants at the point at which they received any further treatments. The DSU then appraised the approach taken by the manufacturer in modelling the cost effectiveness associated with the 'no post-study treatment' group. The DSU highlighted that, compared with the final ITT analyses submitted by the manufacturer, there was an increase in overall survival for the participants that received sunitinib when people who received any further systemic treatments were excluded. The DSU stated that this was counter-intuitive and suggested that randomisation had not been preserved. The DSU stated that this cast serious doubt on the validity of the approach used by the manufacturer for the 'no post study treatment' group cost-effectiveness analysis.

The DSU and Assessment Group's modelling of the Committee's preferred assumptions; taking into account responses from consultation

4.2.12 The DSU were requested to use the following assumptions in the manufacturer's model: 1.06 (12.72 months) and 1.74 (20.88 months) progression-free years for the IFN- α and sunitinib arms, respectively; 2.29 (27.48 months) and 3.13 (37.56 months) life years overall survival for the IFN- α and sunitinib arms, respectively. All data were from the final ITT analysis except for overall survival data for the IFN- α arm, which were from the 'no post-study treatment' group. Using these data in the manufacturer's

model resulted in an ICER of £49,304 per QALY gained for sunitinib compared with IFN- α .

- 4.2.13 The Assessment Group was requested to use the same assumptions as the DSU in the Assessment Group model: progression-free survival 1.06 (12.72 months) and 1.75 (21 months) progression-free years for the IFN- α and sunitinib arms, respectively; overall survival 2.21 (26.5 months) life years and 3.07 (36.84 months) life years for the IFN- α and sunitinib arms, respectively. Again, all data were from the final ITT analysis except for overall survival data for the IFN- α arm, which were from the 'no post-study treatment' group. The inputs used by the Assessment Group differ slightly from those used by the DSU as the Assessment Group model assumes a 10-year time horizon, whereas the manufacturer's model assumes an infinite time horizon. This approach included the agreed pricing strategy of the first cycle of sunitinib being free to the NHS and resulted in an ICER of £54,366 per QALY gained for sunitinib compared with IFN- α .

4.3 Consideration of the evidence

- 4.3.1 The Appraisal Committee reviewed the data available on the clinical and cost effectiveness of sunitinib, having considered evidence on the nature of the condition and the value placed on the benefits of sunitinib 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 treatment is immunotherapy and there are no current treatment options for people whose condition had failed to respond to immunotherapy or who were considered unsuitable for immunotherapy. Moreover there are no 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 sunitinib represents a substantial improvement in first-line treatment for advanced and/or metastatic RCC. The Committee noted the comments received that some individual patients experienced clinical benefit from this drug and that lives of people with RCC had been extended for a number of years following treatment with sunitinib.

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 the manufacturer 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 sunitinib on health-related quality of life. The Committee acknowledged the comments that were received from people with RCC and the public, and that were summarised in a report, stating that some people with RCC had experienced significant improvements in their quality of life as a result of using sunitinib.

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 small patient populations.

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 ITT population analyses of the sunitinib RCT. The Committee noted that 25 out of 375 participants in the IFN- α arm had crossed over and received sunitinib after disease progression. The Committee noted that the ITT censored population analyses accounted for the crossover by censoring the participants who had crossed over from the IFN- α arm to receive sunitinib. The Committee noted that, in these analyses, sunitinib demonstrated significant gains in terms of progression-free and overall survival compared with IFN- α . The Committee noted that the sunitinib trial was only conducted with participants that had a good ECOG performance status of 0 or 1. Therefore the Committee concluded that sunitinib is a clinically effective first-line treatment for advanced

and/or metastatic RCC for patients with an ECOG performance status of 0 or 1.

- 4.3.6 The Committee then considered the estimates provided of the cost effectiveness of sunitinib. For the ITT population the manufacturer's and the Assessment Group's estimates were £72,000 and £105,000 per QALY, respectively. The Committee also noted the manufacturer's estimate of £71,800 per QALY gained for the ITT censored for crossover population. The Committee noted instructions from the Department of Health that all of the cost-effectiveness estimates should include the first cycle of sunitinib as free to the NHS.
- 4.3.7 The Committee understood that in the sunitinib RCT not only had there been crossover after disease progression, but also participants had had second-line treatment after the study had ended. This could be expected to exaggerate overall survival estimates for people in the UK receiving IFN- α in the future, as the Committee accepted testimony from clinical experts that current UK practice is likely to preclude treatment with second-line therapies. The Committee therefore considered that the investigation of outcomes in the participants who received no 'post-study treatment' was appropriate. However, the Committee was concerned about the data and approach used by the manufacturer. The Committee was mindful that this group was not pre-specified and represented approximately half of the original trial population. The Committee noted that even though the baseline demographics of the group appeared similar to those of the whole trial population the findings were suggestive of an unbalanced comparison. In the ITT analysis the differences in progression-free survival and overall survival between treatment groups had been 8.2 and 6.2 months, respectively. For the 'no post-study treatment' group they were 6.5

and 19.1 months, respectively. The Committee agreed that this divergence made the argument that these groups were matched implausible. It could indicate that the 'no post-study treatment' group receiving sunitinib comprised people who had not experienced disease progression and thus had not needed any second-line treatments, whereas the IFN- α group might have included more people who had died before other treatments could be considered. The Committee further considered that the divergence might have been exacerbated by the curve fitting techniques used in the manufacturer's model. For the group with 'no post-study treatment' the progression-free survival curves for IFN- α and sunitinib were fitted independently, but the overall survival curve for sunitinib was estimated by applying the study hazard ratio to the IFN- α overall survival curve.

- 4.3.8 The Committee then considered what cost-effectiveness inferences could be made from the 'no post-study treatment' data provided by the manufacturer. The Committee considered that it was reasonable to accept the reduced overall survival estimate that these data implied for the control (IFN- α) group. However, it agreed that it could not accept that not having a second-line treatment could increase the overall survival of participants receiving sunitinib. The Committee noted the decrease in survival in the sunitinib group when crossover was censored (but participants not excluded completely from the study). Furthermore, the Committee agreed that the best estimates for progression-free survival came from the whole-study ITT population rather than a population lacking over half of the trial participants. The Committee could not therefore accept the manufacturer's ICER of £29,400 for the 'no post-study treatment' group. The Committee proceeded to explore the cost-effectiveness estimates based on its preferred assumptions for the 'no post-study treatment' group.

- 4.3.9 The Committee noted the DSU and Assessment Group analyses based on the Committee's preferred assumptions (see sections 4.2.12 and 4.2.13). These analyses used estimates for progression-free survival derived from the ITT population for both groups (approximately 13 months and 21 months for the IFN- α and sunitinib arms, respectively) and estimates for overall survival of the sunitinib group from the ITT population (approximately 37 months), but overall survival estimates for the IFN- α group from those with 'no post-study treatment' (approximately 27 months) applied to the manufacturer's model (performed by the DSU) and the Assessment Group model (performed by the Assessment Group). The Committee noted the DSU's resulting cost-effectiveness estimate of £49,300 per QALY gained. The Committee noted the DSU's comments that this was likely to be an underestimate and also noted the cost-effectiveness estimate of £54,400 per QALY gained from the same preferred Committee assumptions in the Assessment Group model.
- 4.3.10 The Committee then considered the sensitivity analyses on utility values conducted by the Assessment Group. The Committee was aware that there was a paucity of data on quality of life and acknowledged consultation responses that the difference of 0.08 between the utility assigned to a progression-free health state and a progressed disease health state was too small. The Committee considered that the impact of sunitinib on quality of life may not have been adequately captured, particularly for the progressed disease state. Therefore the Committee agreed that an increased utility difference between the two health states was plausible and noted the Assessment Group's utility sensitivity analyses which suggested a lowering of the final ICER as the utility difference widened. Taking this into account and reflecting back to the proven benefit in median progression-free survival in the ITT sensitivity

analyses, the Committee was persuaded that the ICER for sunitinib 'no post-study treatment group' could be less than £50,000 per QALY gained.

4.3.11 The Committee next discussed whether sunitinib for advanced and/or metastatic RCC fulfilled the criteria for consideration as a life-extending, end-of-life treatment. It was aware that the total number of people with advanced and/or metastatic RCC in England and Wales was approximately 4000. Although the Committee noted that sunitinib was to be aimed at more patient groups than just people with RCC, such as people with gastrointestinal stromal tumours, this was the first indication for which it was being appraised. It therefore considered that for this appraisal, sunitinib should be regarded as meeting this criterion for an end-of-life treatment. The Committee noted from the clinical trials that the normal 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 also noted that evidence from the sunitinib trial suggested that sunitinib increased survival by more than 3 months in comparison with IFN- α alone. It was further persuaded that sunitinib provided a step-change in the first-line treatment of advanced and/or metastatic RCC and noted that more than 20% of the public and patients that responded in consultation highlighted this impressive benefit from sunitinib. In summary, the Committee was satisfied that sunitinib currently meets the criteria for being a life-extending end-of-life treatment, and that the evidence presented for this consideration was sufficiently robust.

4.3.12 The Committee next considered the cost-effectiveness estimates of sunitinib, in light of the appraisal of a life-extending, end-of-life treatment. Firstly, it considered the ITT cost-effectiveness estimates (derived from the whole trial population) of £72,000 per

QALY gained and £105,000 per QALY gained as calculated by the manufacturer of sunitinib and the DSU (using the Assessment Group model), respectively. 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.

- 4.3.13 The Committee then considered the most plausible cost-effectiveness estimate following the sensitivity analysis of the utility values of the group of people that had received no post-study treatments (see section 4.3.10), in light of the appraisal of a life-extending, end-of-life treatment. It considered the impact of giving a greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy person of the same age and 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. The Committee concluded that although it might be at the upper end of any plausible valuation of such benefits, in this case there was a significant step-change in treating a disease for which there is currently so little to offer patients. The Committee concluded that sunitinib as a first-line treatment for advanced and/or metastatic RCC could be recommended as a cost-effective use of NHS resources, if a patient has an ECOG performance status of 0 or 1 and there are no further treatment options available for after first-line sunitinib treatment. The Committee also considered that, because of the additional weight assigned to the original QALY benefit, rigorous data collection investigating the benefits of sunitinib in this group of people should be conducted.

First-line treatment for people suitable for immunotherapy with at least

three of six factors indicating poor prognosis

4.3.14 Very few data were presented to the Committee on the clinical or cost effectiveness of sunitinib compared with IFN- α as first-line treatments for people with a poor prognosis, suitable for immunotherapy. In the absence of robust data, the Committee concluded that sunitinib could not be considered 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

4.3.15 No data were presented to the Committee on the clinical or cost effectiveness of sunitinib compared with best supportive care as a first-line treatment for people who were unsuitable for immunotherapy. In the absence of robust data, the Committee concluded that sunitinib could not be considered a clinically effective first-line treatment for those unsuitable for immunotherapy with advanced and/or metastatic RCC.

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

4.3.16 No data were presented to the Committee on the clinical or cost effectiveness of sunitinib compared with best supportive care as a first-line treatment for people with a poor prognosis who were unsuitable for immunotherapy. In the absence of robust data, the Committee concluded that sunitinib could not be considered a clinically effective first-line treatment for people with a poor prognosis who are unsuitable for immunotherapy.

5 Implementation

5.1 The Healthcare Commission assesses the performance of NHS organisations in meeting core and developmental standards set by the Department of Health in 'Standards for better health' issued in

July 2004. The Secretary of State has directed that the NHS provides funding and resources for medicines and treatments that have been recommended by NICE technology appraisals normally within 3 months from the date that NICE publishes the guidance. Core standard C5 states that healthcare organisations should ensure they conform to NICE technology appraisals.

- 5.2 'Healthcare standards for Wales' was issued by the Welsh Assembly Government in May 2005 and provides a framework both for self-assessment by healthcare organisations and for external review and investigation by Healthcare Inspectorate Wales. Standard 12a requires healthcare organisations to ensure that patients and service users are provided with effective treatment and care that conforms to NICE technology appraisal guidance. The Assembly Minister for Health and Social Services issued a Direction in October 2003 that requires local health boards and NHS trusts to make funding available to enable the implementation of NICE technology appraisal guidance, normally within 3 months.
- 5.3 NICE has developed tools to help organisations implement this guidance (listed below). These are available on our website (www.nice.org.uk/TAXXX).
- Slides highlighting key messages for local discussion.
 - Costing report and costing template to estimate the savings and costs associated with implementation.
 - Implementation advice on how to put the guidance into practice and national initiatives that support this locally.
 - Audit support for monitoring local practice.

6 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 www.ukcrn.org.uk, www.clinicaltrials.gov and www.controlled-trials.com.
- 6.2 The Assessment Group considered that the following well-conducted RCTs reporting health-related utility values in accordance with the NICE methods guide could be of value:
- RCTs to investigate the effectiveness of sunitinib compared with best supportive care in people who are unsuitable or have contraindications for immunotherapy and who have a poor or intermediate prognosis.
- 6.3 The Committee considered that rigorous data collection is needed on the life-extending benefits of sunitinib when no second-line treatments are given.

7 Related NICE guidance

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

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 February 2011.

Andrew Stevens
Chair, Appraisal Committee
February 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.

Professor David Barnett

Professor of Clinical Pharmacology, University of Leicester

Dr David W Black

Director of Public Health, Derbyshire County Primary Care Trust

Mr David Chandler

Chief Executive, Psoriasis and Psoriatic Arthritis Alliance

Mr Peter Clarke

Consultant Medical Oncologist, Clatterbridge Centre for Oncology,
Merseyside

Dr Christine Davey

Senior Researcher, North Yorkshire Alliance R & D Unit

Dr Mike Davies

Consultant Physician, Manchester Royal Infirmary

Mr Richard Devereaux-Phillips

Public Affairs Manager, Medtronic

Dr Rachel A Elliott

Lord Trent Professor of Medicines and Health, University of Nottingham

Mrs Eleanor Grey

Lay member

Dr Peter Jackson

Clinical Pharmacologist, University of Sheffield

Professor Peter Jones

Pro Vice Chancellor for Research and Enterprise, Keele University

Ms Rachel Lewis

Nurse Advisor to the Department of Health

Dr Damien Longson

Consultant in Liaison Psychiatry, North Manchester General Hospital

Professor Jonathan Michaels

Professor of Vascular Surgery, University of Sheffield

Dr Eugene Milne

Deputy Medical Director, North East Strategic Health Authority

Dr Simon Mitchell

Consultant Neonatal Paediatrician, St Mary's Hospital, Manchester

Dr Richard Alexander Nakielny

Consultant Radiologist, Royal Hallamshire Hospital, Sheffield

Dr Katherine Payne

Health Economics Research Fellow, University of Manchester

Dr Danielle Preedy

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

Dr Martin J Price

Head of Outcomes Research, Janssen-Cilag

Dr Philip Rutledge

Consultant in Medicines Management, NHS Lothian

Dr Surinder Sethi

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

Professor Andrew Stevens

Chair of Appraisal Committee C

Dr Cathryn Thomas

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

Dr William Turner

Consultant Urologist, Addenbrooke's Hospital, Cambridge

B NICE project team

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

Rebecca Trowman

Technical Lead

Joanna Richardson

Technical Adviser

Chris Feinmann

Project Manager

Appendix B: Sources of evidence considered by the Committee

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

- Thompson Coon J, 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 alpha)

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