Pfizer Limited
Walton Oaks, Dorking Road, Walton on the Hill,
Tadworth, Surrey KT20 7NS, UK
Telephone: +44 (0)1304 616161

Worldwide Biopharmaceutical Businesses

National Institute for Health and Clinical Excellence

Level 1A, City Tower

Piccadilly Plaza

Manchester

M1 4BD

BY NICE DOCS

25th March 2014

RE: ACD2 on Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment (ID 518)

Dear [redacted],

Thank you for giving us the opportunity to comment on the second Appraisal Consultation Document (ACD) for the above appraisal. We welcome the review of the evidence by the Appraisal Committee and the preliminary positive recommendation for axitinib use in the NHS and the conclusion that axitinib is a cost effective use of NHS resources.

As part of our response we have provided clarification around the additional post appeal evidence provided by Pfizer. This is particularly in relation to the analysis by Grünwald et al., and the end of life criteria considerations in the prior cytokine population.

Yours sincerely,

[redacted]

For and on behalf of Pfizer Limited

Pfizer response to ACD2 on Axitinib for the treatment of advanced renal cell carcinoma after failure of prior systemic treatment (ID 518)

Executive Summary

Pfizer welcome the review of the evidence by the Appraisal Committee and the preliminary finding of the Committee that axitinib is a cost effective use of NHS resources. This preliminary decision means that metastatic renal cell carcinoma (mRCC) patients in England and Wales could have access to a NHS funded second line treatment for the first time.

Pfizer agree with the conclusions of the Appraisal Committee that axitinib is a cost effective end of life treatment and that the results of Grünwald et al. support the simulated treatment comparison (STC) with respect to the post-progression survival benefits of axitinib over best supportive care. Further to these conclusions, we provide clarifications to reassure the Committee with regards to the additional evidence accepted post-appeal and the end of life considerations.

Finally, we note the preliminary recommendation is wider than the licensed indication for axitinib. Medicines regulation has been developed in Europe to assess how medicines should be authorised for use and there is clearly a need to ensure that the special position of the regulatory bodies is recognised. We fully recognise that in making this preliminary recommendation NICE has taken into consideration the views expressed by clinical experts, but we are also concerned to ensure that NICE guidance that is inconsistent with the marketing authorisation cannot be seen to undermine the regulatory framework by inappropriately influencing clinicians' professional obligation to act in the best interests of their patients.

Further comments on the additional evidence submitted

In the majority of phase II and III clinical trials evaluating targeted treatments in mRCC, tumour response is measured in solid tumours using the internationally recognised Response Evaluation Criteria In Solid Tumours (RECIST). These criteria provide guidance on how to quantify the change in a patient's tumour burden from baseline, and how to categorise the quantified response. Specifically, the dimensions of select tumours, referred to as target lesions, are used to calculate the change in tumour burden between images from different time points. The calculated response is then categorised as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). CR is complete disappearance of tumour (- 100%), PR is a change/shrinkage between -100% and -30%, SD is a change/shrinkage between -30% and +20%, and PD is an increase of 20% or greater. Of note, when scans show the appearance of new lesions/tumours the change in tumour burden cannot be quantified numerically, but the response is categorized as PD.

In the age of targeted therapies, there is increased interest in the extent to which tumour response can be used as a prognostic tool. The rationale for the analysis performed by Grünwald et al. was to examine in greater detail the relationship between the extent of tumour response and overall survival.

To quantify the strength and significance of this association between tumour response and overall survival, Grünwald et al. incorporated data from eight Pfizer sponsored trials of first and second line treatments for mRCC. The analysis utilised results from a uniform method of assessing response to treatment across the trials (RECIST as determined by the clinical trial investigators). Tumour response was incorporated into a multivariate Cox-proportional hazard analysis as a categorical variable, with the following categories (the -30% to 0% category was used as the control):

1) Shrinkage of ≤ 100% to < 60%;
2) Shrinkage of ≤ 60% to < 30%;
3) Shrinkage of ≤ 30% to < 0%;
4) Growth of between ≥ 0% to < 20%;
5) Growth of ≥ 20%;
6) Missing data.

The multivariate model showed that in addition to tumour shrinkage, the factors below were also significantly associated with prognosis (all P<0.0001) (Grünwald et al. (slide 9).

- time from diagnosis to treatment, ≥1 vs. <1 yr
- Baseline LDH, >1.5 vs. ≤1.5 ULN
- Baseline corrected calcium, >10 vs. ≤10 mg/dl
- Baseline hemoglobin, >LLN vs. ≤LLN
- Baseline ECOG performance status, 0 vs. 1–2

In addition to the multivariate Cox proportional hazards analysis, a six month landmark analysis was performed to minimise the potential bias associated with the inclusion of maximum tumour shrinkage as a factor in the model. Furthermore, Grünwald et al. also performed Kaplan-Meier analysis of OS for the different categories of response. This

approach demonstrated across a variety of subgroup analyses according to type of intervention and line of therapy, that patients with a worse tumour response have a shorter median OS. In addition, the 95% CIs for OS corresponding to each of the response categories tend to form mutually exclusive, non-overlapping ranges (see Table 1 of previously submitted summary of Grünwald et al. for the 95% CI's of the overall analysis); a finding consistent with the prognostic importance of tumour response.

The analyses by Grünwald et al. were performed on all patients who received study treatment. To this point, it should be noted that the abstract by Grünwald et al. mistakenly refers to the number of sorafenib-treated patients included from the AXIS trial as 335, whereas the actual number of sorafenib-treated patients included in this analysis (355) is correctly stated on slide 11 of the oral presentation.

As all trials included in the analysis were either single arm studies or comparative trials versus an active treatment, no placebo-treated patients were present in the dataset. However, as poorly responding patients have a short median OS independent of therapy received or line of treatment, we would also expect these results to apply to patients receiving a placebo, who also typically have a poor response to therapy. Therefore, the absence of placebo treated patients in the dataset used by Grünwald et al. does not impact the validity of weighting the results of this analysis using the distribution of tumour responses for placebo treated patients from the RECORD-1 trial. This point was further supported by the clinical expert at the Appraisal Committee meeting on the 4th of February.

In summary, the results of the analysis by Grünwald et al. demonstrate that patients with a good tumour response had a significantly longer overall survival than those with a poor tumour response, implying a post-progression survival benefit associated with therapy. As accepted by the Appraisal Committee (Section 4.10 of the ACD), the results of this analysis further supports the results of the STC analysis previously submitted by Pfizer.

Axitinib and end of life criteria in the post-cytokine population

Section 4.22 of the ACD states that for the prior cytokine population, the end of life criteria could only be considered met if best supportive care were the only comparator. This conclusion was reached based on the Committee's view that there was substantial uncertainty that remained around the naive comparisons between axitinib vs. sunitinib and pazopanib.

Pfizer believe that the indirect comparison comparing PFS between axitinib and pazopanib (HR = 0.465, 95% CrI 0.255-0.852)[1] provides robust evidence of at least three months PFS benefit of axitinib over pazopanib, an extent of benefit that would support axitinib meeting the end of life criteria, as per section 6.2.10 of the Guide to the methods of technology appraisal. The extent of PFS benefit associated with the hazard ratio can be estimated using the economic model to predict the median PFS for pazopanib, and comparing it to that of axitinib. More specifically, applying this hazard ratio to axitinib PFS data results in a predicted median PFS for pazopanib of 6.1 months vs. 11.5 months for axitinib (Weibull extrapolation). These additional data support a PFS benefit of 5.4 months for axitinib compared with pazopanib. When these results are considered in the context of the comparison between axitinib and sunitinib, and in addition to the results of the naïve comparison and evidence previously submitted compared with BSC, Pfizer believe that there

is evidence to demonstrate that axitinib meets the end of life criteria against all comparators in the post-cytokine population.

ICER for axitinib compared with BSC in the post-cytokine population

During the consultation on the ACD, Pfizer became aware of a discrepancy between our first ACD response and the addendum on the post-cytokine population with respect to the results of a scenario analysis in the comparison between axitinib and BSC in the post-cytokine population.

This scenario analysis provided an example of what the ICER would be if the OS of post-cytokine patients receiving BSC was less than the 24 months in the base case. The 24 months was an over-estimate derived from the network meta-analysis, which was biased due to cross-over from the TARGET trial. The lower 95% confidence interval of the 24 month was used as an illustration of a lower OS in BSC, but it should be noted that this still results in a high estimate of median OS for post-cytokine patients (17.6 months). As a result the associated ICER is also likely to be overestimated.

The ICER originally submitted using the 17.6 months BSC OS estimate for this comparison was as part of the first ACD response and was £36,493 per QALY. The addendum on the post-cytokine population quoted an ICER of £33,000 per QALY for this population, a difference due to typographical error.

Given the relatively high estimate of OS in the patients receiving BSC (17.6 months), Pfizer feel strongly that the actual ICER for this population will be considerably less than £36,493 per QALY.

Factual inaccuracies

- Section 1.1 of the ACD states that:

  "Axitinib is recommended as an option for treating adults with advanced renal cell carcinoma after failure of treatment with a first-line kinase inhibitor or a cytokine, only if the manufacturer provides axitinib with the discount agreed in the patient access scheme."

  Pfizer suggest that the word "tyrosine" is included in description of the population as "first-line *tyrosine* kinase inhibitor"

- Section 3.43 of the ACD states:

  "Grünwald et al. was a retrospective cohort study correlating tumour shrinkage with progression-free survival and overall survival in patients with metastatic renal cell carcinoma treated with systemic therapy (tyrosine kinase inhibitors, mTOR inhibitors and/or interferon). "

  PFS was not included in the analysis presented by Grünwald et al. at ECCO/ESMO 2013.

References

1. Larkin J, Paine A, Tumur I, Cappelleri JC, Healey PJ Sr, Foley G, Mitchell S, Kroes M, Chen C. Second-line treatments for the management of advanced renal cell carcinoma: systematic review and meta-analysis. Expert Opin Pharmacother. 2013 Jan;14(1):27-39.