Confirmed survival benefit of combined BRAF and MEK inhibition in advanced BRAF^{V600} mutant melanoma

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Approximately half of metastatic cutaneous melanomas harbor a *BRAF*^{V600} mutation, resulting in constitutive activation of the mitogen-activated protein kinase (MAPK) pathway.[1,2] The BRAF inhibitors dabrafenib and vemurafenib were 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.[3,4] 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 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] A common side effect of BRAF inhibition in melanoma consists of secondary cutaneous squamous-cell carcinomas and keratoacanthomas, who develop due to a paradoxical activation of the MAPK pathway in keratinocytes with upstream activation of signaling by preexisting *RAS* mutations.[6,7] This mechanism can theoretically also be blocked with the addition of a MEK inhibitor.[8]

Final results of the COMBI-d study

During the 2015 annual meeting of the American Society for Clinical Oncology (ASCO), *Long et al* presented the final overall survival (OS) data of the phase III COMBI-d study.[9,10] In this double-blind trial, 423 previously untreated patients from *BRAF* mutation–positive, unresectable, stage IIIC or stage IV melanoma were randomly assigned to receive oral dabrafenib at 150 mg twice daily and oral trametinib at 2 mg once daily (N=211) or dabrafenib and placebo (N=212). The primary endpoint was progression-free survival, while overall survival was a secondary endpoint.

In the final analysis of the COMBI-d trial, the median OS was shown to be 25.1 months with the combination group as compared to 18.7 months with dabrafenib monotherapy (HR[95% CI]: 0.71[0.55-0.92]; p= 0.0107). The survival rates for the combination and the dabrafenib monotherapy 74% and 68% respectively at 1 year and 51% and 42% at 2 years. Consistent benefit of the combination was observed across all subgroups. The median progression-free survival was 11.0 months in the combination group *vs.* 8.8 months in the dabrafenib group (HR[95% CI]: 0.67[0.53-0.84]; p= 0.0004).

Combining dabrafenib with trametinib leads to a median survival exceeding 2 years

COMBI-v was a phase III trial comparing the combination of dabrafenib and trametinib with vemurafenib monotherapy in the 1st-line treatment of 704 patients with *BRAF*$^{V600E/K}$ mutation-positive, metastatic melanoma. Crossover was prohibited until the Independent Data and Safety Monitoring Committee recommended stopping the study early for efficacy. After the recommendation, the study protocol was amended to allow patients in the vemurafenib group to cross over to the combination. At the time of data cut-off (March 2015), a total of 19 vemurafenib assigned patients crossed over to the combination treatment. This could potentially have a

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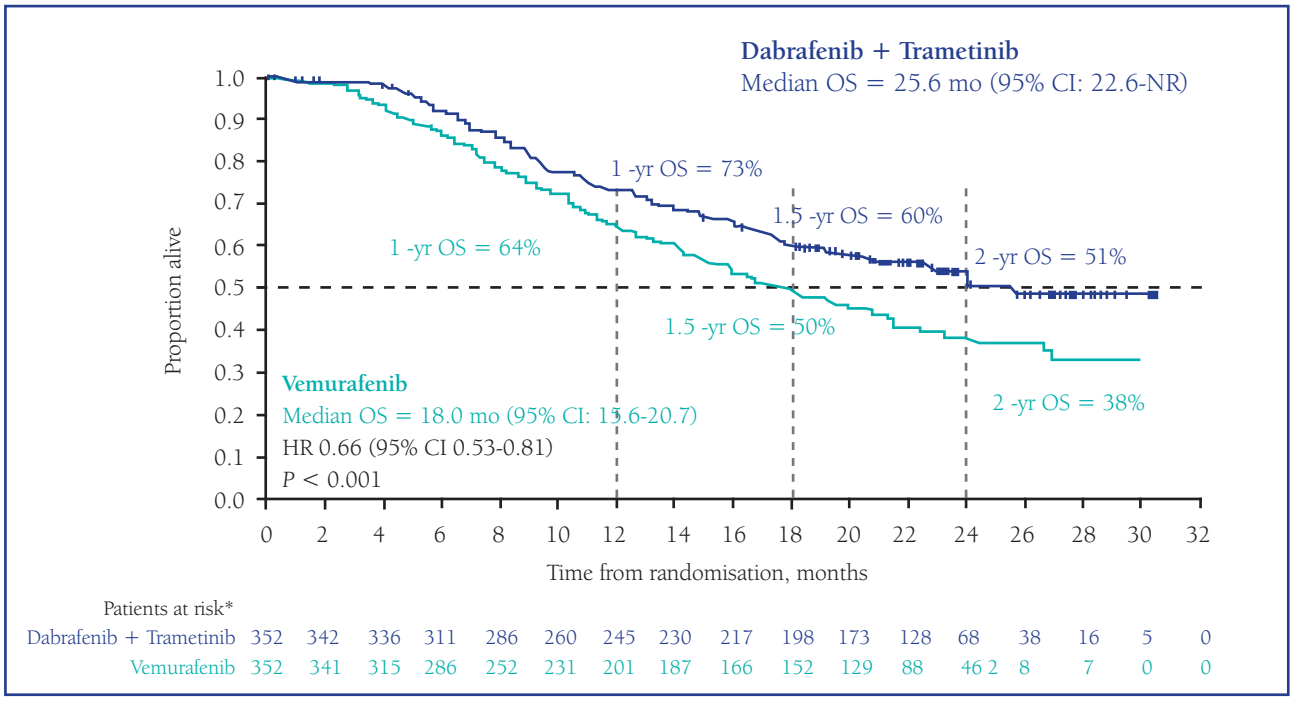

Figure 1. Updated survival analysis of the COMBI-v study confirms the significant OS benefit with the combined dabrafenib-trametinib therapy in advanced melanoma.[11]

favorable impact on the vemurafenib arm. At the time of the presented analysis, approximately 50% of patients in the study had deceased (349 of 704) and the median follow-up was 19 months.

The combination therapy was associated with a reduction of 34% in the risk of dying as compared to vemurafenib monotherapy. The median OS with the combination was 25.6 months as compared to 18 months when vemurafenib was given (HR[95% CI]: 0.66[0.53-0.81]; p< 0.001) (*Figure 1*). Looking at the evolution of the OS in this study, it becomes clear that the OS advantage of dabrafenib plus trametinib increases over time. After one year, 73% of patients treated with the combination was still alive as compared to 64% with vemurafenib. After 2 years, the survival rate with the combination therapy was 51% as compared to 38% with vemurafenib monotherapy. Patients receiving the combination also remained progression-free for a longer period of time (median PFS 12.6 months with dabrafenib-trametinib combination *vs.* 7.3 months with vemurafenib; HR[95% CI]: 0.61[0.51-0.73]; p< 0001). The updated analysis of COMBI-v also confirmed the higher response rate of the combination as compared to vemurafenib (66% *vs.* 53%; p= 0.0008) and confirmed the longer duration of response seen with the dual inhibition (13.8 *vs.* 8.5 months).[11]

patients with an LDH level below, or equal to the upper limit of normal (ULN) had the largest benefit of the combined treatment with dabrafenib and trametinib. In this subgroup of patients, the median PFS with the combination therapy was 17.5 months (versus 9.2 months with vemurafenib monotherapuy; HR[95% CI]: 0.55[0.43-0.70]), while the median OS was not reached in these patients (versus 21.5 months with vemurafenib; HR[95% CI]: 0.56[0.42-0.75]).[11]

Conclusion

The updated analysis of the COMBI-v study demonstrates that combining dabrafenib with trametinib results in a median OS of more than 2 years in patients with *BRAF*-mutation positive advanced melanoma. This is the longest median OS ever reported in a clinical trial in this setting.

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