Comments on Axitinib Renal ACD

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I will make a few general comments and then specific ones:

General points

1. It does not seem helpful to go over differences of opinion in the CHMP now Axitinib is licenced. As indicated in my summary at the meeting Axitinib appears to be a more potent VEGF inhibitor and therefore it is entirely reasonable that there should be incomplete cross-resistance to other less potent VEGF inhibitors. In addition, there is indeed evidence that resistance to VEGF TKIs is reversible (Zhang et al., 2011).
2. There is an obvious inherent flaw in the system that we are trying to estimate cost per QALY where all seem to agree there is insufficient data to define a cost per QALY accurately. What Axitinib has been shown to do is produce responses and PFS benefit in previously treated patients – responses in around 22.6% of patients (11.3% in prior sunitinib patients and around 32.5% in prior cytokine patients) and a PFS benefit of 2 months (5.6 months in prior cytokine patients and 1.4 months in prior sunitinib patients). These are entirely consistent with some but incomplete resistance following prior VEGF TKI exposure. These are also statistically significant and meaningful for patients – albeit somewhat limited in the sunitinib pre-treated group. There is no proven survival benefit in either group and that is increasingly common in kidney cancer studies where there are multiple potential salvage therapies available to confound the outcome. Hence in my view it would be far better to assess a cost per "quality adjusted PFS" rather than using complex adjustments of doubtful value to assess QALYs. These will always be very uncertain and is illustrated by the wide variation in all estimates regardless of who produces them and of the most plausible figure chosen!

Specific Points

In terms of the NICE accepted cost per QALY there appear to be a number of scenarios that have been examined most of which make little difference. The key question seems to be the post-Axitinib survival gain the modelling of the post treatment period. The point is made that this in not seen in the Axis trial result and also was not used in the model for post cytokine therapy. I will address each of this point separately;

(i) **Post**-Axitinib it is certainly plausible that there will be a QALY gain as well as while on Axitinib. On stopping the treatment there will be some utility gain from reduction in side effects and also patients will on average start with less disease. There are no "waterfall plots" given in the Axis trial publication but previous publications suggest that even though the response rate may be low many patients have some reduction in the size of the tumour. Because of the way progression is calculated (30% increase from **minimum size not from baseline**) this will also mean the tumour burden is on average lower in those patients progressing after Axitinib (or any active therapy) than patients on placebo. Given the small difference in PFS and ORR between Sorafenib and Axitinib the difference may be small and not seen in the Axis results per se, but it would be larger compared to placebo which is the agreed relevant comparator. Thus I feel it is inappropriate to assume **no** benefit post progression as in section 4.13 of ACD. I cannot comment on whether the Pfizer assumptions are correct or if some compromise is more appropriate but either way it would reduce the ICER to nearer £50,000.

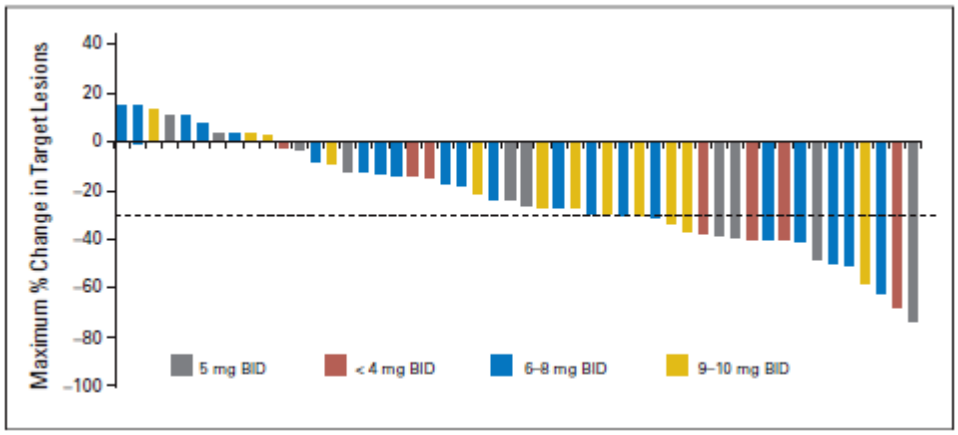

Figure 1 : Waterfall plot of tumour sizes from Rini et al., 2009 – a post Sorafenib population.

(ii) **Post** –Cytokines, I feel the same comments apply but perhaps more so – the response rates are better and the extent of response tends to be better (see Figure 2). Again there are no published results from the Axis study but I have no reason to believe these are not similar. Again given the way progression is calculated I would expect a significant number of patients to have much lower disease bulk on progression and thus to survive longer (and perhaps to get other therapies). I cannot explain why the Pfizer model did not show this and we discussed this amply at the meeting. If this were properly taken into account, I believe, it would greatly reduce the ICER for the post-cytokine group – I accept this is a small patient population (probably less than 100 per year now).

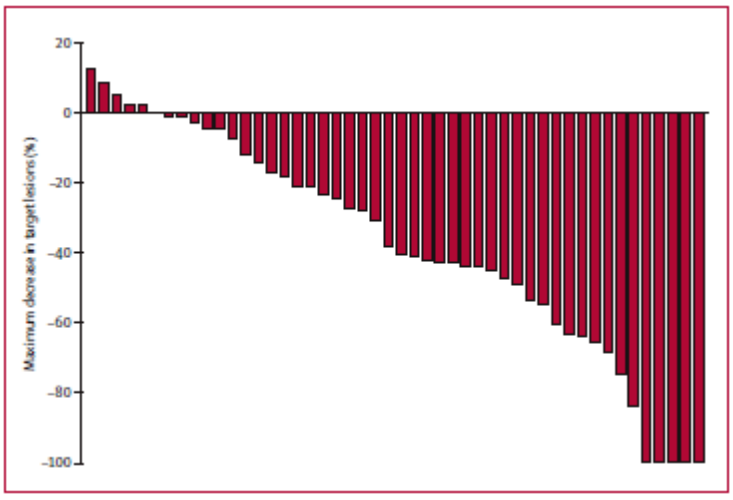

Figure 2: Waterfall plot of tumour sizes from Rixi et al., 2007 – a post Cytokine population.

A further key point is the size of the patient population. It may well have been over-estimated. If Axitinib were to be approved there would effectively be two available therapies (Everolimus and Axitinib) and clinicians will need to make a rational choice. There is no direct data but there is some data to support those who did well on prior TKI doing better with a second TKI. Data presented by Rini et al (figure 3) suggest that the PFS of patients on Axitinib who have a PFS of 9 months or more do better (have PFS of 6.3 months compared to the overall 4.8 months for total post-Sunitinib population. Since the median PFS on sunitinib is around 9-11 months this would suggest around 50% might

be “prime-candidates” for Axitinib. Ideally, this type of stratification might be assessed formally but it is often difficult as a non-commercial study as the NHS has delayed or no access to new drugs and there is no incentive for drug companies to do these studies when they are not required internationally.

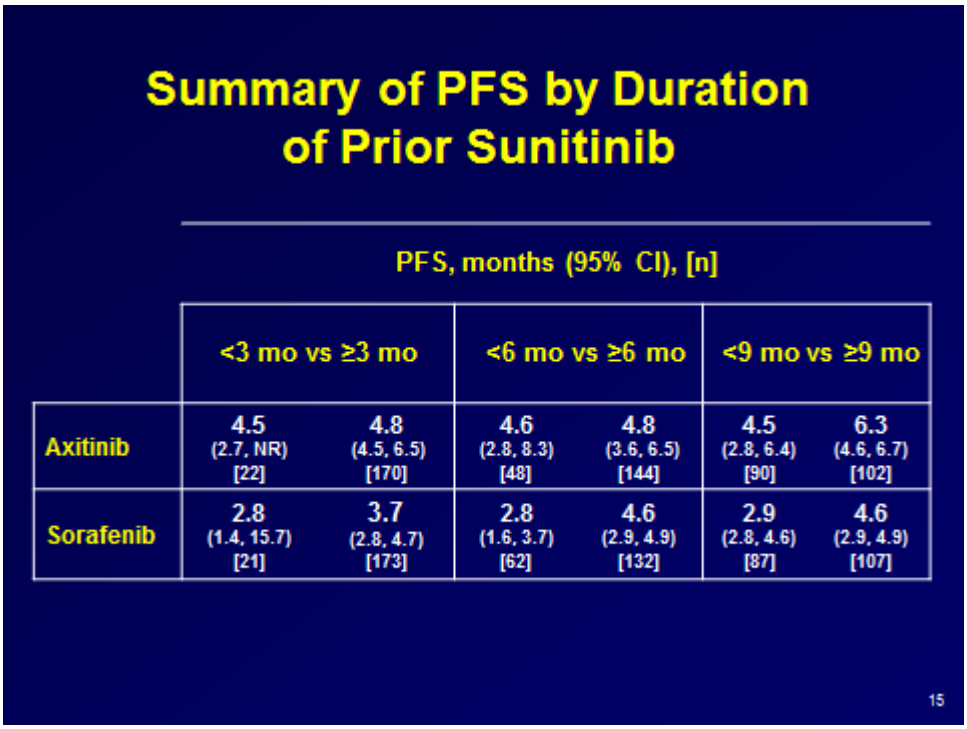

Figure 3: Slide from Rini et al., ASCO GU 2012

References

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