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

Pfizer comments to accompany Grünwald *et al* 2013

In relation to the Single Technology Appraisal submitted on 13th August 2012

Submitted by Pfizer Ltd.

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Summary
The abstract and slides by Grünwald *et al* were presented at a plenary oral session by Dr Grünwald at the European Cancer Conference organised by ECCO and ESMO in September 2013. The analysis demonstrated that tumour response is a significant independent predictor of overall survival (OS) in mRCC patients and the results suggest that patients with increase in their tumour size during treatment had a median OS of less than approximately 10 months.

In the context of the evidence base of the appraisal, Grünwald *et al* analysis and results offer an alternative surrogate method of estimating the median OS in metastatic renal cell carcinoma (mRCC) patients receiving best supportive care (BSC). By using the distribution of tumour responses of placebo (BSC) treated patients from RECORD-1 we estimated a weighted median estimate of BSC OS of 8.2 months (95%CI: [redacted]) which is consistent with previous estimates with the simulated treatment comparison. This evidence increases the robustness and reliability of the STC results which underpin the £33K per QALY in our base case analysis in the prior sunitinib population.

When considering the uncertainty of this OS estimate for BSC in the prior sunitinib population in the context of the base-case economic analysis, for all OS values within the 95% confidence intervals for BSC, the ICER will be below £50K per QALY, demonstrating that axitinib should be considered a cost-effective treatment option for a small group of patients with a very high unmet need.

Grünwald abstract results in the context of the existing evidence base of the axitinib NICE appraisal

As outlined in the response to the ACD January 2011, it is recognised that the arbitrary cut-off of a reduction of 30% in terms of measuring objective response according to RECIST is increasingly being challenged in the era of targeted therapy and the aim of analysis by Grünwald *et al* was to investigate the prognostic significance of the magnitude of tumour shrinkage (1).

The Grünwald *et al* analysis was performed on a pooled patient population from eight Pfizer-sponsored clinical trials conducted between 2003 and 2011. The trials incorporated data from a range of first and second line treatments, including tyrosine kinase inhibitors (TKIs) (sunitinib, n=1059; axitinib, n=359; sorafenib, n=355), mTOR inhibitors (temsirolimus, n=208) and interferon-alpha (IFN-alpha, n=560). Patients were classified into one of six categories according to the magnitude of maximum tumour response compared to baseline at any time on study. These categories were: decrease of -100% to <-60%, decrease of -60% to <-30%, decrease of -30% to <0%, increase of 0% to <+20%, increase of ≥+20%, and no post-baseline scan available.

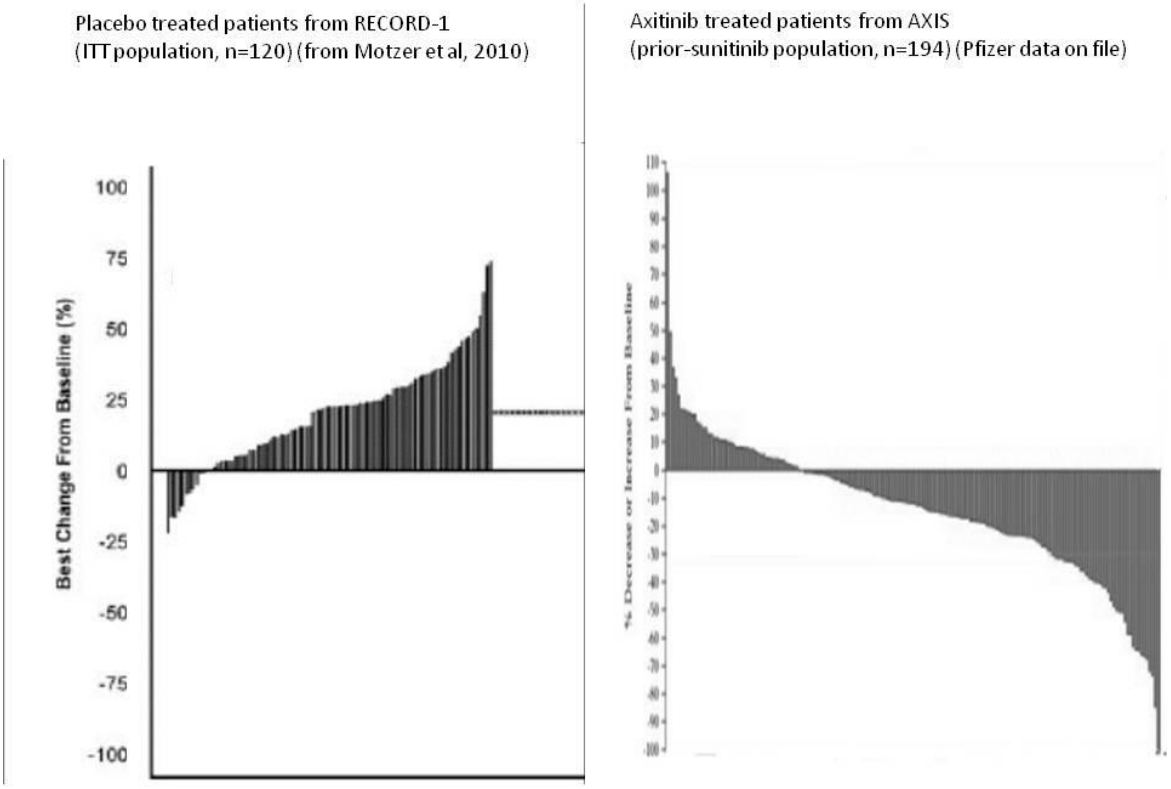
To minimise the effect of bias on quantifying the association between tumour response category and OS, a multivariate Cox-proportional hazard analysis was performed to determine the statistical significance of the association between maximum response at any time on treatment and OS. This calculated the hazard ratio (HR) of death and significance of the tumour response groups when compared to the -30% to 0% decrease group. The results of this analysis were then verified with a separate landmark analysis at 6 months. Lastly, the Kaplan-Meier method was used in each of the tumour response categories for the overall population to estimate the median OS.

- Magnitude of tumour response is a significant independent predictor of overall survival (as determined by multivariate analysis using Cox regression, and verified via a 6 month landmark analysis), suggesting tumour response can be used as a surrogate endpoint for survival analysis.
- Patients with an increase in tumour size are associated with significant shorter median OS relative to those patients with a decrease in tumour size. The results of the median OS and 95% confidence intervals of the Kaplan-Meier analysis for the overall population are summarised in Table 1. Patients with an increase in tumour size have a median overall survival of less than approximately 10 months, independent of systemic therapy (as shown through comparison of Kaplan-Meier curves (see slide 11).

Figure 1 demonstrates the marked difference in tumour response presented as waterfall plots for the placebo (BSC) treated patients from RECORD-1 (ITT population) (2) and the axitinib treated patients from AXIS (prior sunitinib population). It is notable that the majority of patients from RECORD-1 receiving BSC experienced a tumour increase (i.e. above the line of 0% change), while the majority of patients treated with axinitib from AXIS had decreased tumour size (below the line).

On the basis of the observations from the median OS from Grünwald *et al*, in which patients who respond with a ≥+20% growth in tumour size have a median OS of only 7.33 months, and those who respond with a tumour growth of 0% to <+20% have a median OS of 10.36, we would therefore expect the median OS of the BSC patients to be well below 10.36 months.

Figure 1 A comparison of waterfall plots of best response from the placebo treated patients from RECORD-1 and the axitinib treated patients from AXIS.



An alternative estimate of the OS of the BSC patients can be calculated using the distribution of tumour responses of placebo treated patients from RECORD-1 to weight the estimates of median OS from the analyses by Grünwald *et al* (see Table 1). Note the discrepancy between the number of patients in the waterfall plot (n=120) and the number of patients in Table 1 (N=139) is due to the patients who were unevaluable/had no post-baseline scan. The estimate of weighted median OS for the placebo treated patients using this method was 8.194 months (95% CI: [redacted]).

Table 1 Summary of median OS for the overall population from Grünwald et al and analysis of weighted median OS

		Results relating to analysis by Grünwald *et al*		Calculation of weighted median OS	
Tumour Shrinkage Category		**Median OS (months) for all patients (N=714)**	**95% CI for median OS for all patients**	**Number of patients from placebo arm of RECORD-1) (N=139) N, (proportion)**	**Weighted median OS in months (median OS x proportion of patients)**
Increase in tumour size	≥+20%	7.33	[redacted]	75 (0.540)	3.96
	0% to <+20%	10.36	[redacted]	31 (0.223)	2.31
Decrease in tumour size	-30% to <0%	16.56	[redacted]	14 (0.1)	1.66
	-60% to <-30%	26.38	[redacted]	0 (0)	0
	-100% to <-60%	54.53	[redacted]	0 (0)	0
-	No post-baseline scan	1.97	[redacted]	19 (0.137)	0.27
Weighted median OS (95% CI)					**8.194** [redacted]

NA: not available a: calculations of median OS and 95% CIs made using Stata IC® V13.1 using the *metan* package SJ9_2: sbe24_3.

The weighted median OS for BSC based on the above calculation (8.2 months, 95% CI: [redacted]) is consistent with the prediction based on the visual comparison of the waterfall plots of AXIS and RECORD-1, and is lower than the maximum median OS for patients who have a tumour growth of 0% to <+20% (10.36 months). It should be noted that in fact, in the distribution of BSC treated patients of RECORD-1, over half (54%) were classified as the worst response category with a best response of ≥+20% change in tumour size.

This analysis provides an alternative method of estimating the OS of BSC treated patients. Therefore the results of Grünwald *et al* provide important context and validation to the estimates of OS in BSC patients previously submitted by Pfizer. The weighted median estimate OS of 8.2 months is also in line with both the results of the baseline analysis using the STC methodology previously submitted (8.3 months) although is still higher than estimates of OS for BSC patients from UK real world data 4.1 months (2) and 4.3 months (3).

This surrogate approach to estimate the median OS for BSC in the prior sunitinib population relies on the relationship between tumour response and OS established in 8 mRCC trials. Applying this relationship to the tumour responses of the RECORD-1 trial, which was not included in the dataset of Grünwald et al assumes that this relationship is constant between the trials settings of RECORD-1 and the Grünwald et al dataset. On this point, it is important to note that around three quarters of the patients in the RECORD-1 trial experienced an increase in tumour size. The analyses performed by Grünwald indicate that the relationship between tumour response and survival in this group of patients is relatively consistent, with a maximum median OS of around 10 months (see slide 11 and 12). We would therefore expect that this relationship between tumour response and survival would also exist in the patients experiencing an increase in tumour size in RECORD-1 BSC arm.

In addition, in light of the discussion above on the consistency of the relationship between tumour response and OS in patients who experience tumour growth, we suggest that when comparing the median OS estimate of this analysis to the axitinib OS from AXIS in the prior-sunitinib population, differences in baseline characteristics of the trials will have little impact. Regardless of the trial setting, patients who experience an increase in tumour size are not expected to survive longer than approximately 10 months.

It is important to note that when considering the results of the OS for BSC in the prior sunitinib population compared with axitinib data in the context of the base-case economic analysis, for all OS BSC estimates within the range of the 95% confidence intervals, the ICER of axitinib versus BSC will be below £50K per QALY. Therefore the statistical uncertainty inherent in estimating of the OS should not be considered a barrier to cost effectiveness.

Reference List

(1) Seidel C, Busch J, Weikert S, Steffens S, Bokemeyer C, Grunwald V. Tumour shrinkage measured with first treatment evaluation under VEGF-targeted therapy as prognostic marker in metastatic renal cell carcinoma (mRCC). British Journal of Cancer 2013;109:2998-3004.

(2) Poffiri E, Miscoria M, Lim L, Shamash J, Chowdhury S, Powles T. The outcome of patients who fail sunitinib and do not have access to sunitinib therapy. Annals of Oncology. 2010. Ref Type: Abstract

(3) Miscoria M, Pirrie S, Baijal S, Tew A, James ND, Porfiri E. Analysis of survival after disease progression in patients with renal cell carcinoma (RCC) who failed treatment with sunitinib. J Clin Oncol 2011;29((suppl; abstr e15154)).