Supplementary Requests

The ERG believes the presented clinical results do not allow for exploration of issues related to time-to-events. Therefore, the ERG would like to request the following additional results in the format of Product-Limit Survival tables (that is, using SAS LIFETEST procedure, an example is included at the end of this document) showing for each event time:

- Time-to-event from baseline (days)
- Product-limit estimate of survival proportion
- Standard error of survival proportion
- Number of patients failed
- Number of patients remaining at risk

Please provide full Product-Limit Survival tables as follows:

A1. For patients receiving at least 1 dose of randomised treatment, who subsequently had a non-fatal disease progression event recorded (i.e. survived at least 1 day after the date of disease progression), please provide the following:

- A progression free survival from the March 2011 cut of the BRIM3 trial data by trial arms (vemurafenib and dacarbazine).
- Post-progression survival from the date of non-fatal disease progression by trial arms (vemurafenib and dacarbazine), with dacarbazine patients data censored at the date of cross-over to vemurafenib, using the March 2011 cut of the BRIM3 trial data.

Introduction

As highlighted above we have substantial concerns on the potential application of the data requested by the ERG to attempt to validate Roche's model or to conduct de novo economic modelling.

The 2 main reasons for this are outlined in further detail below.

In summary, a substantially higher proportion of dacarbazine patients (209 of 338; 62%) than vemurafenib patients (149 of 337; 44%) had progressed at the time of the March 2011 data-cut. Inevitably, those patients who progress earliest are those who have the poorest underlying prognosis, and so by comparing a smaller group of vemurafenib patients with a larger group of

dacarbazine recipients one is, in effect, comparing the worst prognosis vemurafenib patients with the generality of dacarbazine patients.

As detailed below, this analysis would violate randomisation, dismiss a wealth of evidence (i.e. the outcomes of all patients who were censored for PFS at the point of data cut-off) and is subject to clear confounding due to imbalances in known prognostic patient characteristics and second line treatments received.

In concordance with the STA process we would be happy to explore alternative approaches to incorporating time to event data into the model if the Appraisal Committee deems it appropriate.

1) Imbalances in baseline characteristics of patients who received at least 1 dose of randomised treatment, who subsequently had a non-fatal disease progression event recorded

Table 1 below provides the baseline characteristics of the patients whose outcomes would be considered in the requested analysis. In total the provision of this analysis would result in the dismissal of evidence on the outcomes of 47% of the population randomised to BRIM3.

Table 1 Baseline characteristics of patients in requested analysis

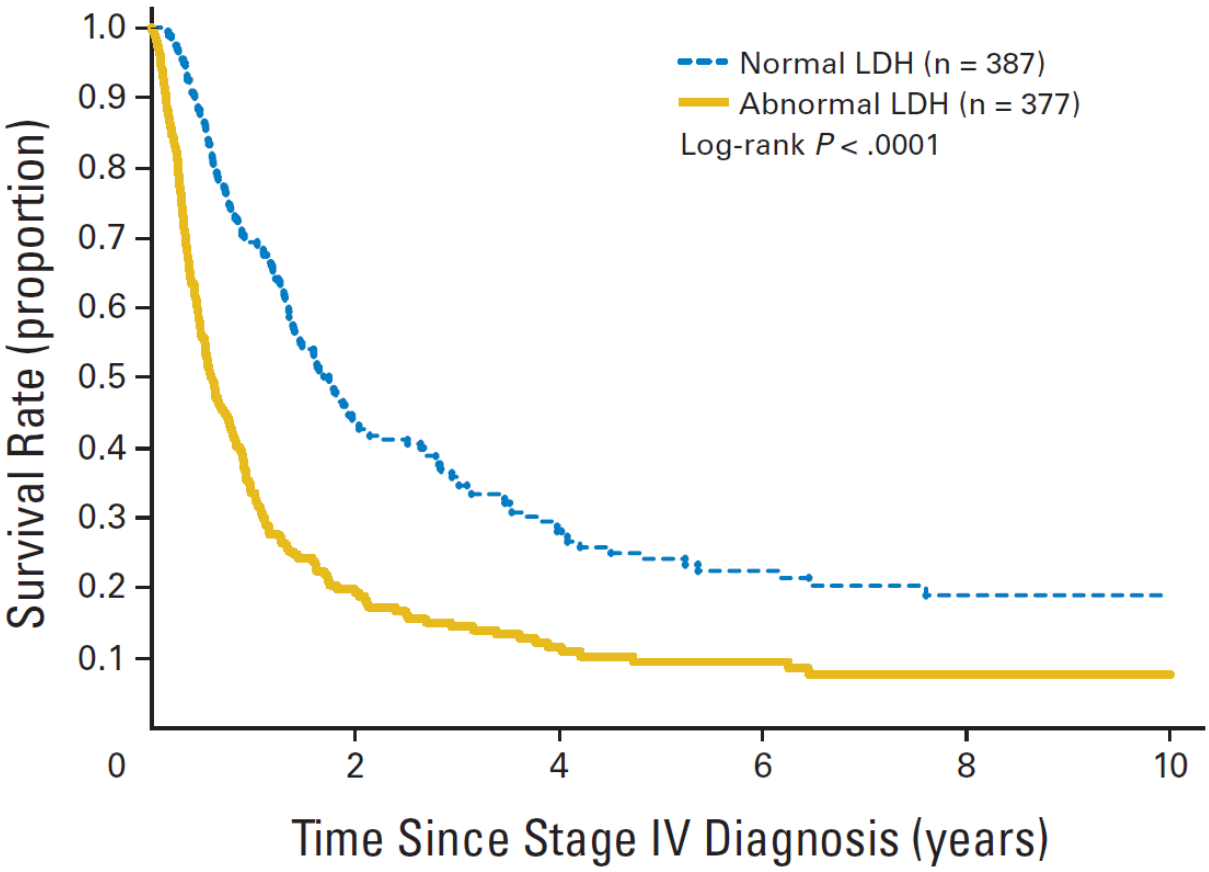
	Dacarbazine (N=209; 62% of BRIM-3 population) **n (%)**	**Vemurafenib (N=149; 44% of BRIM-3 population)** **n (%)**
Lactate dehydrogenase (LDH)		
Elevated	92 (44)	79 (53)
Normal	117 (56)	70 (47)
Age		
<65 years	167 (80)	114 (77)
>= 65 years	42 (20	35 (23)
Disease stage		
M1A	21 (10)	10 (7)
M1C	137 (68)	103 (70)
M1B	43 (21)	28 (19)

Unresectable IIIC	8 (4)	8(5)
Disease at diagnosis		
Local/regional	163 (78)	110 (74)
Metastatic	36 (17)	31 (21)
Unknown	10 (5)	8 (5)
Gender		
Female	91 (44)	54 (36)
Male	118 (56)	95 (64)
ECOG Performance Status		
0	138 (66)	93 (62)
1	71 (34)	56 (38)

The vemurafenib group includes more patients with elevated LDH, more patients over the age of 65, a higher proportion of female patients, more patients diagnosed with metastatic disease and less patients in the best Performance Status category. Each of these imbalances favours the dacarbazine arm, with the result that any comparison of the outcomes of patients in these two post-hoc defined groups will be heavily confounded by these imbalances, and any subsequent extrapolation of the post-progression outcomes on the whole population based on this subgroup would be biased.

For example, the significant impact of elevated (abnormal) LDH in determining the prognosis of patients diagnosed with melanoma is well illustrated in Figure 1 below (Balch et al. 2009). Clearly if the dacarbazine arm of the post-hoc defined group features a higher proportion of patients with normal LDH than the vemurafenib arm this will result in any assessment being biased against the vemurafenib arm. We therefore believe the using requested analysis to explore time to event issues is inappropriate.

Figure 1 LDH levels have a significant impact upon patient prognosis



2) Imbalances in post-progression treatments received by patients in BRIM3

In BRIM3 substantially more patients in the dacarbazine arm received systemic post-progression treatment than those in the vemurafenib arm (37.3% vs 19.0%). Notably, many more (16.9% vs 5.9%) dacarbazine patients than vemurafenib recipients received ipilimumab – the only therapy shown to improve survival in a randomised controlled trial in the second-line setting.

In addition 6.7% of dacarbazine patients received an experimental BRAF inhibitor other than vemurafenib or MEK inhibitor (both classes of drug with known activity in BRAF mutant melanoma) compared with 0.9% of vemurafenib recipients.

The most likely explanation for this imbalance is that patients who had only received dacarbazine first-line would have been eligible for recruitment into trials with unlicensed products (including at that point ipilimumab) whereas vemurafenib recipients would be precluded from most studies having had recent exposure to an experimental therapy, leaving them with no effective treatment

options at relapse. As such this imbalance in second-line therapies would not be seen in clinical practice.

These post-progression imbalances in non-vemurafenib based therapy are not accounted for in the analysis requested and will confound the results of the post-progression survival outcomes estimated. We therefore believe the requested data is not suitable for informing post-progression mortality rates in a decision model.

A2. For patients receiving at least 1 dose of vemurafenib treatment, please provide the following:

- Define two mutually exclusive subgroups of patients: those who continued on vemurafenib treatment until disease progression, death or censoring for data cut-off; those who discontinued vemurafenib treatment prior to disease progression, death or censoring for data cut-off.
- Based on the above definitions, please carry out a Kaplan-Meier analysis comparing these two subgroups in terms of progression free survival and overall survival using the March 2011 cut of the BRIM3 trial data.

Please see the attached file providing the data requested.

References

Balch, C. M., Gershenwald, J. E., Soong, S., Thompson, J. F., Atkins, M. B., Byrd, D. R., Buzaid, A. C., Cochran, A. J., Coit, D. G., & Ding, S. 2009, "Final version of 2009 AJCC melanoma staging and classification", *Journal of Clinical Oncology*, vol. 27, no. 36, pp. 6199-6206.