Dear Chris

Re: Consultation on the second ACD for renal cell carcinoma drugs, including Nexavar

Thank you for the opportunity to respond to the second appraisal consultation document (ACD) containing recommendations for Nexavar for the treatment of renal cell carcinoma. We are disappointed that NICE have been unable to recommend Nexavar as a treatment post immunotherapy, despite the Committee recognising it as a clinically effective therapy with robust data in a group of patients for whom there are no other treatment options available.

Please find below Bayer's response to the ACD. These are based on both requested general headings as well as a section outlining factual issues contained within the document.

Factual issues

Nexavar is indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy. Section 3.2.1 incorrectly states that the "condition has failed to respond to" immunotherapy; patients may have responded initially to such therapy, but consequently failed. This statement is also included throughout the document when referring to the indication and treatment line setting of Nexavar (e.g. 4.2.8, 4.1.20, 4.2.10, 4.3.2).

We can confirm that the price of Nexavar is now £2,980.47. Please can you update Section 3.2.3 so that it no longer discusses the previous price of £2504.60, and update 4.2.10 so that it does not refer to "the new price" but rather "the price".

The list price of temsirolimus has not been included in Section 3.4.1 although the list price has been available for several months. Although it is not currently listed in the BNF (edition 56), it is currently listed by MIMs (February 2009) as £620.00 for a 1.2ml vial (25mg/ml concentrate). In section 4.2.21 you refer to having confirmed the price with the BNF.

The survival findings reported in 4.1.16 refer to the first interim analysis. Please can you update this section to reflect this.

The updated analysis on progression free survival (PFS) was undertaken at crossover rather than before crossover occurred (section 4.1.17). The median PFS values shown and statements made are only partly correct. Escudier et al. (2007) report the following:

- Independent assessment (pre planned, Jan 2005) – 2.8m vs 5.5m (HR 0.44; 95% CI 0.35 to 0.55)
- Investigator assessment (pre planned, Jan 2005) – 2.8m, vs 5.9m (HR 0.44; 95% CI 0.35 to 0.44)
- Investigator assessment (at crossover, May 2005) – 2.8m vs. 5.5m (HR 0.51; 95% CI 0.43 to 0.60)

Please can you update the section to reflect this.

The statistical significance referred to in 4.1.18 refers to both partial response and stable disease, although it only refers to those with a partial response. The number (percentage) with stable disease was 333 (74%) and 239 (53%) for the Nexavar and placebo group, respectively.[1]

The Committee concluded that the prior cytokine sub group was not pre-specified (Section 4.3.19) Although this is not stated in the TARGET publication (Escudier et al. 2007), we can confirm, as previously stated, that this and other sub-groups analysed were pre-planned.

In Section 4.3.19, it states that the Committee "was aware that some of the participants in the 'no prior cytokine' subgroup in the trial [TARGET] would have received sunitinib as a first-line treatment". The exclusion criteria for the clinical trial, TARGET, included patients who had any prior medicines that are licensed or investigational that target VEGF and VEGF receptors (for example, sunitinib).

The health related quality of life section (4.1.19) refers to a 30 week treatment period. This should be 32 weeks (the first four cycles were 6 weeks long, the 5th cycle 8 weeks long). The same section also refers to a significantly greater number of adverse events experienced in the Nexavar arm. The paper on which this section is based (Bukowski et al. 2007) does not report either this or the adverse events that you report.[2] The statistical significance of $p<0.0001$ refers to "bothersome side effects of treatments" rather than actual adverse events. The paper then concludes that Nexavar appeared "to have no impact on energy, fatigue, quality of sleep, pain, or weight change, items that may be negatively impacted by cancer treatment" which have not been mentioned in this section of the ACD.

The ACD recommends that further research on the impact of Nexavar on health related quality of life (HRQoL) should be undertaken (Section 6.2). However, from the Committee's appraisal of Nexavar under the end of life criteria, the Committee believe that the additional HRQoL required would be too great to fall within the current threshold range (4.3.21). If the Committee's argument is correct, there would therefore be no point in NICE recommending further HRQoL studies for Nexavar.

Interpretation of clinical and cost-effectiveness

The Committee expressed concern about the difference in the ICER for the prior cytokine group in the original analysis and resubmission (Section 4.3.19). Furthermore, in Section 4.2.30, the ACD states the DSU observations on our revised ICER, concluding "that no explanation for this [change in results] was provided by the manufacturer". However, the reason for this should have been self-explanatory to the DSU – namely that the modelling approach was changed to that adopted by PenTAG, utility values and costs were changed to reflect those preferred by PenTAG and that a considerably more complete dataset for the prior cytokine group was provided in the resubmission compared to the original analysis. Furthermore, the assumption of proportional hazard was shown to not hold (see Section 4.2.31), which also resulted in a marked difference in the ICER estimated for the overall group by PenTAG themselves (shown at the public part of the 14th Jan 2009 Committee meeting).

Many of these reasons were explained to the Committee by PenTAG in the public part of the Committee meeting (14th Jan 2009) and some of these reasons are also highlighted

in the ACD (Section 4.2.10). Please can you update the relevant sections (e.g. 4.2.30, 4.3.19) to reflect the reason why the ICERs changed for not only our own estimates, but those by the academic group.

Has all relevant evidence been taken into account

Based upon the Phase III trial, TARGET,[1] the Committee "concluded that, as the data were limited, sorafenib as a first-line treatment for those unsuitable for immunotherapy with advanced and/or metastatic RCC could not be considered to be clinically effective" (Section 4.3.15). There are relatively low patient numbers in the Phase III trial for patients who are unsuitable for immunotherapy. However, as provided in the original submission in January 2008, two large, expanded access programmes of Nexavar in a real world setting within Europe and North America both included patients who were ineligible for immunotherapy.[3, 4]

In the North America programme, 224 patients who had Nexavar as first line treatment and were evaluated in the extension protocol had a median PFS of 35.1 weeks (8.1 months).[5, 6] [a] In the European expanded access programme, 28% of patients (n=318) were unsuitable for cytokine therapy. The median PFS for these patients was 6.0 months.[7] These data demonstrate that Nexavar is a clinically effective option in this patient group, as recognised by the EMEA when the indication was approved.

Suitability of the provisional recommendation

Bayer supports that clinicians should have a range of treatments available for their patients, choosing the pathway which they believe will be in the best interest of the patient presenting to them. There is limited clinical evidence on sequencing available in the UK metastatic and/or advanced RCC population due to low uptake of the treatments under consideration to date. However, Nexavar still provides a clinically effective treatment post immunotherapy, and our exploratory analysis, based on estimations and/or assumptions from the academic group themselves, does indicate that immunotherapy followed by Nexavar is a clinically relevant option to clinicians, and may also offer savings to the NHS overall. The importance of clinician choice is particularly acute when specific patient groups are considered (see next section).

Equality related issues

Not all advanced RCC patients will be suitable for sunitinib based on the guidance in the FAD (e.g. poor performance status and/or are cytokine unsuitable). The current recommendations proposed throughout the overall MTA, including the first line recommendation for sunitinib, have important equality issues for four specific sub-groups of patients.

1. Patients who are unsuitable for immunotherapy will only be allowed to receive best supportive care i.e. they cannot benefit from any of the new technologies, including sunitinib. Nexavar is indicated for this patient group, having demonstrated clinical benefit. We have highlighted the main clinical evidence

[a] In total there were 1247 (out of 2502) patients who received Nexavar as a first line therapy. As the US license was granted earlier than expected, at which point enrolment stopped, 224 first line patients were evaluated within the extension protocol to estimate median PFS.

supporting Nexavar in this patient group in the section "Has all relevant evidence been taken into account". Possible reasons that a patient may be considered unsuitable for immunotherapy includes clinically significant organ impairment, low likelihood of response to therapy, presence of hepatic metastases, two or more metastatic organ sites, and contraindications such as liver dysfunction or brain metastases.[8, 9]

2. Patients who may be suitable for immunotherapy but not sunitinib. Potential patient groups who may be less suitable for sunitinib include those with congestive heart failure, poor nutritional state and impaired mobility;[10] it should also be noted that patients with hypertension or clinically significant cardiovascular events were excluded from the sunitinib Phase II trial.[b11] These patients will only be able to receive the less effective immunotherapy as a first line treatment and consequently will not benefit from any of the new treatments, although Nexavar has demonstrated to the Committee that it is a clinically-effective treatment after immunotherapy.[11]
3. Those patients who may rapidly progress (or not respond) on sunitinib, but would benefit from a subsequent treatment. Based on the progression free survival curve from the Phase III trial against interferon, approximately 10% on sunitinib had progressed within one month.
4. Those patients who do not continue on sunitinib due to tolerability issues. Section 4.1.8 of the sunitinib FAD concluded that 8% of patients on sunitinib discontinued in the trial due to adverse events as well as acknowledging the emerging concerns in the published literature about the frequency of cardiovascular events associated with sunitinib. Khakoo et al. (2008) found that average time of symptomatic onset of heart failure associated with sunitinib occurred within 22 days of initiation in patients who developed symptomatic cardiac dysfunction without any other obvious cause.[12]

For those patients who are unfortunate enough not to be able to benefit from sunitinib, Nexavar can offer a clinically relevant treatment option,[7, 13-17] as long as they are not contraindicated and are unsuitable for immunotherapy. Immunotherapy after a tyrosine kinase inhibitor (TKI) should be used with caution due to tolerability issues.[18] Sablin et al. (2007) has shown that there appears to be a lack of cross resistance between Nexavar and sunitinib.[15] Furthermore, the evidence of effect of Nexavar post sunitinib has been demonstrated, with a median PFS of patients of between 4 and 5 months,[7, 14] despite such patients likely to be in a poorer performance status than the general advanced RCC population.[7] The use of Nexavar post sunitinib was also confirmed by the clinical expert at the Committee meeting (public part, 14th Jan 2009) as being a potential clinical option especially where there are tolerability issues related with sunitinib; clinical experience of Nexavar and sunitinib has shown that toxicities experienced with the two therapies are different,[16, 19] allowing clinicians to take these factors into account when recommending subsequent therapies for patients.

[b] In the Phase II trial for Nexavar, TARGET, patients with hypertension were not excluded.[1]

Conclusion

In the FAD, the Committee acknowledged that sunitinib should, along with current practice, immunotherapy, be available as treatment options for clinicians. Whilst sunitinib has demonstrated clinical benefit over immunotherapy in those patients who are suitable for immunotherapy, there does remain a group of patients for whom sunitinib or immunotherapy provides no or limited benefit, or for whom sunitinib is less suitable. These are those unsuitable for immunotherapy and/or sunitinib and those patients who commence sunitinib but withdraw due to cardiovascular toxicity reasons or because they do not respond. For these patients, the current ACD recommendations mean that these unfortunate patients will not be able to benefit from any other active treatment such as Nexavar.

We would like the Committee to take into consideration the information provided within this letter in making a final recommendation on Nexavar. In particular, we ask that special consideration is given to the clinical benefit of Nexavar in both the immunotherapy unsuitable patient group and post sunitinib patient group, and, most importantly, the equality implications for the four patient groups from the Committee's provisional recommendations. When making their recommendation, we believe the Committee should evaluate these four patient groups under the end of life criteria, acknowledging that they represent a small patient group who, based on current clinical practice and recommendations by the Committee, have no other treatments available to them except best supportive care, and for whom Nexavar can provide a substantial clinical benefit.

Yours sincerely

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