Special Edition

Combined PD-1 and CTLA4 inhibition delays progression in advanced melanoma

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Less than a decade ago, metastatic melanoma was associated with a very poor prognosis, with a median overall survival (OS) of approximately 6 months. Increased insights into the molecular basis of melanoma dramatically transformed the treatment landscape. With respect to immunotherapy, ipilimumab monotherapy was shown to significantly prolong the survival of patients with advanced melanoma as compared to chemotherapy. In fact, 20% of patients treated with ipilimumab is still alive after 3 years, with a proportion of patients surviving more than 10 years.[2] Phase III studies evaluating monotherapy with the anti-PD1 antibody nivolumab in advanced melanoma demonstrated a 1-year OS rate of 73% and an objective response rate (ORR) of 40% in untreated patients.[3] In patients previously treated with ipilimumab, or with a BRAF-inhibitor, nivolumab monotherapy induced an ORR of 32%.[4]

Following positive phase I data, a larger phase II study demonstrated that a nivolumab-ipilimumab combination yielded a significantly higher ORR in patients with untreated advanced melanoma as compared to ipilimumab alone (59% *vs.* 11%).[5,6] These findings formed the basis for a larger phase III study (CA209-067, CheckMate-067).

Nivolumab outperforms ipilimumab in Checkmate-067

CheckMate-067 randomized 945 untreated patients equally to placebo plus either 3mg/kg of nivolumab every 2 weeks (N= 316) or 3mg/kg of ipilimumab every 3 weeks (N= 315) for 4 doses, or a combined PD-1/CTLA-4 inhibition with 1mg/kg of nivolumab plus 3mg/kg of ipilimumab every 3 weeks for 4 doses followed by 3 mg/kg of nivolumab every 2 weeks (N= 314). The co-primary outcome measures were PFS and OS, with ORR and safety as secondary endpoints.[7,8]

With at least 9 months of follow-up, the median PFS with nivolumab/ipilimumab was 11.5 months *vs.* 2.9 months with ipilimumab alone (HR[95%CI]: 0.42[0.31-0.57]; p< 0.00001). With a median PFS of 6.9 months, single-agent nivolumab also significantly delayed disease progression as compared to ipilimumab monotherapy (HR[95%CI] 0.57[0.43-0.76]; p< 0.00001).[7,8] The results also suggested that nivolumab/ipilimumab improved PFS versus nivolumab monotherapy (HR[95%CI]: 0.74[0.60-0.92]), however, the trial was not statistically powered for this comparison. The ORR was 57.6% and 43.7% for the nivolumab combination and single-agent arms, respectively, and 19% with ipilimumab monotherapy. The complete response rates were 11.5%, 8.9% and 2.2% respectively. The median reduction in tumor burden was -51,9% and -34,5% in the combination and single-agent nivolumab groups as compared to +5,9% with ipilimumab. The duration of response was not yet reached in any of the three arms. At the time of this analysis, the OS data were still immature and are not expected to be reported until 22 months of follow-up.[7,8]

PD-L1 expression: a biomarker for nivolumab benefit?

In PD-L1–positive patients (expression ≥5%), the ligand was not a biomarker for outcome, with a PFS of 14 months in both nivolumab arms, and 3.9 months with ipilimumab. However, PD-L1–negative patients seemed

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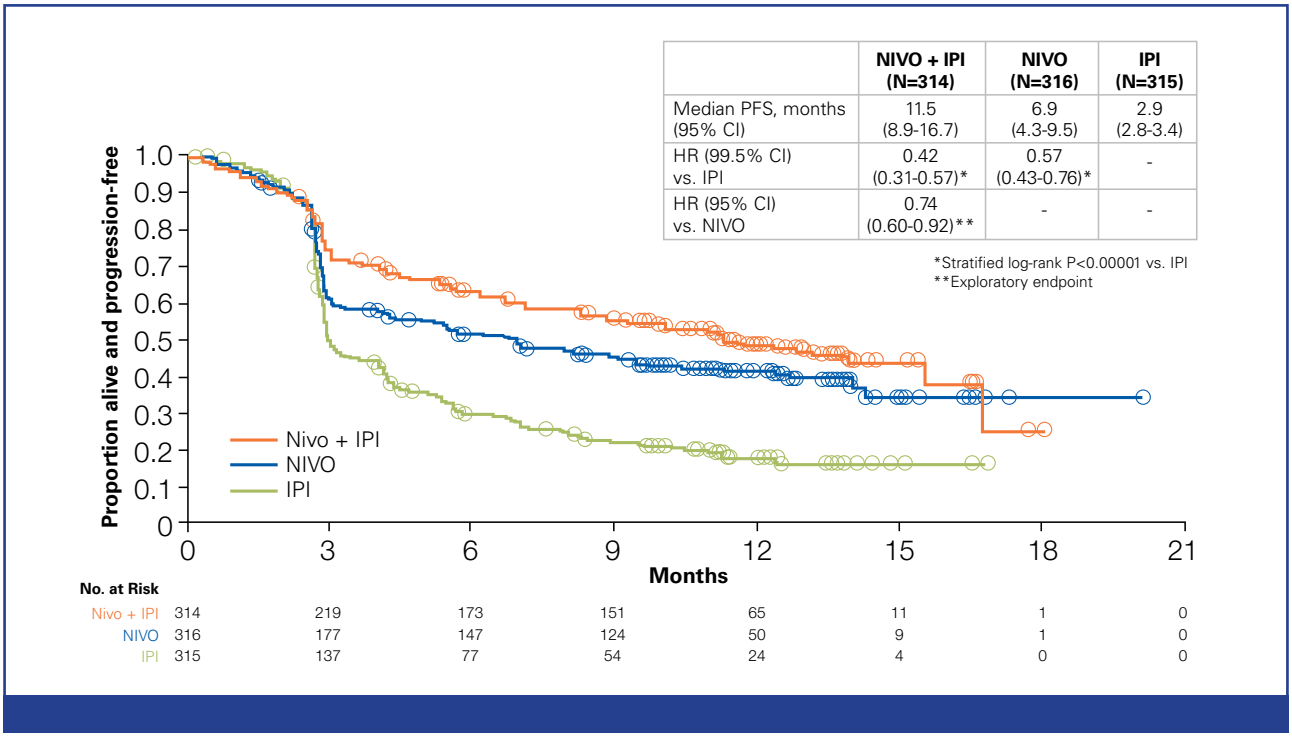

Figure 1. Superior PFS with nivolumab and nivolumab/ipilimumab as compared to ipilimumab monotherapy in the CheckMate-067 study.[7,8]

to benefit more from the combination treatment as compared to the single agent regimens, with a PFS of 11.2 months versus 5.3 and 2.8 months in the single-agent nivolumab and ipilimumab arms, respectively.[7,8] The response to the combination therapy was significantly higher for patients with a PD-L1 expression of 5% or higher (72.1%) as compared to PD-L1 negative patients (54.8%). A similar observation was made for nivolumab monotherapy with an ORR of 57.5% in PD-L1 positive patients and 41.3% in PD-L1 negative patients.[7,8]

Safety

The safety data were consistent with outcomes previously reported for both drugs. All grade adverse-events (AEs) were 95.5%, 82.1%, and 86.2%, in the combination, nivolumab, and ipilimumab arm respectively. The most frequent grade 3/4 toxicities reported with the ipilimumab/nivolumab combination compared with nivolumab and ipilimumab were diarrhoea (9.3%, 2.2%, 6.1%) colitis (7.7%, 0.6%, 8.7%), increased lipase (8.6%, 3.5%, 3.9%), increased ALT levels (8.3%, 1.3%, 1.6%) and increased AST levels (6.1%, 1.0%, 1.6%). Rates of treatment-related discontinuations with the combination, single-agent nivolumab and ipilimumab arms were 36.4%, 7.7%, and 14.8%, respectively. Of note, there was still a 68% response rate among the group of patients who discontinued the combination regimen, with half of those responses occurring after the patient stopped receiving treatment.[7,8]

Conclusion

Combined PD-1 and CTLA4 inhibition with nivolumab and ipilimumab is superior to ipilimumab monotherapy in terms of PFS and ORR. In addition to this, nivolumab monotherapy was also shown to be associated with a delayed disease progression as compared to ipilimumab. The benefit of combined nivolumab and ipilimumab was most pronounced in patients whose tumors had <5% PD-L1 expression. The incidence of adverse events was highest with the combination therapy and lowest in the nivolumab monotherapy arm.

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