Special Edition

Co-inhibition of BRAF and MEK signalling delays progression in BRAF^{V600}-mutant metastatic melanoma

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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 3 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 also 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 to 7 months.[3,4] The most common mechanism underlying this acquired resistance is the result of reactivated oncogenic signaling by means of the MAPK pathway. The finding of multiple genetic mechanisms of escape in individual patients implies that upfront inhibition of both MEK and the mutant BRAF kinases might be a strategy to obtain more durable responses than the inhibition of BRAF alone.[5]

Common side effects of BRAF inhibition in melanoma consists of the development of secondary cutaneous squamous-cell carcinomas and keratoacanthomas, which occur in approximately 14 to 26% of patients treated with a BRAF inhibitor, usually within the first 2 to 3 months of therapy.[6,7] These skin tumors develop due to a paradoxical activation of the MAPK pathway in keratinocytes with upstream activation of signaling by pre-existing *RAS* mutations. This mechanism can theoretically also be blocked with the addition of a MEK inhibitor.[8] These findings formed the rationale for the combined use of a BRAF inhibitor and a MEK inhibitor in the treatment of advanced *BRAF*^{V600}-positive melanoma. The feasibility and the clinical efficacy of this approach was demonstrated in 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.[9] During the 2014 annual meeting of the European Society for Medical Oncology (ESMO), the results of 2 large phase III studies evaluating combined MEK and BRAF inhibition in advanced *BRAF*^{V600}-positive melanoma were presented (coBRIM and COMBI-v).[10,11]

In the ongoing coBRIM study, 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 (960mg, twice daily), combined with either cobimetinib or placebo (60mg daily from days 1-21). The primary endpoint of the study consisted of investigator-assessed progression-free survival. The baseline patient characteristics were generally well balanced between both study arms, although the patients in the vemurafenib-placebo arm had a slightly worse ECOG performance status. Approximately 60% of the patients in the study had stage IV M1c disease and approximately 45% presented with elevated LDH levels.

Patients in the combination arm of the study showed a significantly improved median PFS of 9.9 months, compared to 6.2 months in the placebo arm. This

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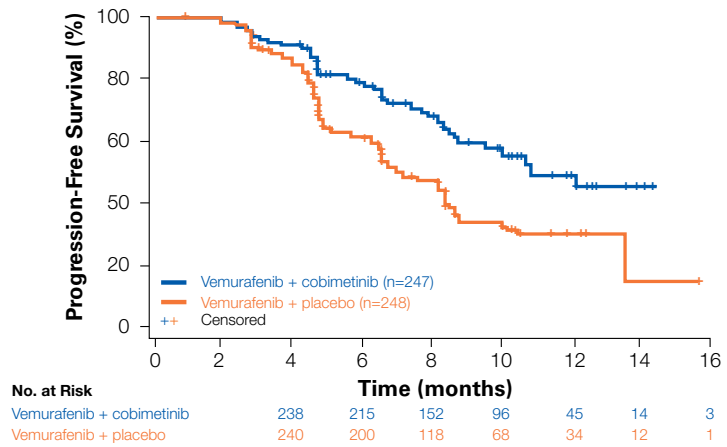

	Vemurafenib + Placebo	Vemurafenib + Cobimetinib
PFS events, n	128	79
Median PFS (95% CI), mo	6.2 (5.6-7.4)	9.9 (9.0-NE)
HR (95% CI)	**0.51 (0.39-0.68)**	
***P* value**	**P < 0.0001**	

Figure 1. Investigator-assessed PFS in the coBRIM study.[10]

translated into and an impressive 49% reduction in the risk of progression (HR[95%CI]: 0.51[0.39-0.68]; p< 0.0001) (*Figure 1*). This PFS in favour of the combination therapy was observed in all investigated subgroups, irrespective of age, disease stage, sex, ECOG performance status and baseline LDH level. Researchers observed a response rate of 68% in the combination arm versus 45% in the control arm, including a complete response in 10% of patients treated with combination therapy compared to 4% of patients treated with vemurafenib alone. At the time of analysis, the OS were immature but indicated a numerical advantage in favour of vemurafenib plus cobimetinib (51 *vs.* 34 events; HR[95%CI]: 0.65[0.42-1.00])

The combination therapy did lead to a greater number of grade 3 and above adverse events compared to vemurafenib alone (mainly pyrexia, diarrhea, nausea and photosensitivity). However, it is to be noted that these adverse events were mainly asymptomatic lab abnormalities, without clinical implications. As such, this did not lead to a difference in the percentage of patients discontinuing therapy between both arms (12% with vemurafenib *vs.* 13% with the combination). Interestingly, treatment with cobimetinib and vemurafenib also reduced the incidence of skin-related side-effects known to occur with vemurafenib therapy (hyperkeratosis and alopecia). Cutaneous squamous cell carcinoma was seen in 11% in the vemurafenib arm compared to 3% in the patients treated with the combination, and also keratoacanthoma was observed more frequently with vemurafenib alone than with cobimetinib-vemurafenib (8% *vs.* 1%). Serous retinopathy, a transient and reversible eye disorder, and decreased ejection fraction are known side effects of MEK inhibition and were more common in the combination arm. These events were however manageable and reversible.

In summary, the coBRIM study provides clear and definitive evidence that cobimetinib combined with vemurafenib results in improved PFS and an increased ORR as compared to vemurafenib alone in advanced melanoma patients. Moreover, the combination was tolerable and the adverse events profile was consistent with previous studies with the combination. As was expected, adding a MEK inhibitor to a BRAF inhibitor resulted in a reduction of the typical skin toxicity seen with a BRAF inhibitor. The presented results of the COMBI-v study evaluating the combination of the BRAF inhibitor dabrafenib with the MEK inhibitor trametinib were completely in line with what was presented in coBRIM. If the mature data of both studies confirm these very promising findings, combined BRAF and MEK inhibition will become the new standard of care for $BRAF^{V600}$-positive advanced melanoma.

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