in collaboration with:

Single Technology Appraisal:

Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment

ERG Response following specific questions from NICE

Produced by	Kleijnen Systematic Reviews Ltd. in collaboration with Erasmus University Rotterdam and Maastricht University
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NICE Questions:

NICE would like the ERG to provide:

1. The assumptions leading to the £33,000 ICER, including the HR for the OS, and the PFS:OS ratio. There may be other factors that have been brought forward from the indirect comparison for the ICER of £33,000 for axitinib versus BSC.

2. What the assumptions are behind the <£55,000 ICERs for axitinib versus sunitinib, and versus pazopanib. The manufacturers explained their reasoning about the 24 month OS for BSC, while the OS for pazopanib and sunitinib were 22.7 and 23.9. Are there any other assumptions underlying this figure?

It will be important for Committee decision making to have a solid understanding of the basis for the £33k ICER, whether it is in fact £33k or if it is £36k, and what assumptions underlie the manufacturer's analyses.

ERG Response

Ad 1) The base case ICER reported by the manufacturer for the prior cytokine population is equal to £55,284. This is based on a mean HR for overall survival in BSC vs axitinib equal to 0.63 (95% CI (0.41, 0.99)). The associated median OS for BSC from the indirect comparison is 23.82 months (24 months reported by the manufacturer). The PFS:OS ratio, computed as the total number of incremental life-years gained divided by the number of incremental life-years gained in PFS state is equal to 0.94.
When the lower limit of the 95% CI for the OS HR was used (i.e. 0.41), an ICER equal to £36,493 was found. In this case the median OS for BSC is 17.46 months (17.6 months reported by the manufacturer), and the PFS:OS ratio is equal to 1.60.

	ICER	HR OS	BSC median OS	PFS:OS (Life years)
Base case	£55,284	0.63	23.82	0.94
Lower limit HR	£36,493	0.41	17.46	1.60
ICER £33k	£33,015	0.343	15.35	1.82

Thus, the ERG could not reproduce the £33,000 ICER for the prior cytokine group that was reported by the manufacturer by changing the HR for overall survival to the lower limit of the 95% confidence interval. Unless the manufacturer made changes to the model that we are not aware of, an ICER equal to £36,493 per QALY gained with the PAS should have been reported, as this matches the version of the model with all updates and the latest PAS. Also, for that value of the hazard ratio, the ratio of PFS:OS would be 1:1.6, and not 1:1.8 as reported by the manufacturer.
The ERG explored how much the HR should decrease to achieve an ICER of £33,000, and found a HR of 0.343. For that HR, the ratio of PFS:OS will be 1:1.8.
Note that assuming the OS HR is equal to 0.41, the manufacturer reported a median OS for BSC equal to 17.6 months. However, using the latest version of the model (dated 15 Nov 2013), the ERG calculated 17.46 months (Weibull extrapolation).

Ad 2) The base case ICER reported by the manufacturer is equal to £55,284 and it is based on a median OS for BSC from the indirect comparison (24 months) which is higher than the median OS for pazopanib (22.7 - 95% CI: 19.3–28.3) or sunitinib (23.9 - 95% CI: 14.1-30.7). Since it may reasonable be assumed (though no evidence is provided) that active treatment with pazopanib or sunitinib is more expensive than BSC, and BSC is also more effective (when comparing medians), it follows that BSC dominates pazopanib and sunitinib.

If on the other hand the lower estimate for BSC OS is used (i.e. 17.6 months) this claim of dominance no longer holds, and it becomes relevant to estimate the ICERs of axitinib versus sunitinib and pazopanib. When we had an OS of 24 month, the ICER was £55,284. To assess what might be concluded for the ICERS of sunitinib and pazopanib it is easiest to look at the formula of the ICER. The base case ICER of axitinib versus BSC can be expressed as:

$$\frac{C_{Axi} - C_{BSC}}{OS_{Axi} - OS_{BSC}} \approx 55{,}000$$

Now we know that $OS_{Sun} \approx OS_{BSC}$ and $C_{Sun} > C_{BSC}$ (hence $C_{axi} - C_{Sun} < C_{Axi} - C_{BSC}$), so as the numerator becomes smaller with the same denominator, it must follow that the ICER of axitinib versus sunitinib must be smaller than that of axitinib versus BSC.

$$\frac{C_{Axi} - C_{Sun}}{OS_{Axi} - OS_{Sun}} < 55{,}000$$

A similar argument can be made for pazopanib, though there the $OS_{Paz} < OS_{BSC,}$ hence $OS_{axi} – OS_{Paz} > OS_{Axi} - OS_{BSC}$. So now, we still have a smaller numerator, but also a larger denominator, again leading to the conclusion that the ICER of axitinib versus pazopanib must be smaller than that of axitinib versus BSC.