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FROM ASCO—TARGETED THERAPIES

Anti-PD-1 approaches—important steps forward in metastatic melanoma

Several new studies presented at the recent ASCO annual meeting in Chicago have shown promising results for the use of targeted therapies against programmed cell death protein 1 receptor (PD-1) and its ligands PDL1 in patients with advanced melanoma. Expressed on the surface of activated T cells, B cells and macrophages, PD-1 regulates immune responses differently to the inhibitory receptor cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), which is targeted by ipilimumab.

One of these studies was a phase IB study of lambrolizumab (previously known as MK-3475), which is a humanized monoclonal antibody against PD-1. "Once results were noted in our phase IA study in a high frequency of patients," explains lead investigator Antoni Ribas, "we opened several nonrandomized cohorts with three different dosing regimens in patients with advanced melanoma." The researchers enrolled 135 patients who had disease progression on ipilimumab or who were treatment-naive. Patients received lambrolizumab (10 mg per kg body weight) every 2 or 3 weeks or a reduced dose of the drug (2 mg per kg) every 3 weeks.

Almost 80% of patients experienced some grade of treatment-related adverse event, although the rate of grade 3 or 4 events was a modest 13%. Common adverse events were fatigue (30% of patients), rash (21%), pruritus (21%) and diarrhoea (20%).

The secondary end point of the study was an analysis of the antitumour activity, which was measured every 12 weeks. Some immunotherapies currently in use in melanoma show a durable tumour response, but only in a small proportion of patients (approximately 15%). "This ceiling of antitumor activity has been broken with anti-PD-1 antibodies, with response rates consistently beyond 30% in patients with advanced melanoma," says Ribas. Indeed, lambrolizumab achieved an overall

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response rate (according to RECIST 1.1) of 38%, with 90% of these patients achieving durable responses lasting 7–18 months. At the highest dosing regimen, the response rate was 52%.

"The future is bright for the continued testing of anti-PD-1 antibodies, as well as those against its ligand, in melanoma and in many other cancers. I think it is safe to predict that this class of agents will be the most impactful new agents in oncology in coming years," muses Ribas.

This prediction is supported by the results of another phase I study presented at ASCO, led by Jedd Wolchok. This study looked at a combined regimen of ipilimumab and the anti-PD-1 antibody nivolumab. "Blockade of both the CTLA-4 and PD-1 pathways in mouse models resulted in enhanced tumour rejection, which prompted our study to test the safety and efficacy of the combination in patients with metastatic melanoma," Wolchok explains.

Nivolumab and ipilimumab were administered intravenously every 3 weeks for four doses, followed by nivolumab alone every 3 weeks for four doses—the concurrent treatment was given every 3 months for patients showing evidence of clinical benefit ($n = 53$). In assessing sequenced treatment, patients previously treated with ipilimumab received the anti-PD-1 agent fortnightly for up to 48 doses ($n = 33$). The maximum tolerated doses were determined to be nivolumab at 1 mg per kg and ipilimumab at 3 mg per kg.

In patients receiving the maximum tolerated dose of the concurrent regimen, >50% achieved an objective response. "All responding patients in this cohort had >80% reduction in baseline tumour burden by the time of the first radiographic assessment," explains Wolchok. Also, patients whose disease had previously progressed on ipilimumab therapy responded to nivolumab treatment in the sequenced cohorts.

"If a recently launched phase III trial (NCT01844505) shows that the combination produces superior overall survival compared with single agents, then the first-line therapy for metastatic melanoma could change to become the combination," concludes Wolchok.

Clearly, the development of novel targeted therapies in melanoma is an exciting and progressing field of research, with major trials looking into important questions. Whether single agents or combinations are used, PD-1 is sure to be targeted.

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Original articles Hamid, O. *et al.* Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N. Engl. J. Med.* doi:10.1056/NEJMoa1305133 | Wolchok, J. D. *et al.* Nivolumab plus ipilimumab in advanced melanoma. *N. Engl. J. Med.* doi:10.1056/NEJMoa1302369

Further reading Hamid, O. *et al.* Clinical activity, safety, and biomarkers of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic melanoma (mM) [abstract 9010]. *J. Clin. Oncol.* **31** (Suppl.), a9010 (2013) | Weber, J. S. *et al.* Phase I/II trial of PD-1 antibody nivolumab with peptide vaccine in patients naive to or that failed ipilimumab [abstract 9011]. *J. Clin. Oncol.* **31** (Suppl.), a9011 (2013)