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SKIN CANCER

BRAF and MEK inhibitors—good news comes in twos!

Single-agent BRAF-inhibitor therapy has a proven survival benefit for patients with advanced-stage melanoma and is approved for this indication; however, downsides of this approach are early acquired resistance and toxicity. Evidence indicates that concomitant targeting of BRAF and MEK might improve outcomes. Now, interim data from two phase III trials (coBRIM and COMBI-D) add considerable support for combined BRAF and MEK inhibition.

Both trials comprised patients with untreated, unresectable, locally advanced or metastatic *BRAF*-mutated melanoma. These patients "frequently develop acquired resistance due to reactivation of MEK, and a subset of patients develop secondary skin cancers through paradoxical activation of MEK," explains Antoni Ribas. He continues, "adding the MEK inhibitor cobimetinib to the BRAF inhibitor vemurafenib was hypothesized to increase tumour responses, make them more durable, and also decrease the skin adverse effects compared with single-agent BRAF-inhibitor therapy." Ribas and colleagues evaluated this combination in the coBRIM trial. A different BRAF and MEK inhibitor combination, dabrafenib and trametinib, was used by Georgina Long and co-workers in the COMBI-D trial.

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Significant improvements in progression-free survival were demonstrated with combination therapy versus BRAF inhibitor plus placebo in both the coBRIM study (median 9.9 months versus 6.2 months; $P<0.001$) and the COMBI-D trial (median 9.3 months versus 8.8 months; $P=0.03$); overall response rates were also markedly improved. "The data are too immature for an 'overall survival' analysis, but at this early stage we saw an amazing separation of the survival curves with the combination being much better," says Long. The hazard ratio for death was 0.63 ($P=0.02$) in favour of the combination in the COMBI-D trial, and 0.65 ($P=0.046$) in the coBRIM study.

Adverse-effect rates were similar between the combination and control groups in each study, but the rate of grade 3–4 events was ~65% in the coBRIM study versus ~35% in the COMBI-D trial. In both studies, the rate of secondary cutaneous cancer was reduced by combined BRAF–MEK inhibition.

"This trial should lead to the approval of the vemurafenib–cobimetinib combination by regulatory agencies worldwide," Ribas concludes. Long reinforces this point, stating "the US FDA have approved the combination of dabrafenib and trametinib for use in metastatic melanoma, and I hope other countries follow."

David Killock

Original articles Larkin, J. *et al*. Combined vemurafenib and cobimetinib in *BRAF*-mutated melanoma. *N. Engl. J. Med*. doi:10.1056/NEJMoa1408868 | Long, G. V. *et al*. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. *N. Engl. J. Med*. doi:10.1056/NEJMoa1406037