To: NICE (for circulation)

From: PenTAG

Dated: 30th June 2008

Re: Bevacizumab, sorafenib, sunitinib and temsirolimus for RCC

Thank you for providing PenTAG with the opportunity to respond to the comments made by Consultees on the Assessment Report.

There appear to be several common areas of comment amongst the Consultees, and we have addressed what we see as the major issues amongst these comments under the clinical/cost-effectiveness questions addressed/presented in the PenTAG report.

In addressing some of these issues we refer to points raised by manufacturers, where we see that such references are helpful. We acknowledge that similar issues may have also been raised by other Consultees, such as Kidney Cancer UK, RCN, RCP and NHS Quality Improvement for Scotland.

Whilst we have not submitted here a detailed response to all issues raised, we feel that the response below captures the main issues of importance to the NICE technology appraisal process. We feel that other issues raised are adequately addressed in the report and protocol. All suggested typographical errors have been examined and appropriate action will be taken, where necessary, prior to submission to the NCCHTA published monograph series.

PenTAG Question 1: Sunitinib / bevacizumab plus IFN vs. IFN alone

The use of baseline data for interferon from the AVOREN trial

A number of Consultees raise several interesting points related to the use of baseline data for interferon from the AVOREN trial published by Escudier and colleagues. As outlined in the report (Section 4.5.4.3 p.134) PenTAG made a judgment that the data from this trial were the most appropriate for the modeling of baseline progression, from the two primary sources/choices available.

Although Consultees have raised as a concern that the progression of disease in the AVOREN trial (results used) was assessed solely by the investigators, PenTAG consider that as the trial is described as double-blind the need for independent assessment of PFS is reduced. Overall survival data, which is shown in PenTAG analysis to have the greatest impact on cost-effectiveness estimates, is not affected by the concern raised.

Consultees have commented that in the AVOREN trial second line therapies were used after treatment with IFN. PenTAG would note that whilst the published paper includes the statement that "*Other neoplastic agents were allowed subsequent to progression or toxicity*", we are unaware of any published evidence to suggest that TKIs or temsirolimus were used as second line therapies. We were therefore unable to adjust the IFN baseline overall survival data to reflect the use of second line treatment options.

In addition, had it been clearer that the treatment protocol in the AVOREN trial could potentially introduce bias, due to use of second line therapies, we are unable to identify a clear and robust method for making any adjustment to the data to consider such uncertainty.

We also suggest for potential discussion that the use of other therapies after failure of IFN may be more representative of clinical practice, where other drugs are made available.

The use of the AVOREN data for modeling of baseline progression when on IFN treatment is a stated area of uncertainty in the PenTAG model. The uncertainty associated with our assumption to use this data [AVOREN data on IFN treatment] was assessed (i) using probabilistic methods when applying the AVOREN data, and (ii) in sensitivity analysis in which the baseline data from the trial of sunitinib versus IFN published by Motzer and colleagues was used (tables 45 and 46, p.159 and 162).

The base case assumption that IFN treatment will be for a maximum of 12 months duration

There is uncertainty surrounding the expected duration of interferon treatment (as evidenced by the different approaches/protocols in the AVOREN trial and the trial reported by Motzer and colleagues, and comments by Wyeth in their response to NICE). Whilst we assumed a 12 month treatment period in the base case, the effect of this assumption was explored in sensitivity analysis presented in Tables 45 and 46 (p.159 and 162).

Incorporation of the final results for the A6181034 study (sunitinib data submitted recently by Pfizer)

Several Consultees have commented on the newly available data from the Pfizer study above. PenTAG did not have this data, and were not able to use it to inform their review of the clinical and cost-effectiveness of drugs for RCC. However, this additional data has been presented to NICE by the manufacturer, and commented on by others (Consultee comments). Since submitting the PenTAG report, we have considered, in outline, the data contained within the conference abstract and accompanying slides provided by Pfizer (forwarded by NICE, 19th June 2008). In summary we would comment that, as described within the PenTAG report, PenTAG have not considered [across the scope of the report] data collected post crossover in the assessment of clinical or cost effectiveness. There are therefore two additional analyses of interest within the abstract; the data for overall survival conducted (i) for the overall treatment group (censored for crossover), and (ii) in a reduced sub-group of individuals who did not receive any post study treatment. We note that the summary statistic for overall survival in the full trial group reports a much reduced treatment impact on overall survival i.e. the data for OS in the ASCO abstract/submission (censored for crossover) is a hazard ratio of 0.808 (which would result in a greater cost per QALY compared to the PenTAG base case). On the subgroup data presented for individuals who did not receive any post study treatment, whilst the information provided is interesting, we feel it is important to highlight that this sub-group of patients was not pre-defined within the study protocol and we are unsure how such a subgroup would be identified prospectively (pre-selection?) in the clinical setting.

The data provided in the submitted abstract (and accompanying materials) indicate, in individuals who did not receive any post study treatment, a poorer survival pattern during IFN treatment in the early months of follow-up, but with a better survival profile over the longer term. We suggest that such a survival profile would probably lead to a lower cost per QALY in this subgroup, all else equal. However, the PenTAG modeling framework is structured to use data on both progression-free-survival and overall survival from the same source – consistent across all cost-effectiveness analyses undertaken for the broader review - to estimate cost-effectiveness. We believe this to be the correct approach given the modeling framework used. Therefore we are unable to provide cost-effectiveness estimates using this additionally supplied data on OS for either sub-group.

Exploration of utility values

Within the report we highlight the paucity of data in this area and acknowledge the limitations in the choices we have made (p.141). We have also explored the effects of absolute and relative changes in utility values and provide further discussion on p.202. We acknowledge that this is an area in which further sensitivity analysis may be useful. Whilst the rationale for other utility assumptions is speculative PenTAG presents here further sensitivity analyses using alternative assumptions for health state utility associated with health states of PFS and PD. Consultees (Pfizer) have suggested that further sensitivity analyses be undertaken using a greater difference in utility values between PFS and PD health states, on this see sensitivity analyses (ICERs) in the attached Table S1.

Estimates of drug costs using dose intensities

Roche have suggested that PenTAG have misinterpreted dose intensity data, used in the analysis, from the trial reported by Escudier and colleagues. The PenTAG modeling framework used dose intensity data reported by Escudier et al (AVOREN), and assumes that treatment continues (with costs adjusted via published dose intensity data) when people are in the PFS health state. Roche have suggested that dose intensity should be at a lower level than that assumed in the PenTAG model (PenTAG assume 88% for bevacizumab plus IFN treatment), suggesting a lower ICER for bevacizumab plus IFN versus IFN alone.

Roche have used data on treatment duration from the safety population to illustrate the point made. PenTAG have not used effectiveness data from the safety population, preferring to use data from the controlled trial (AVOREN), and we also note that dose intensity data are not reported for the safety population.

For the trial reported by Escudier et al the median time on treatment (bevacizumab, in the bevacizumab plus IFN group) was reported at 9.7 months (range 0-24.4 months) and the median time in PFS is reported at 10.2 months. Given that the trial protocol states that no dose reductions were allowed other than related to Grade 3 or 4 adverse events, and that treatment was continued until disease progression, or withdrawal (due to unacceptable toxicity or withdrawn consent), it seemed reasonable to assume the reported dose intensity for bevacizumab plus interferon of 88% in the PenTAG model.

We do not find the point raised by Roche to be clearly made, especially as it relates to data from the safety population. Similarly, in the PenTAG review of the Roche model, we found the estimation of drug costs to be unclear. PenTAG note that Roche present a treatment duration of 7.13 months (bevacizumab) in their reported safety population analysis, and there is a related mean time in PFS of over 11 months (Table 29, Roche submission). PenTAG are unclear on how these data are related (i.e. the difference between PFS time and time on treatment).

On a general note, PenTAG accept that the cost per QALY estimates are sensitive to assumptions surrounding cost of drug treatments (impact of dose intensity data), as noted in PenTAG sensitivity analyses.

Assumptions associated with resource use and costs surrounding monitoring, drug administration, and best supportive care

The decisions and justifications for the resource use and costs associated with monitoring, drug administration, and best supportive care can be found in Section 4.5.4.5 (p.143) of the PenTAG report. We also highlight the lack of available data to inform the estimates/assumptions made (sections 4.5.4.5, p.143), acknowledge that this is a possible limitation of the report (section 5.5, p.205), and present sensitivity analysis against the

assumptions made (table 45, p.159 and table 46, p.162). For example, in sensitivity analysis PenTAG assume that the administration cost associated with bevacizumab (+IFN) is zero (£0) and this reduces the base case ICER from £171K per QALY to £152K per QALY.

NICE guidance was to use the most up-to-date cost data. PenTAG note that the analysis undertaken has applied measures of uncertainty around cost estimates in probabilistic analysis (see PenTAG report, Appendix 9, page 260). Where possible, standard errors have been calculated from data on interquartile range, for use in the probabilistic analysis. We acknowledge that there is uncertainty with cost data used.

Further scenario analyses

Consultees have highlighted areas of uncertainty within the PenTAG model (generally these are areas already acknowledged as uncertain by PenTAG). Pfizer have presented results against one of numerous possible multi-way sensitivity analyses. PenTAG find similar results to those presented by Pfizer for the multi-way sensitivity analysis presented.

PenTAG Question 3: Temsirolimus vs. IFN

Pricing for temsirolimus in PenTAG analysis

The price for temsirolimus has still to be confirmed to PenTAG by the manufacturer/NICE (20th June 08). Wyeth are correct in highlighting that the PenTAG report has been completed using the price assumption of £618 per 30 mg vial, an assumption agreed with NICE, in the absence of a confirmed price for temsirolimus.

We acknowledge that if the price of temsirolimus is indeed confirmed at £515 per 30mg vial, the current base case estimates of cost effectiveness are an overestimate of the cost per QALY. In sensitivity analysis the submitted PenTAG report has presented the cost per QALY estimate based on a price of £515 per dose (see Table 49: £81,867 per QALY). To assist the Appraisal Committee, PenTAG provide here a supplement [see Appendix 1] reporting base case analysis using a price of £515 per 30mg vial for temsirolimus, holding all other base case assumptions as reported in the PenTAG report. Such an assumption would make redundant comments by PenTAG on issues related to cost per vial and waste associated with costing assumptions. Appendix 1 reports tables common to the PenTAG report (but with an 'S' suffix), with analysis updated based on the expected temsirolimus price per 30mg vial.

Resource use / costs associated with administration of IFN

Wyeth raise a concern over the PenTAG assumption on the self administration of IFN by patients. PenTAG assumptions surrounding resource use are described in section 4.5.4.5 of the report (p.143); where PenTAG assume 75% of treated patients will self-administer IFN in their own home.

In summary, Wyeth suggest that IFN should not be self administered by patients, but also suggest that IFN will be administered in 50-100% of cases in the patients own home setting. PenTAG understand, from clinical input, that IFN is self administered by patients (3 administrations per week), although prescription of IFN is under the general guidance of a physician. The PenTAG model assumes one outpatient appointment per month for people treated with IFN. The PenTAG base case assumption is that 25% of people treated with IFN will have injections from a district nurse in their own home. This issue is addressed in sensitivity analysis, assuming a scenario with a much greater cost associated with IFN

administration (30% of those treated with IFN having each administration in a hospital setting).

PenTAG review of the industry submission and modeling framework received from Wyeth

In the comments on the PenTAG appraisal report, Wyeth have provided much additional information on the methods used to estimate the cost-effectiveness of temsirolimus in their submission to NICE. The additional information makes the Wyeth approach much clearer, however, the PenTAG review was based on the materials submitted to NICE initially (and PenTAGs interpretation of the original submission).

Presentation of cost-effectiveness estimates for sub-groups

Wyeth comment that some of the estimates of cost effectiveness for sub-groups appear illogical. We agree that some of these figures are surprising; however they are based on the data provided. On the whole, the reasons for the differences in time on treatment within the PenTAG model are as a result of differences in the HRs for PFS (see Table 36 on p.139). For example, in the analysis of people with Motzer poor prognosis, people receive temsirolimus for 12 months which is longer than the duration of temsirolimus treatment in the base case (7.6 months). This is a reflection of the lower hazard ratio for PFS in this subgroup (0.69 vs. 0.74). As described earlier (in PenTAG report), we felt it was important to highlight differences in the definition of prognosis used in the temsirolimus trial (for cross comparison between trials) and we believed it was interesting to look at the subgroup of patients fitting the alternative definition of prognosis. However we acknowledge that this is not directly relevant to the assessment of cost effectiveness of temsirolimus since it represents a deviation from the licensed indication.

The reason for a longer time on treatment in the subgroup with poor prognosis is that the hazard ratio for that group is lower indicating longer in PFS and hence longer time on treatment. The reasons for the results in the clear cell and non clear cell subgroups are similar. We note (Table 36) that the PFS data for clear cell vs non-clear cell is uncertain, with HRs not statistically significant. For non-clear cell the HR is very low, but also with great uncertainty with wide confidence intervals (0.36; 0.22-1.59). The use of this data leads to a mean time in PFS (on treatment) of 22 months for patients treated with temsirolimus (base case = 7.6 months) and a related increase in total costs to £71,732 (base case = £28,171 for temsirolimus treated patients). Therefore, the balance of costs and benefits changes given the nature of the PFS data.

Use of independent versus investigator assessed PFS data

As Wyeth comment, the PenTAG modeling of temsirolimus vs IFN uses the PFS data reported in Hudes et al 2007 trial which was assessed by the investigators. This is the only survival data (PFS curve) available to PenTAG to allow modeling of disease progression (within the PenTAG CEA framework). The Wyeth model applies data on PFS from an independent assessment of disease progression. The hazard ratio for both assessments is the same. PenTAG assume that the independent assessment is undertaken at a time point after the investigator assessment, when temsirolimus treatment was already stopped (median duration of treatment was 3.92 months, and median PFS for investigator assessment at 3.8 months) – although this is not confirmed in the trial/submission. The authors of the paper (Hudes et al 2007) suggest that the reason for the discrepancy in estimates of PFS is that the investigators were using other clinical indicators of progression whereas the independent assessment was based solely on imaging. It is difficult to know which estimate of PFS is most indicative of the clinical situation. Both independent and investigator assessments of

PFS were classed as secondary outcomes. Data on OS is more important (for CEA estimates) in the model than data on PFS and this was obviously unaffected by this issue (independent vs. investigator assessment).

Wyeth suggest PenTAG Figures 8 and 9 (page 124-125) are not accurate. Figure 9 is for overall survival and is not related to the comment raised by Wyeth on independent versus investigator assessments/analysis. PenTAG believe Figure 9 to be accurate. Whilst PenTAG believe Figure 8 to be accurate, we do acknowledge that the presentation of data could have been clearer. Figure 8 presents the data reported by Hudes et al (survival curve) for PFS (investigator assessment) and compares the PenTAG fit to that data, and the Wyeth fit for IFN from the independent assessment (as reported in the Wyeth model submitted to NICE, derived from transition probabilities). PenTAG highlight differences between the modeling of data by Wyeth and the data reported (in published trial results) by Hudes et al 2007. PenTAG note that in Figure 8 the median PFS would appear to be higher than the reported median PFS of 3.2 months in the independent assessment of PFS.

PenTAG acknowledge that Wyeth have modeled disease progression using patient level data from the RCT, using a different modeling framework than that available to PenTAG. PenTAG contrast the findings. When comparing modeling approaches more generally (PenTAG vs. manufacturer models) the PenTAG Table 52 reports some analysis using the Wyeth modeling framework (as submitted to NICE) with adjustments made against the cost inputs for of administration IFN.

PenTAG Question 4: Sorafenib vs. BSC

Bayer query the PenTAG modeling approach, and the greater effectiveness predicted by the PenTAG model

The PenTAG report documents the modeling approach developed, which involved making a judgment as to the most appropriate method to model available data. When making this judgment, we felt it was important to use a consistent modelling approach across all research questions (drugs) considered in the report. Bayer, when considering the sorafenib specific data, make an interesting observation, that it is possible to model the survival curve of sorafenib without the of the hazard ratio (summary effectiveness data). Where the PenTAG model (HR applied to baseline prediction of disease progression for BSC) does predict a greater treatment effect (time in PFS) than the Bayer approach (TARGET data), rather than favouring the treatment arm, greater treatment effect creates a higher cost per QALY than a lesser treatment effect (as shown in PenTAG sensitivity analyses). Where time in PFS is shorter (as suggested by Bayer analyses), with overall survival data remaining unaltered, the ICER (cost per QALY) falls because the model then predicts that patients treated with sorafenib (incurring drug costs when in PFS) spend less time in PFS and more time in the PD health state. Where PenTAG use a Weibull survival curve approach to predict PFS with sorafenib, we find a cost per QALY of £86,491 (compared to base case of £102,498).

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Table S1: PenTAG CEA, Question 1, Sunitinib / Bevacizumab versus IFN alone. Effect of changes in utility value on the base case cost effectiveness estimates

Assumptions on utility values for health states (PFS, PD)	ICER (£ per QALY)	
	Sunitinib versus IFN	**Bevacizumab plus IFN versus IFN**
Base case **(diff between states = 0.08)**		
Utility PFS = 0.78; Utility PD = 0.70	**£71,462**	**£171,301**
Scenario One **(diff between states = 0.20)**		
Utility PFS = 0.80; Utility PD = 0.60	**£65,042**	**£166,416**
Scenario Two **(diff between states = 0.25)**		
Utility PFS = 0.80; Utility PD = 0.55	**£63,259**	**£166,162**
Scenario Three **(diff between states = 0.30)**		
Utility PFS = 0.80; Utility PD = 0.50	**£61,570**	**£165,909**

Appendix 1:

Cost-effectiveness of temsirolimus vs. IFN using update price of temsirolimus

The following cost-effectiveness results are based on the updated price of temsirolimus given in Table S38 below (price advised by Wyeth to NICE, email correspondence).

Table S38 (extract): Drug costs (temsirolimus vs. IFN).

Drug	Brand	Dose and frequency	Cost *	Cost per 6-week cycle
interferon-☐ (18MU)	Roferon-A	18MU† 3 times per week	£90.39 per 18MU††	£1,265 first model cycle, £1,627 future cycles
temsirolimus	Torisel	25mg once per week	£515 per dose‡‡	£3,090 ‡‡

* The cost of interferon-☐ is taken from British National Formulary (BNF) No. 55, and the cost of temsirolimus which was provided by Wyeth.

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

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

‡‡ £515 per 30 mg vial, which assumes some wastage of temsirolimus (i.e. for 25mg dose).

Table S47: PenTAG base case cost-effectiveness analysis: mean costs and effects for temsirolimus vs. IFN as first line therapy in patients with poor prognosis.

	interferon-α	temsirolimus	temsirolimus vs. interferon-□
Life Years	1.07	1.52	0.45
QALYs	0.53	0.77	0.24
Time on treatment (months)	4.6	7.6	3.0
Drug cost	£2,823	£14,982	£12,159
Drug admin cost	£367	£6,215	£5,848
Medical management	£729	£1,176	£447
BSC in PD	£2,599	£3,422	£822
Total costs	£6,519	£25,794	£19,276
Cost / LYG			**£42,902**
Cost / QALY			**£81,687**

Table S48: PenTAG subgroup cost-effectiveness analysis; temsirolimus vs. IFN.

Subgroup	Cost (£) / LYG	ICER (£ / QALY)
MSKCC poor prognosis	£69,935	£117,481
Clear-cell	£68,599	£128,872
Non-clear-cell	£58,378	£89,394
Prior nephrectomy	£79,596	£132,778
No prior nephrectomy	£34,091	£64,680

Table S49: PenTAG sensitivity analysis – temsirolimus vs. IFN as first line therapy in patients with poor prognosis

	Base case assumption	Sensitivity analysis assumption	ICER (£ /QALY) temsirolimus vs. interferon-α
General			
Base case	n/a	n/a	**£81,687**
Time horizon	10 years	5 years	£91,143
Discounting	3.5% p.a. costs and benefits	0% p.a. costs and benefits	£77,829
Effectiveness			
HR PFS	0.74	0.60 (lower 95% CI)	£99,321
		0.91 (upper 95% CI)	£65,104
HR OS	0.73	0.58 (lower 95% CI)	£49,359
		0.92 (upper 95% CI)	£217,243
Costs			
Cost associated with death	£0	£3,923	£81,357
Cost for BSC in PD (per 6-weeks)	£435	£1,297*	£88,601
Cost interferon-□ admin (per 6-weeks)	£112	£0	£83,242
		£224	£80,132
Cost temsirolimus admin (per 6-weeks)	£1,179	£0	£55,348
		£2,359	£108,026
Cost monitoring outpatient appointment (per 6-weeks)	£154	£0	£80,379
		£308	£82,995
Cost CT scan (per 6-weeks)	£65	£0	£81,137
		£130	£82,237
Dose intensity	92% temsirolimus, 56% interferon-□	100% both treatments	£77,808
Utilities			
Utilities	0.60 PFS, 0.45 PD	0.78 PFS, 0.70 PD**	£57,887
		PFS utility 0.48 (lower 95% CI)	£92,565
		PFS utility 0.72 (upper 95% CI)	£73,097

	PD utility 0.37 (lower 95% CI)	£87,862
	PD utility 0.52 (upper 95% CI)	£76,455

* Based on Remak & Brazil (2004)

** Taken from Motzer et al (2007) RCT

Figure 1: Cost-effectiveness acceptability curve for temsirolimus versus interferon-α

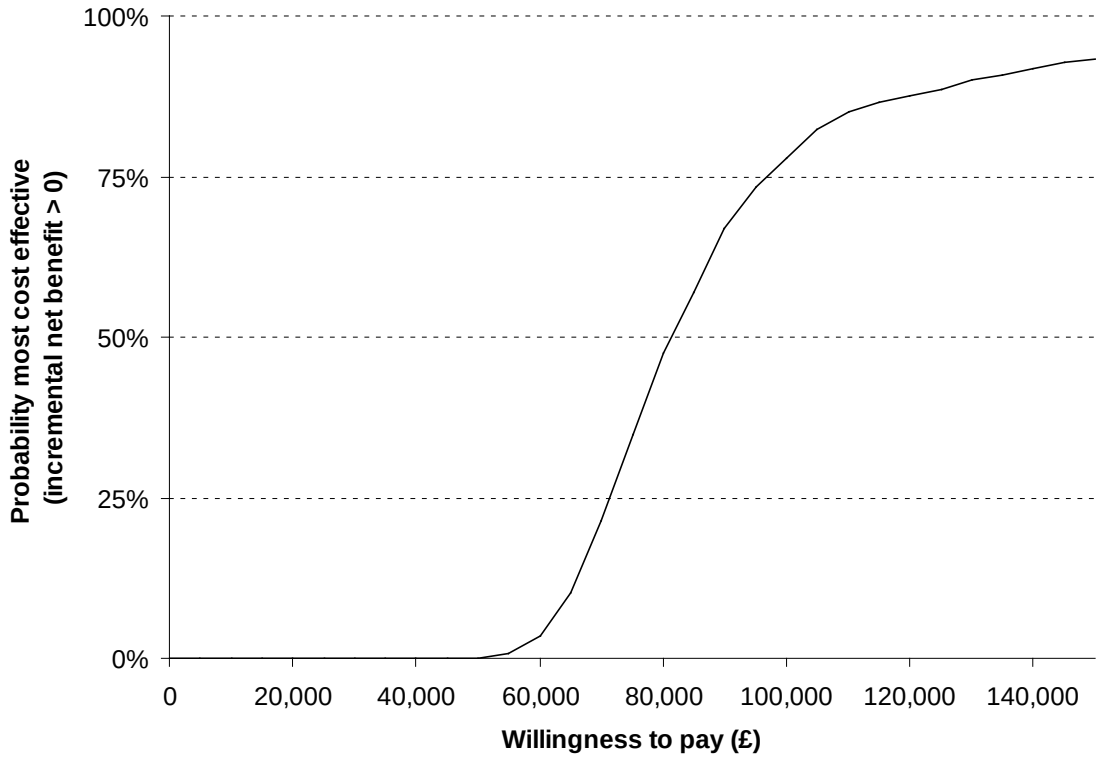
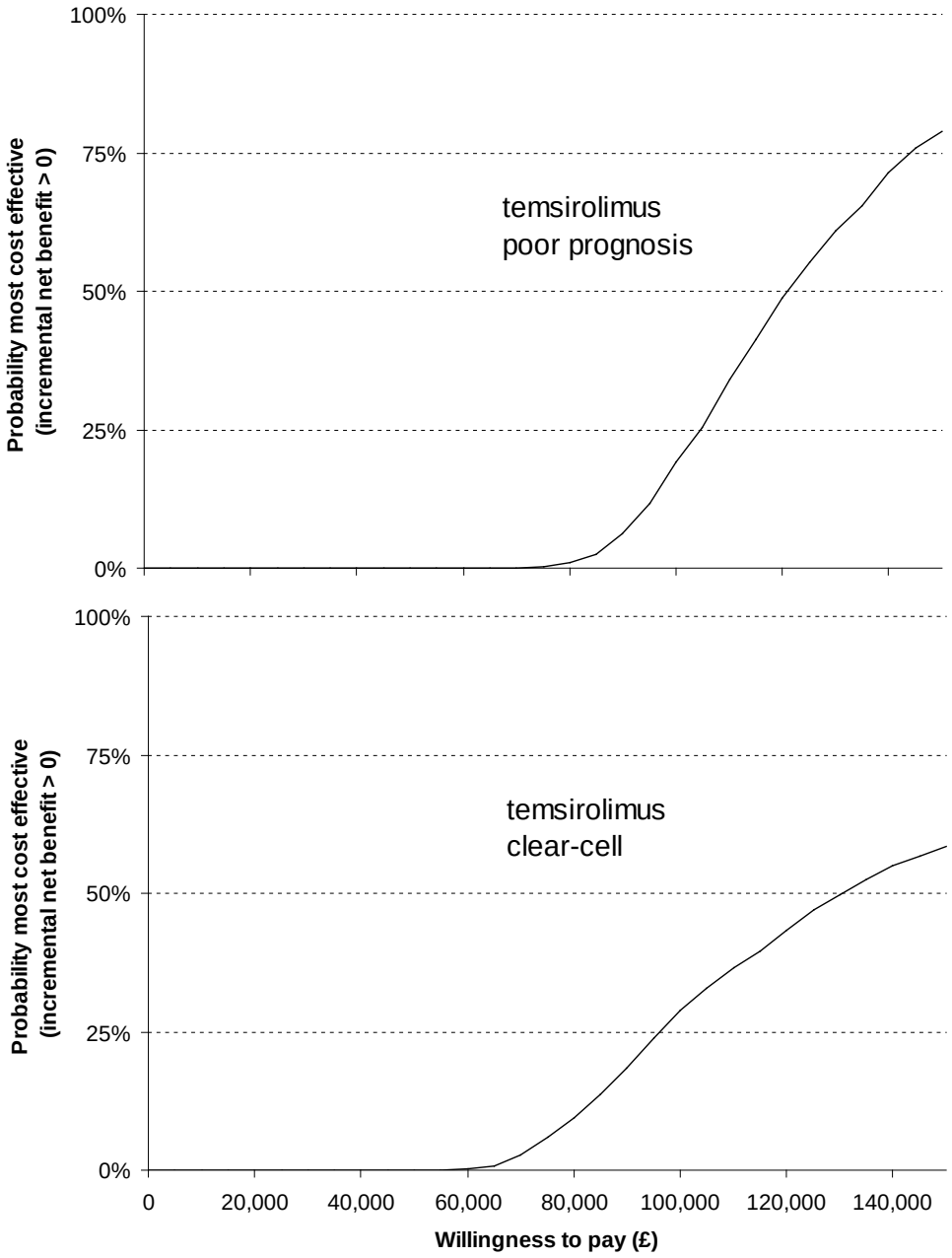
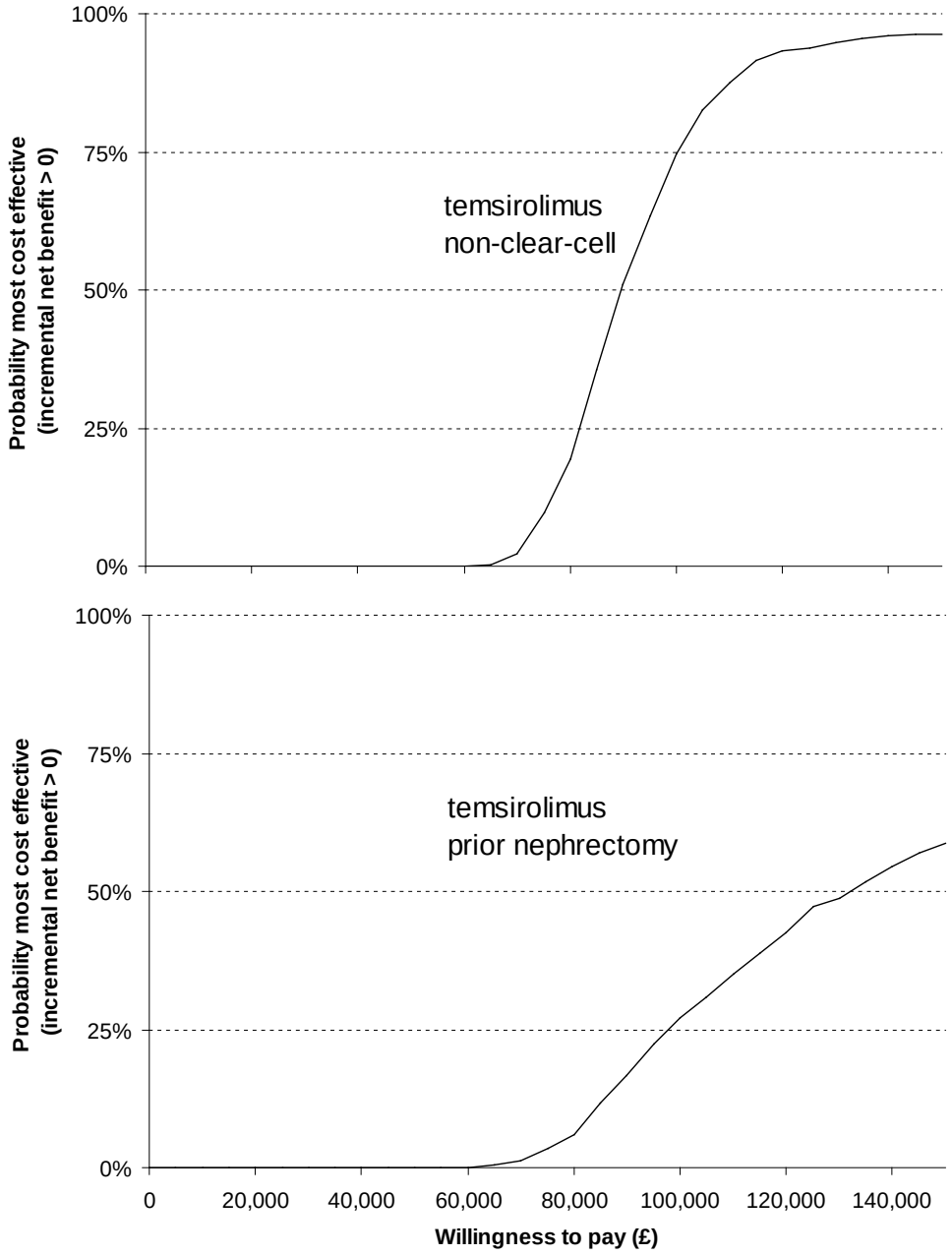


Figure 2: Cost-effectiveness acceptability curves for patient subgroups for temsirolimus vs. interferon-α




100%
75%
50%
25%
0%
Probability most cost effective (incremental net benefit > 0)
temsirolimus
non-clear-cell
100%
75%
50%
25%
0%
Probability most cost effective (incremental net benefit > 0)
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prior nephrectomy
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120,000
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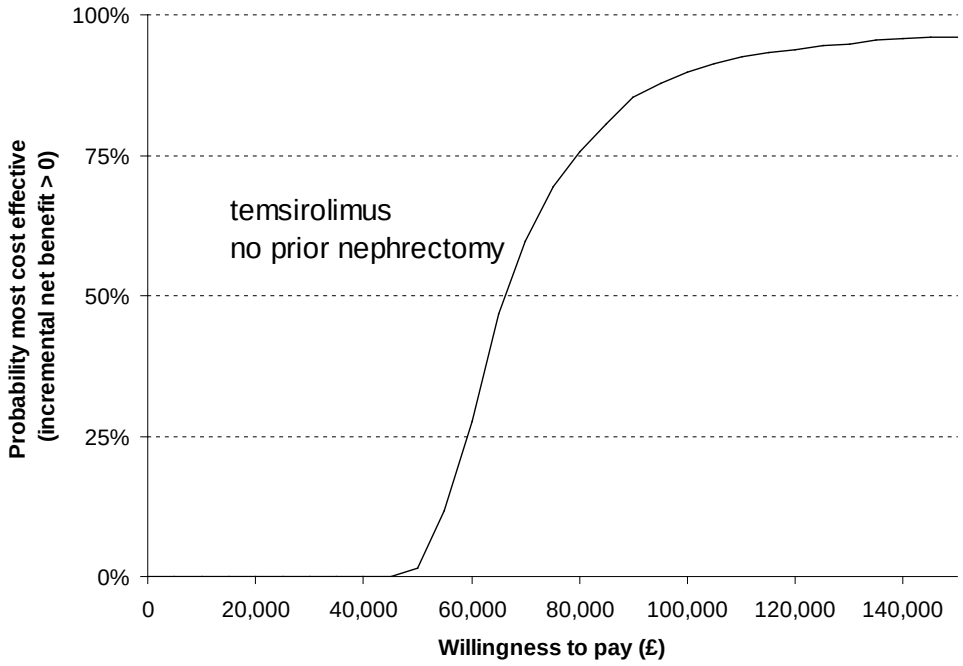
Willingness to pay (£)


100%
75%
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Probability most cost effective
(incremental net benefit > 0)
temsirolimus
no prior nephrectomy
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Willingness to pay (£)