Prolonged Survival in Metastatic Melanoma

Wolchok JD, Chiarion-Sileni V, Gonzalez P, et al. Overall survial with combined nivolimub and ipilimumab in advanced melanoma. N Engl J Med 2017;377:1345–56.

Study Overview

Objective. To compare clinical outcomes and toxicities between combined nivolumab plus ipilimumab (N+I) versus ipilimumab alone (I) or nivolumab alone (N) in patients with advanced melanoma.

Design. Randomized controlled trial 1:1:1 of N+I (nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab 3 mg/kg every 2 weeks) versus N (3 mg/kg every 2 weeks) versus I plus placebo (3 mg/kg every 3 weeks for four doses).

Setting and participants. Adult patients with previously untreated stage III (unresectable) or stage IV melanoma and ECOG performance status of 0 or 1 (on a scale of 0–5 with higher score indicating greater disability). Patients with active brain metastases, ocular melanoma, or autoimmune disease were excluded. This study took place in academic and community practices across the United States, Europe, and Australia. 945 patients were randomized. If patients progressed, additional therapies were at clinician discretion.

Main outcome measures. Primary end points were progression-free survival and overall survival. Secondary end points were objective response rate, toxicity profile, and evaluation of PD-L1 (programmed death-ligand 1) as a predictive marker for progression-free survival and overall survival.

Main results. Baseline patient characteristics were published previously [1]. There were no significant differences among groups except that the I only group had a higher frequency of brian metastases (4.8%) vs the N only group (2.5%). At censored follow-up of a minimum of 36 months, median overall survival was not reached in the N+I group, was 37.6 months in the N only group and was 19.9 months in the I only group (hazard ratio [HR] for death 0.55 ($P < 0.001$) for N+I vs. I and 0.65 ($P < 0.001$) for N vs. I). Overall survival at 3 years was 58% in the N+I group vs. 52% in the N only group vs. 34% in the I only group. The rate of objective response was 58% in the N+I group vs. 44% in the N only group vs. 19% in the I only group. Progression-free survival at 3 years was 39% in the N+I group, 32% in the N only group and 10% in the I only group. The level of PD-L1 expression was not associated with response or overall survival. Grade 3 or 4 treatment-related adverse events occurred in 59% of the N+I group vs. 21% in N vs. 28% in I group. As therapy after progression was left to clinician discretion, crossover was common with 43% of the I only group receiving nivolumab as second-line therapy and 28% of the N only group receiving ipilimumab as second-line therapy.

Treatment-related events that lead to therapy discontinuation occurred much more frequently in those who received N+I (40%) vs. N (12%) vs. I (16%). However, among the N+I patients who discontinued after a median of 3 cycles of treatment, 67% were still alive at 3 years. In addition, when adverse events were treated with safety guidelines, most immune-mediated adverse events resolved within 3 to 4 weeks. The most common grade 3 or 4 adverse events in the N+I group were diarrhea (9%), elevated lipase (11%), and elevated liver transaminases (9%). A total of 2 treatment-related deaths were reported in the N+I group.

Conclusion. Both the combination therapy of nivolumab + ipilimumab and nivolumab alone offer superior 3-year overall survival and progression-free survival compared with ipilimumab alone in advanced melanoma, with acceptable toxicity profiles.

Commentary

Historically, unresectable and metastatic melanoma has had a dismal prognosis, with responses to chemotherapy in about 10% to 15% and rarely were these responses durable [2]. The previous standard of care was high-dose IL-2, a form of immunotherapy which leads to long-term survival in a small minority of patients (~15%)

[3]. The encouraging results seen in this small minority lead to optimism for efficacy from additional immune-modifying agents.

The novel immunotherapy agents, known as checkpoint inhibitors, are antibodies directed against PD-1 (nivolumab and pembrolizumab), PD-L1 (atezolizumab, avelumab, and urvalumab), and CTLA-4 (ipilimumab). Each of these antigens are critical in a T cell process known as checkpoint inhibition. When these antigens are activated they inhibit T cells, a process critical for self recognition in the healthy human without cancer. However, many malignancies have developed molecular mechanisms to activate these checkpoint pathways and turn off T cell anti-tumor activity. By implementing checkpoint inhibitor antibodies, as done in this study, these drugs allow the T cells to be disinhibited and therefore exert anti-tumor activity. These drugs have been truly ground-breaking and are now FDA-approved in a number of malignancies, including bladder cancer, non–small cell lung cancer, head and neck squamous cell carcinoma, refractory Hodgkin lymphoma, mismatch repair–affected GI adenocarcinomas, renal cell carcinoma, and Merkel cell carcinoma. They offer the additional advantage of often an improved toxicity profile compared with traditional cytotoxic chemotherapy, as they are not typically associated with cytopenias, nausea, or hair loss, for example [4].

In this study, 3-year data from the CheckMate 067 trial is reported. As reported in this study, checkpoint inhibition has lead to truly remarkable improvements in outcomes for patients with advanced melanoma. In this study, the authors have demonstrated superiority of nivolumab plus ipilimumab and nivolumab alone versus ipilimumab alone. These results are similar to those seen in the KEYNOTE-006 trial which compared pemrolizumab (another anti-PD-1 antibody) to ipilimumab. In the KEYNOTE-006 trial, overall survival at 33 months was 50% in the pembrolizumab group versus 39% in the ipilimumab group.

In this study, the combination therapy was more toxic, requiring more frequent treatment discontinuation, though importantly, 3-year overall survival was 67% even among those who discontinued therapy. Grade 3 or 4 toxicity events seem to be associated with efficacy in this study. This is not surprising as this has been seen in some other tumor types as well [5], though it deserves more dedicated investigation as a prognostic marker in this population.

Applications for Clinical Practice

In this well-designed and -executed multicenter randomized trial, funded by Bristol-Myers Squibb and implemented in a selected population with good performance status, all 3 immunotherapies demonstrated impressive improvements in the management of advanced melanoma. The combination nivolumab and ipilimumab was the most effective, with markedly higher survival and response rates, but also with higher toxicity requiring treatment discontinuation, though this did not decrease the efficacy of the therapy. Both the combination nivolumab plus ipilimumab and nivolimab alone are acceptable treatments for patients with advanced melanoma and good performance status; cost and comorbidities will be critical in personalizing therapy.

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References

1. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.
2. Hill GJI, Krementz ET, Hill HZ. Dimethyl triazeno imidazole carboxamide and combination therapy for melanoma. Cancer 1984;53:1299–305.
3. Atkins MB, Lotze MT, Dutcher JP, et al. High-dose recombinant interleuken 2 therapy for patiens with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol 1999;17:2105–16.
4. Michot JM, Bigenwald C, Champiat S, et al. Immune-related adverse events with immune checkpoint blockade: a comprehensive review. Eur J Cancer 2016;54:139–48.
5. Haratani K, Hayashi H, Chiba Y, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. JAMA Oncol 2017 Sept 21.