Sustained benefit of combined dabrafenib/trametinib in patients with advanced melanoma

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In three-year follow-up data from the phase III COMBI-d study, presented at the 2016 annual meeting of the American Society for Clinical oncology (ASCO), the combination of dabrafenib and trametinib continued to demonstrate impressive overall survival (OS) and progression-free survival (PFS) findings in patients with *BRAF*-mutant metastatic melanoma. With this combination, 44% of patients were alive after three years and an impressive 22% was still free of progression. Furthermore, this updated analysis confirmed that the best outcomes based on clinical features were seen in patients with normal LDH levels and less than 3 disease sites.[1]

In the phase III COMBI-d trial, a total of 423 patients with $BRAF^{V600E/K}$–mutant, unresectable stage IIIC/IV melanoma were randomized to receive dabrafenib with trametinib (N= 211) or dabrafenib with placebo (N= 212). In order to be eligible for the study, patients needed to be treatment-naïve and have an ECOG performance status of 0 or 1. Patients with brain metastases were excluded from the trial, unless they were treated and stable for at least 12 weeks. At the time of the 3-year follow-up, 26 patients had crossed over from the single-agent group to the combination. The primary endpoint of the study was investigator-assessed PFS, while secondary objectives included OS, overall response rate (ORR), duration of response, and safety. The baseline characteristics were well balanced between the two arms. The median age of patients in the combination arm was 55 years and most were male (53%). The most common stage of cancer was M1c (67%) and 73% of patients had an ECOG performance status of 0. The majority of *BRAF* alterations were found in V600E (85%) and approximately one-third of patients in each arm had elevated LDH levels. The analysis presented at ASCO 2016 represents an additional 13 months of follow-up.

As reported earlier, the median PFS with the combination therapy was 11 months *vs.* 8.8 months with dabrafenib alone (HR[95%CI]: 0.67[0.53-0.84]; p= 0.0004). The median OS was 25.1 months with the combination as compared to 18.7 months with dabrafenib alone (HR[95%CI]: 0.71[0.55-0.92]; p= 0.0107). The 1- and 2-year survival rates that were reported earlier were 74% and 51% with dabrafenib/trametinib and 68% and 42% with dabrafenib alone. The ORR was 69% with dabrafenib/trametinib versus 53% with dabrafenib alone (p= 0.0014).[2] The medians for PFS and OS were well established and did not change in this follow-up analysis. Looking at the 3-year PFS and OS rates, the long-term benefit of combined BRAF and MEK inhibition was confirmed. With the combination therapy, the 3-year OS and PFS rates were 44% and 22% respectively as compared to 32% and 12% with dabrafenib alone, despite cross-over (*Figure 1*). Of note, 58% of the patients that were still alive in the combination arm were still on therapy after 3 years. Overall, 48% of patients in the combination arm went on to receive post-study anticancer therapy as compared to 62% with the single-agent treatment. The most common post-progression therapies in the combination and monotherapy arms, respectively, were ipilimumab (19% *vs.* 31%), radiother-

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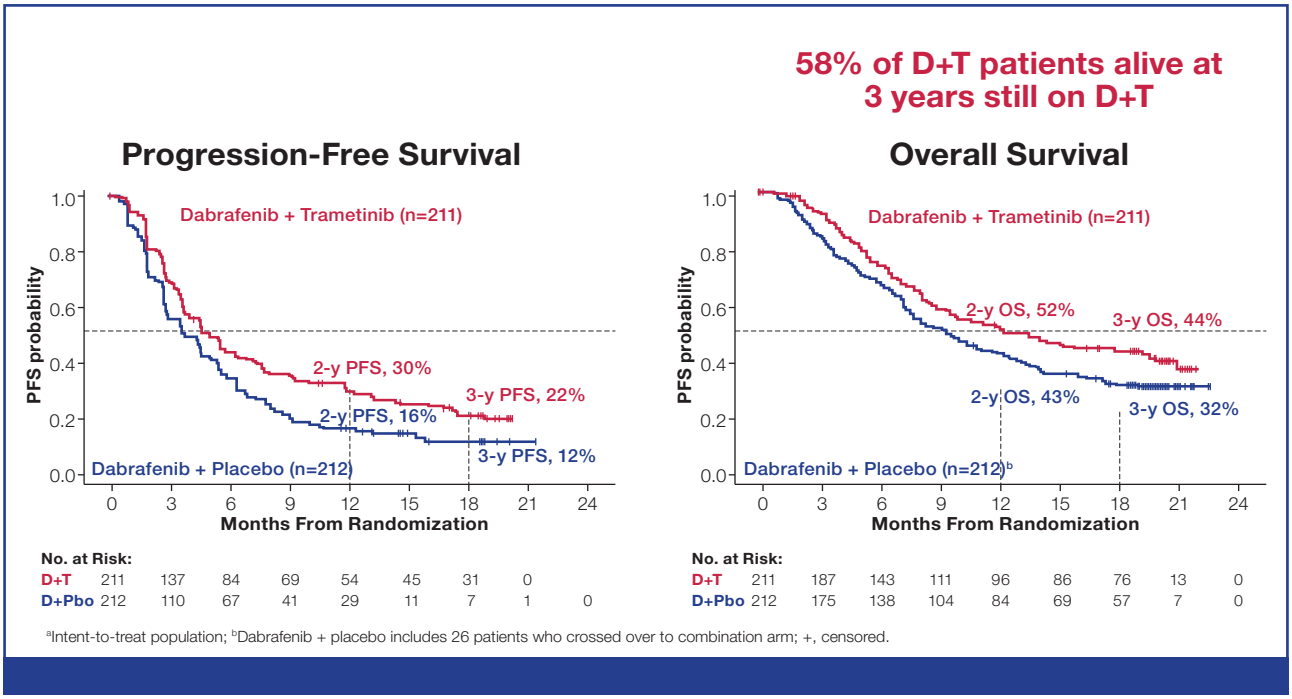

Figure 1. PFS and OS after 3-years of follow-up in the phase III COMBI-d study.[1]

apy (24% *vs.* 27%), chemotherapy (18% *vs.* 24%), and small molecule targeted therapy (10% *vs.* 16%)[1]

In the subgroup of patients with elevated LDH levels (N= 76), the combination showed a 3-year PFS rate of 13% *vs.* 4% with single-agent dabrafenib (at 2-years this was 17% *vs.* 8%). The 3-year OS rates in this group were 25% with the combination and 14% with single-agent dabrafenib (at 2-years this was 27% *vs.* 17%). These findings indicate that a subgroup of patients with elevated LDH levels do have a long-term benefit of combining dabrafenib with trametinib. In the patients with nor-

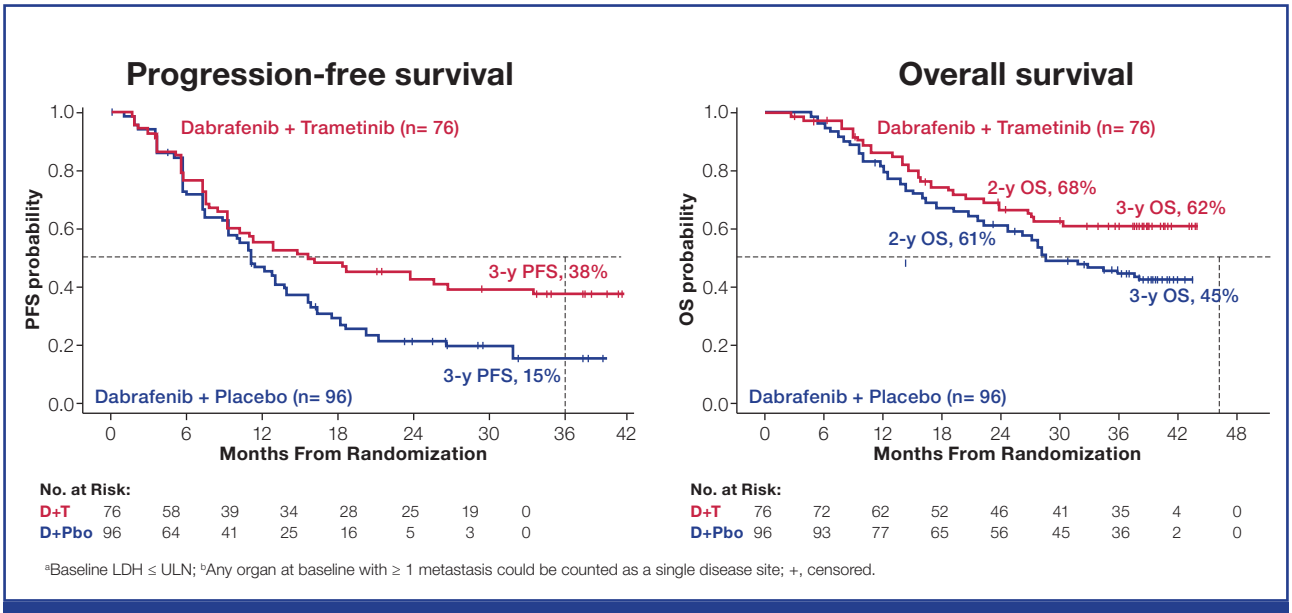

Figure 2. PFS and OS after 3-years of follow-up in the subgroup of patients with a normal LDH level and less than 3 disease sites in the COMBI-d trial.[1]

mal LDH levels (N= 133), the 3-year PFS rates were 27% with the combination and 17% with dabrafenib alone. In this subgroup, the 3-year OS rates were 54% and 41% with the combination and single-agent dabrafenib, respectively. Digging deeper into the clinical features that were previously reported to be associated with outcome, it became clear that patients with both normal LDH and less than 3 disease sites at baseline (N= 76) did best on the combination, with a 3-year PFS rate of 38% (vs. 15% with dabrafenib alone) and 62% of patients still alive at 3-years (vs. 45% with dabrafenib alone) (*Figure 2*).[1]

The safety profile did not change with longer follow-up. All-grade adverse events (AEs) occurred in 97% of patients in each arms, with fewer grade 3/4 events in the combination arm (48% *vs.* 50%). The most common all-grade AEs with the combination versus single-agent were pyrexia (59% *vs.* 25%), fatigue (29% *vs.* 37%), nausea (36% *vs.* 27%), headache (34% *vs.* 29%), chills (32% *vs.* 17%), and diarrhea (31% *vs.* 17%). The incidence of cutaneous squamous cell carcinoma was 12% with single-agent dabrafenib and 4% with the combination. As reported earlier, the incidence of all other skin-related AEs was lower with the combination.[1,2]

References

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2. Long G, Stroyakovskiy D, Gogas H et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. Lancet. 2015;386(9992):444-51.