

# Anti-PD-1 antibodies in melanoma

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The programmed death 1 (PD-1) receptor is a negative regulator of T-cell effector mechanisms that limits immune responses against cancer. Two recent phase 1 studies of anti-PD-1 antibodies indicate that these agents exhibit considerable antitumor activity alone or in combination with ipilimumab in patients with advanced melanoma.

## Lambrolizumab in advanced melanoma

In a phase 1 expansion study reported by Hamid and colleagues,<sup>1</sup> 135 patients with advanced melanoma, including 48 with prior ipilimumab treatment and 87 without, received lambrolizumab IV at 10 mg/kg every 2 or 3 weeks or 2 mg/kg every 3 weeks. Overall, patients had a mean age of 60 years, 59% were men, 99% were white, 99% had ECOG performance status of 0 or 1, and 19% had known *BRAF*-mutant status. Visceral metastases (stage M1c) were present in 54% of patients, 27% had elevated lactate dehydrogenase (LDH), and 9% had a history of brain metastases. Prior treatments included immunotherapy (excluding ipilimumab) in 25% and chemotherapy in 35%, with 31% having no prior systemic treatment.

The confirmed response rate across all dose groups on central radiologic review using RECIST criteria was 38% (95% CI, 25%-44%). On immune-related criteria, the confirmed objective response rate was 37%. The majority of responses were observed at the time of the first imaging at 12 weeks. The highest confirmed response rate was in the group receiving 10 mg/kg every 2 weeks (52%; 95% CI, 38%-66%); response rates were 27% in the 10 mg/kg every 3-week group and 25% in the 2 mg/kg every 3-week group. In the total population, there were an additional 8 unconfirmed responses (for an overall response rate of 44%). Response rates did not differ between patients who had received prior ipilimumab treatment (38%; 95% CI, 23%-55%) and those who had not (37%; 95% CI 26%-49%). Responses were durable in the majority of patients; no median response duration had been reached after median follow-up of 11 months. Of patients with response, 81% were still receiving treatment at the time of analysis. Overall, median progression-free survival among the 135 patients was longer than 7 months.

The most frequent treatment-related adverse events of any grade were fatigue (30%), rash (21%), pruritus (21%), diarrhea (20%), and myalgia (12%). The incidence of treatment-related adverse events was highest in the 10

## What's new, what important

Physicians have tried using immunotherapy against cancer since 1891, when William Coley treated patients with intratumoral injections of *Streptococcus pyogenes* and *Serratia marcescens* (Nature. 2011;480;22-29). Scientists and patients alike are fascinated by the potential of harnessing the immune system to cure major illnesses, including cancer. This fascination could be the result of amazing success stories of the polio and smallpox vaccines, which almost eradicated those diseases after they had plagued humanity for centuries. Early attempts to use immunotherapy for cancer with agents such as interleukin-2 were at the best marginal or disappointing, but thanks to the perseverance of cancer immunologists, we are finally entering into a more promising cancer immunotherapy landscape. Three key steps in tumor immunology that could also be possible areas for immunotherapeutic intervention are:

- The tumor antigens are recognized and processed by the dendritic cells, which present the tumor antigens into the lymph node.
- In the lymph nodes, the antigen-presenting dendritic cells stimulate production of CD8 effector T cells with cytotoxic potential.
- The cytotoxic T cells are primed to attack the cancer, but the tumor initiates several immune suppressive signals to inactivate the T-cell response. This could be mediated by a variety of surface molecules such as programmed death ligands 1 or 2 (PD-L1 or PD-L2) that engage receptors on the surfaces of activated T cells (PD-1), causing T-cell exhaustion.

PD-L1 is upregulated in large number of tumors and is correlated with poor outcome, which makes it an effective therapeutic target. Early clinical trials in variety diseases, including melanoma and lung cancer have shown that targeting PD-1 or PDL-1 could be a highly effective strategy to enhance T-cell-mediated antitumor activity. Two monoclonal antibodies targeting PD-1, lambrolizumab and nivolumab and another monoclonal antibody targeting PD-L1 (MPDL3280A) are discussed here in detail. This could well be the beginning of a new class of highly effective cancer agents with unique efficacy and side effect profile.

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## How I treat melanoma

Melanoma is treated with surgery when it is a primary lesion or regional disease (stages 1, 2, or 3) and with medical therapies (targeted therapy, immunotherapy, and conventional chemotherapy) when the disease is metastatic and inoperable. Thin melanoma (< 1 mm thick) can be managed with wide local excision alone. Sentinel lymph node biopsy is recommended for deeper melanoma ( $\geq 1$  mm thick). If the regional lymph nodes are clinically involved or microscopically positive (sentinel node positive), then a complete lymph node dissection is necessary to provide adequate local regional control of disease. Metastatic melanoma is managed with medical therapies except when a single site of metastasis is present and it can be easily resected.

Medical therapy for advanced melanoma has evolved greatly in recent years and now includes a number of new drugs, besides the conventional cytotoxic chemotherapy. Metastatic melanoma is clinically and biologically a very heterogeneous disease. Consequently, the treatment approach is based on the clinical pattern of metastases to different organs and by the pace of growth and the volume of metastatic tumor. Some patients have small-volume and indolent disease that is asymptomatic, others may have rapidly progressive tumor with

bulky metastatic lesions resulting in a compromised performance status. Serum lactate dehydrogenase level is typically indicative of the rate of progression of disease and is commonly used as guide to selection of therapy. Furthermore, the molecular characterization of melanoma is now a critical part of treatment decision making, with measurement of BRAF-mutation status being essential for all patients with metastatic melanoma. About 50% of patients have BRAF-mutated melanoma. This discovery has led to the development of targeted therapies in the form of BRAF inhibitors such as vemurafenib and dabrafenib and MEK inhibitors such as trametinib. Another option of therapy is immunotherapy, which has played an important role in the management of advanced melanoma more than in any other malignancy.

The options of immunotherapy include interleukin-2 and ipilimumab, and some investigational therapies, such as nivolumab, lambrolizumab, and MPDL3280A. In addition, chemotherapy continues to play a significant role, using drugs such as dacarbazine (DTIC), cisplatin, and the taxanes (paclitaxel, nab-paclitaxel) alone or in combination.

– Sewa S. Legha, MD, FACP

mg/kg every 2-week group. Treatment-related grade 3 or 4 adverse events occurred in 13% of patients, and consisted of rash in 2% of patients and hypothyroidism, diarrhea, abdominal pain, fatigue, increased AST, renal failure, and pruritus in 1% each. Four cases of treatment-related pneumonitis were reported (all grade 1 or 2). Grade 3 renal failure in 2 patients was considered potentially immune-related.

## Nivolumab plus ipilimumab in advanced melanoma

In a phase 1 trial reported by Wolchok and colleagues,<sup>2</sup> patients with advanced melanoma received concurrent (53 patients) or sequential treatment (33 patients) with the anti-PD-1 antibody nivolumab plus ipilimumab. Ipilimumab is an antibody directed against cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). CTLA-4 and PD-1 appear to have complementary activities in regulating adaptive immunity, and preclinical data suggest that combined blockade results in greater antitumor activity.

In the concurrent regimen group, patients received IV nivolumab plus ipilimumab every 3 weeks for 4 doses, followed by nivolumab alone every 3 weeks for 4 doses, and then combined treatment every 12 weeks for up to 8 doses. Nivolumab was given at doses of 0.3-10 mg/kg and ipilimumab at 1-10 mg/kg

in 5 dose cohorts. In the sequenced regimen, patients who had received at least 3 previous doses of ipilimumab, with the last dose administered 4 to 12 weeks before the administration of nivolumab, were given nivolumab at either 1 or 3 mg/kg every 2 weeks for up to 48 doses. For the concurrent and sequenced treatment groups, median ages were 58 and 64 years and most patients were men (60% and 55%, respectively), had ECOG performance status of 0 or 1 (98% and 100%), and disease status of M1c (57% and 55% groups). LDH was elevated in 38% and 36% of patients. In the concurrent treatment group, 38% of patients had received prior systemic therapy. Most patients (73%) in the sequenced regimen group had radiographic disease progression during prior treatment with ipilimumab.

The objective response rate based on modified World Health Organization criteria was 40% among patients receiving concurrent treatment. Evidence of clinical activity (conventional, unconfirmed, or immune-related response or stable disease for  $\geq 24$  weeks) was observed in 65% of patients in this group. At the maximum doses associated with an acceptable level of adverse events – that is, nivolumab 1 mg/kg and ipilimumab 3 mg/kg – 53% of patients had objective response, all with tumor reduction of  $\geq 80\%$ . Responses were ongoing in 19

of 21 patients in the concurrent regimen group at the time of analysis, with duration of response ranging from 6.1 to 72.1 weeks. The objective response rate in the sequenced regimen group was 20% and evidence of clinical activity was found in 43% of patients. Responses to nivolumab were observed in some patients without response to prior ipilimumab treatment.

In the concurrent regimen group, the most frequent treatment-related adverse events were rash (55%), pruritus (47%), fatigue (38%), and diarrhea (34%). Treatment-related grade 3 or 4 adverse events occurred in 53%, with the most frequent being elevated lipase (13%), elevated AST (13%), and elevated ALT (11%). Serious adverse events occurred in 49% of patients, including hepatic events (15%), gastrointestinal events (9%), and renal events (6%). Dose-

limiting treatment-related events occurred in 21% of patients. In the sequenced regimen group, the most frequent treatment-related events of any grade were pruritus (18%) and elevated lipase (12%). Grade 3 or 4 treatment-related events occurred in 18%, with lipase elevation being the most frequent (6%). Serious adverse events occurred in 21% of patients, and 9% of patients discontinued treatment due to treatment-related events.

## References

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