Editorial

Melanoma Management

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Anti-PD-1 and PD-L1 antibodies in metastatic melanoma

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"Genetic mutations and dysregulation of the immune system may be related in some patients and may have an important impact on the efficacy of therapies."

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The advent of monoclonal antibodies that target CTLA-4 (ipilimumab) or PD-1 checkpoints (nivolumab and pembrolizumab) has increased hopes of improved outcomes in advanced melanoma. However, resistance remains an important issue. Genetic mutations and dysregulation of the immune system may be related in some patients and may have an important impact on the efficacy of therapies.

Clinical trials with anti-PD-1s in metastatic melanoma

Nivolumab has been shown to significantly prolong survival in patients with metastatic melanoma, with an overall survival (OS) rate of 41–42% at 3 years and 35% at 5 years [1]. In the Phase III CheckMate 037 study in patients with BRAF mutant and BRAF wild-type advanced melanoma progressing after ipilimumab, overall response rate (ORR) was higher with nivolumab compared with investigator's choice chemotherapy (32 vs 11%) [2]. However, there was no statistical difference in median OS between nivolumab and chemotherapy (15.7 vs 14.4 months; $p = 0.71$). This may have been due to an imbalance between the two study arms, with more patients in the nivolumab group having elevated LDH levels or brain metastases. Another explanation may be that patients who progressed in the chemotherapy arm may then have received pembrolizumab. In the CheckMate 066 study in patients with previously untreated BRAF wild-type advanced melanoma, ORR was also higher with first-line nivolumab compared with chemotherapy (dacarbazine; 40 vs 13.9%) [3]. Median OS of patients treated with nivolumab was not reached [4].

The other approved anti-PD-1, pembrolizumab, has shown a similar benefit as nivolumab. The Phase I KEYNOTE 001 study showed a median OS of 20 months for all studied doses and was 28 months in ipilimumab-naive patients. Similar results were seen at 3 years [5]. The Phase II KEYNOTE 002 study showed the benefit of pembrolizumab compared with chemotherapy in patients previously treated with ipilimumab and a BRAF or MEK inhibitor, with an ORR of 22.2 and 27.6% for pembrolizumab 2 and 10 mg/kg, respectively, compared with 4.5% with chemotherapy. Median progression-free survival (PFS) at 2 years was significantly prolonged with pembrolizumab at both doses, but median OS was only significantly improved in patients treated with pembrolizumab 10 mg/kg (14.7 vs. 11 months with chemotherapy; $p = 0.01$; hazard ratio = 0.74) [6]. In the KEYNOTE 006 Phase III trial, first- or second-line pembrolizumab in BRAF mutant or wild-type melanoma patients had a higher response rate compared with ipilimumab. OS at 2 years with pembrolizumab was 55 versus 43% with ipilimumab [7]. At median follow-up of nearly 3 years, 33-month OS and PFS rates with pembrolizumab compared with ipilimumab were 50 versus 39% and 31 versus 14%, respectively [8]. Moreover, responses were durable in 104 patients who stopped pembrolizumab treatment after 2 years as per the study protocol; at a median follow-up of at 9.7 months after completing 2 years of pembrolizumab, estimated PFS was 91% (95% in patients with complete responses, 91% in patients with partial responses and 83% in patients with stable disease).

Various combinations involving anti-PD-1s with anti-CTLA-4s are also being investigated. In the Phase III CheckMate 067 trial, response rates were 58.9% for nivolumab and ipilimumab in combination, 44.6% for nivolumab alone and 19% for ipilimumab alone [9]. PFS was 11.7, 6.9 and 2.9 months, respectively. Median OS

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was not reached in the combination or nivolumab arms but was 18.5 and 24.6 months for ipilimumab-treated BRAF wild-type and BRAF mutant patients, respectively. Median OS for patients with PD-L1-positive tumors did not differ between the combination and nivolumab alone arms (72 vs 68%). However, in PD-L1-negative patients, median OS was longer in the combination arm, a result consistent with previous data showing prolonged PFS with combination therapy in patients with PD-L1-negative tumors [10].

The combination of pembrolizumab and ipilimumab is also being assessed. In preliminary data from the Phase IB KEYNOTE 029 trial, ORR was 57% and disease control rate was 78% in 153 patients receiving pembrolizumab 2 mg/kg and ipilimumab 1 mg/kg for four doses every 3 weeks followed by pembrolizumab alone until disease progression. Median PFS and OS were not reached after a median follow-up of 10 months [11].

The potential of anti-PD-1s in combination with other novel agents is also being explored. Entinostat is an selective histone deacetylase inhibitor shown to enhance immune checkpoint inhibitor activity in preclinical studies. In preliminary data, entinostat plus pembrolizumab showed promising activity with in patients (n = 13) refractory to previous treatment with checkpoint inhibitors [12]. However, toxicity was high with 62% of patients reporting treatment-related grade 3–4 adverse events. Similarly, addition of the antilymphocyte activation gene-3 (anti-LAG-3) agent BMS-986016 to nivolumab showed encouraging initial efficacy and a similar safety profile to nivolumab monotherapy in patients whose disease progressed on/after anti-PD-1/PD-L1 therapy [13]. In 48 heavily pretreated patients, ORR was 13%, with a 20% response rate in patients with LAG-3 expression ≥1 versus only 7% in LAG-3-negative (<1%) patients.

Brain metastases

Anti-PD-1/anti-CTLA-4 combination therapy is also being assessed in patients with melanoma metastatic to the brain. In the Phase II CheckMate 204 study, nivolumab plus ipilimumab had a high intracranial ORR of 56% (19% complete responses) and no unexpected neurologic safety signals [14]. Similarly, in a Phase II trial in patients with melanoma brain metastases and no previous checkpoint inhibitor treatment, intracranial ORR was 53% in patients who were BRAF inhibitor-naive (vs 16% in BRAF inhibitor previously treated patients) [15]. Although nivolumab monotherapy also showed clinical activity, patients with symptomatic or leptomeningeal metastases or who had previous local therapy responded poorly to nivolumab alone.

Resistance to anti-PD-1/PD-L1s in metastatic melanoma

Anti-PD-1 therapy has improved clinical outcomes in advanced melanoma, but the majority of patients, approximately 60–70%, do not respond, possibly due to intrinsic resistance [4,5]. Moreover, patients who initially show a response may have disease progression due to acquired resistance. In a recent study, nearly 25% of patients with melanoma who had received an objective response to anti-PD-1 therapy had disease recurrence at a median follow-up of 21 months [16].

Theories regarding intrinsic resistance vary. It was recently shown that intrinsic resistance to anti-PD-1 therapy may correlate with increased expression of certain genes, such as those involved in mesenchymal transition, extracellular matrix remodeling, angiogenesis and wound healing [17]. In addition, an absence of T cells in the tumor may suggest no benefit from anti-PD-1 blockade [18]. Other hypotheses have focused on receptor and ligand targets. A meta-analysis of 11 studies showed a positive correlation between PD-L1 tumor expression and higher responses rates with PD-1/PD-L1 agents [19]. Comparing ORR between patients with PD-L1 tumor expression more than 1% and those with PD-L1 less than 1%, the odds ratio was 2.81 (95% CI: 1.64–4.82; p = 0.0002), while for PD-L1 more than 5% patients versus PD-L1 less than 5% patients, it was 2.22 (95% CI: 1.71–2.87; p < 0.00001). However, over half of PD-L1-positive tumors are not responsive, indicating biological questions still remain. To date, the characterization of tumor phenotypes that display intrinsic resistance to anti-PD-1s is still largely unknown.

Acquired resistance, defined as disease progression following an objective response, is also a problem. In a retrospective analysis of 488 patients with metastatic melanoma treated with anti-PD-1, acquired resistance was identified 36 patients [20]. These patients had more than one poor prognostic factor (stage M1C, elevated LDH or brain metastasis) and 67% had previously been treated with ipilimumab. Partial responses were observed in 89% of patients, with complete responses in 11%. Median time to resistance (PFS) was 11.1 months (range 4.3–32.8 months). 78 patients experienced isolated progressions that occurred during treatment. Among these patients, 15 received a local therapy such as surgery or radiotherapy and showed a significant improvement in PFS (≥15 months) compared with patients with systemic progression. Two of these patients experienced a subsequent

response to anti-PD-1. These findings are of interest, since they suggest that acquired resistance to anti-PD-1 may be overcome, in particular for patients with isolated progression, by the addition of local therapy.

Other mechanisms of acquired resistance are under evaluation in preclinical models. Among these, defects in the interferon signaling pathway have been proposed as a potential mechanism of cancer escape [21,22]. Also, some studies are considering genetic mechanisms that include acquired mutations in other genes. In particular, Hugo *et al.* [17] analyzed mRNA and DNA samples from melanoma patients before and after anti-PD-1 treatment and showed that high mutational load may not be predictive of response to anti-PD-1 therapy, but may be related to improved OS. BRCA2 loss of function mutations were frequently found in responders, while a signature referred to as the innate anti-PD-1 resistance (IPRES) signature, consisting of RNA transcripts relating to mesenchymal transition, angiogenesis, hypoxia and would healing, was identified in nonresponders. This IPRES signature may also be present in BRAF mutant melanoma patients treated with anti-BRAF therapy. In fact, these patients are frequently treated first with BRAF or MEK inhibitors and then, at disease progression, with anti-PD-1 therapy. In some of these melanoma patients with the IPRES signature, the resistance developed after BRAF inhibitor therapy may also predict resistance to anti-PD-1 therapy.

Conclusion

Anti-PD-1/PD-L1 antibodies alone or in combination have improved response rates and survival of patients with metastatic melanoma. However, the possibility to prolong survival still further remains a challenge. Research to address issues relating to the selection of patients for the right treatment with the aim to overcome resistance is required. Biomarkers such as higher expression of PD-L1 may be useful to predict higher responses but may not relate to longer survival. For this reason, PD-L1 expression should not be used to select melanoma patients for treatment.

Other issues regarding anti-PD-1/PD-L1 therapy relate to the dose and the duration of treatment. Nivolumab dosage is under evaluation, in particular in combination with ipilimumab. Duration of anti-PD-1 therapy has been approved until disease progression or unacceptable toxicity, which in some cases would mean until resistance or poor clinical conditions that could preclude other therapeutic possibilities for patients. Ongoing and future studies will hopefully help address these issues.

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