Confirmed clinical benefit of BRAF and MEK co-inhibition in BRAF^{V600}-mutant metastatic melanoma: updated data from coBRIM and BRIM7

T. Feys, MSc, MBA

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Approximately 50% of metastatic cutaneous melanomas harbor a BRAF^{V600} mutation, resulting in constitutive activation of the mitogen-activated protein kinase (MAPK) pathway.[1,2] These discoveries led to the development of agents that specifically target this driver mutation. The BRAF inhibitor vemurafenib was approved worldwide on the basis of results from a phase III trial showing improved progression-free (PFS) and overall survival (OS), as compared with chemotherapy alone.[3] The relative reduction in the risk of death was 63% and in the risk of disease progression was 74%.[3] Similar results were reported for another BRAF inhibitor, dabrafenib, which has also been approved widely.[4] Unfortunately, progression after a period of tumor response (acquired resistance) is common with single-agent BRAF-inhibition resulting in a median progression-free survival (PFS) of 6-7 months.[3,4] The most common mechanism underlying this acquired resistance is the result of reactivated oncogenic signalling by means of the MAPK pathway.[5]

This formed the rationale for the combined use of a BRAF inhibitor and a MEK inhibitor in the treatment of advanced BRAF^{V600}-positive melanoma. A phase II study reported by Flaherty et al. demonstrated a reduction in the incidence of proliferative skin lesions and an increase in the PFS when both a MEK inhibitor and a BRAF inhibitor were used.[6] During the 2014 ESMO meeting in Madrid, McArthur et al. reported the first data of the phase III coBRIM study in which 495 treatment-naïve patients with BRAF^{V600}-mutation-positive, unresectable, locally advanced or metastatic melanoma were randomised to receive a 28-day treatment cycle of vemurafenib, combined with either cobimetinib or placebo. The combination arm of the study showed a significantly longer median PFS of 9.9 months, compared to 6.2 months in the placebo arm. This translated into and an impressive 49% reduction in the risk of progression (HR [95%CI]: 0.51[0.39-0.68]; p< 0.0001).[7] During ASCO 2015, updated coBRIM data were presented together with data on the impact of coexisting oncogenic mutations in pretreatment samples.[8] In addition to this, extended follow-up data of the phase 1B BRIM7 study, evaluating the same treatment combination, were presented.

Confirmed clinical benefit of combining vemurafenib with cobimetinib

The updated PFS results of the coBRIM study, confirmed the findings reported by McArthur et al. The median PFS for the combination arm was 12.25 months as compared to 7.20 months with vemurafenib alone, translating into a hazard ratio for progression or death of 0.58 (95%CI: 0.46-0.719), which is in line with the HR of 0.51 reported earlier.[7,8] This PFS benefit of the combination strategy was seen irrespective of disease stage, age, sex, geographic region, ECOG performance status, LDH level, the use of prior adjuvant therapy and the BRAF^{V600} mutation status (V600E, or V600K). The updated data showed an objective response rate of 69.6% with the cobimetinib-vemurafenib combination (15.8% complete response, 53.8% partial response) *vs.* 50% with vemurafenib-placebo (10.5% complete response, 39.5%

Ariez International, Ghent, Belgium.

Please send all correspondence to: T. Feys, MSc, MBA, Ariez International, Oude Houtlei 118, 9000 Ghent, Belgium, email: t.feys@ariez.com.

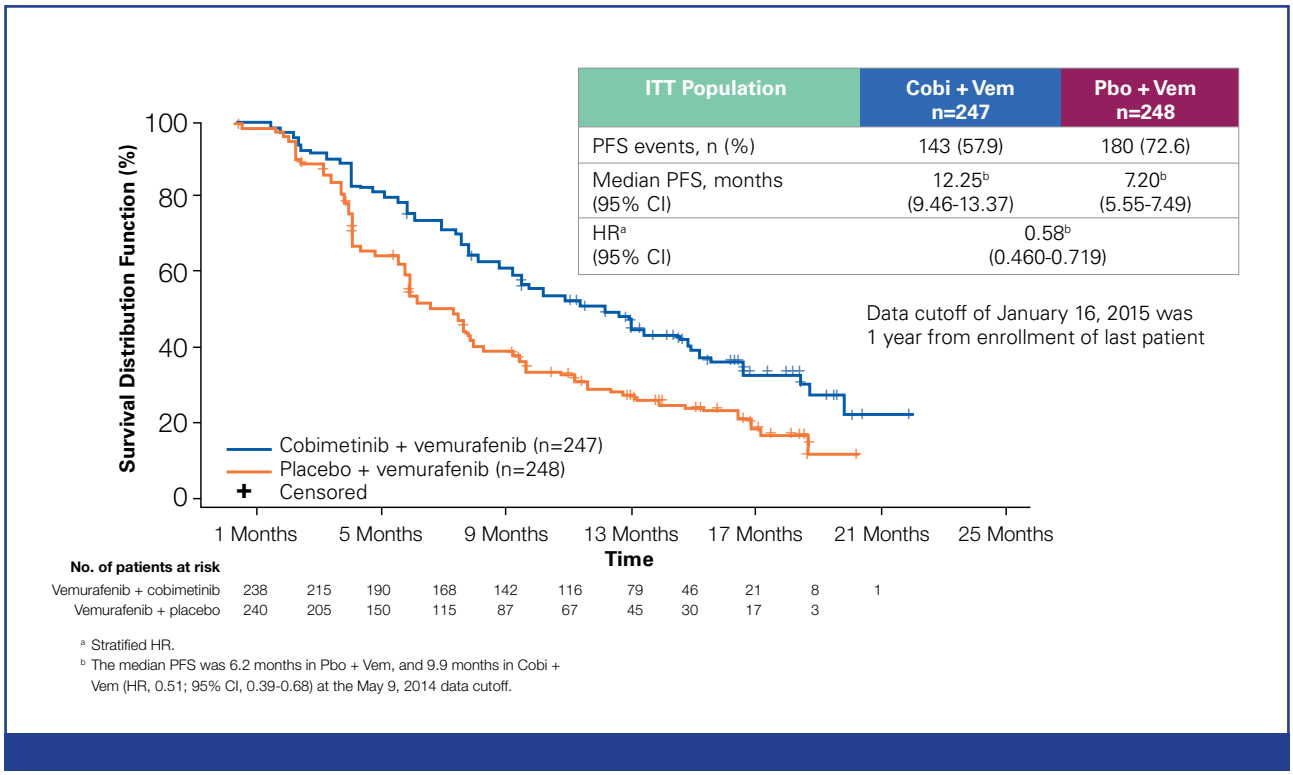

Figure 1. Updated PFS results of the coBRIM confirm the PFS benefit with combined cobimetinib and vemurafenib.

partial response). The median duration of response was 12.98 months with the combination as compared to 9.23 months with vemurafenib alone.[8]

To assess the impact of coexisting oncogenic mutations on the response, 423 pretreatment DNA samples were screened for mutations in 528 hotspots in 17 oncogenes. In total 55 of 423 (13%) had coexisting oncogene mutations (46 in RAS, RAF or a receptor tyrosine kinase [RTK], 11%). These coexisting baseline RAS/RAF/RTK mutations were however not associated with a worse PFS or ORR (60% in RAS/RAF/RTK wildtype *vs.* 61% in RAS/RAF/RTK mutant patients) in coBRIM patients.[8]

In the phase 1B BRIM7 study, the combined use of cobimetinib and vemurafenib was assessed in both BRAF-inhibitor naïve (N=63) and vemurafenib progressive (N=66) advanced melanoma patients.[9] Among the vemurafenib exposed patients, the confirmed response rate was 15% with a disease control rate (DCR) of 42% and a duration of response of 6.8 months. In the vemurafenib-naïve population, the confirmed response was 87%, including a complete response rate of 16%. Of note, for most patients who experienced a CR, the CR occurred after continued treatment with cobimetinib and vemurafenib. In some patients it took more than 30 weeks after treatment initiation before a CR was seen. In vemurafenib-naïve patients, the median duration of response was 14.3 months. For vemurafenib progressors, the median PFS was 2.8 months, while this was 13.8 months in vemurafenib-naïve patients. The median OS was 8.4 and 28.5 months for vemurafenib-pretreated and vemurafenib-naïve patients respectively.

Conclusion

Both the updated coBRIM data as well as the long-term follow-up data of BRIM7 demonstrate the safety and clinical efficacy of the combined use of cobimetinib and vemurafenib in patients with $BRAF^{V600}$ mutated advanced melanoma. In fact, coBRIM shows a median PFS in excess of 12 months for the combined treatment with a high ORR. The final OS analysis of the coBRIM is expected end of 2015.

References

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