

Targeting the programmed cell death 1 pathway: A new approach to the treatment of advanced melanoma

Sir,

Melanoma is the deadliest form of skin cancer. In its early stage, it can usually be cured with surgery alone, but once it metastasizes throughout the body, treatment options are limited.^[1] The median survival time for the patients of advanced melanoma remained less than a year, and more effective treatments are desperately needed. Over the past 10 years, our understanding of the biology of melanoma and the body's natural defensive responses to this disease has increased dramatically. This knowledge has been translated into many new therapies. Indeed, in last few years, clinical trials testing several new treatments have demonstrated substantial tumor shrinkage, a prolonged remission interval, and even improved overall survival. Recent breakthroughs in targeted therapy and immunotherapy have improved the outcomes in patients with advanced melanoma. Until just this year, the five prior Food and Drug Administration (FDA) approved drugs for melanoma include: Ipilimumab (2011), peginterferon alfa-2b (2011), vemurafenib (2011), dabrafenib (2013), and trametinib (2013). On September 4, 2014, the FDA approved pembrolizumab (Keytruda, made by Merck Sharp and Dohme Corp., US) for the treatment of patients with inoperable or metastatic melanoma who had progressive disease following treatment with ipilimumab and/or a BRAF inhibitor (if BRAF V600 mutation positive).^[2]

Pembrolizumab (MK-3475; Lambrolizumab^[3]) is a drug that targets the programmed cell death 1 (PD-1) receptor meant to treat metastatic melanoma.^[4] Pembrolizumab is the first approved PD-1 receptor blocker and sixth new melanoma treatment approved since 2011. It has got a rapid approval in the American market and has beaten the other similar drugs including nivolumab (Bristol-Myers Squibb/Ono), MPDL-3280A (Roche/Genentech/Chugai) and MED14736 (AstraZeneca/Medimmune) [Table 1].

Approval was based on the results from a multicenter open-label randomized phase 1b clinical trial,^[5] in which 173 patients with inoperable or metastatic melanoma who experienced progressive disease within 24 weeks of the last dose of ipilimumab and/or prior treatment with a BRAF inhibitor, were randomly assigned to receive 2 mg/kg ($n = 89$) or 10 mg/kg ($n = 84$) of pembrolizumab intravenous 3 weekly until further disease progression or unacceptable toxicity. The overall response rate was 24% (95% confidence interval: 15–34) in the 2 mg/kg arm, similar overall response rates were seen in the 10 mg/kg arm. The duration of response was at least 1.4–8.5 months, with most patients having a response, which continued beyond that. Pembrolizumab's safety was established in the trial population of 411 participants with advanced melanoma. The common side effects were fatigue (47%), cough (30%), nausea (30%), pruritus (30%),

Table 1: PD-1 cellular pathway blockers

Therapeutic	Target	Latest clinical stage	Indications (all clinical stages)	Company
Nivolumab	PD-1	Phase 3	Melanoma, RCC, NSCLC, many others	Bristol-Myers Squibb/Ono
Pembrolizumab (MK-3475)	PD-1	Phase 3	Melanoma, NSCLC, Head and neck, bladder	Merck
MED14736	PD-L1	Phase 3	NSCLC, melanoma, other advanced cancers	AstraZeneca/Medimmune (AZN)
MPDL-3280A	PD-L1	Phase 3	NSCLC, RCC, bladder, other advanced cancers	Roche/Genentech/Chugai

PD-1: Programmed death-1, NSCLC: Nonsmall cell lung cancer, RCC: Renal cell carcinoma

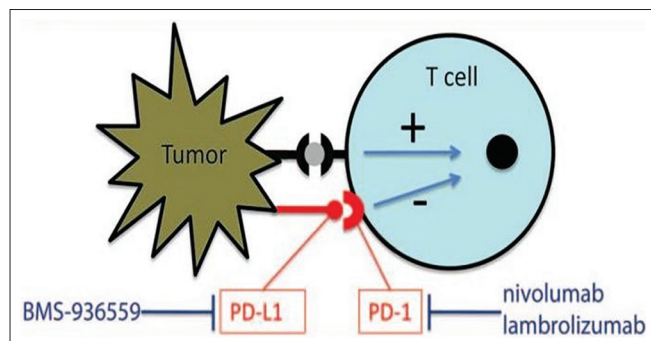


Figure 1: The programmed cell death 1/programmed cell death ligand 1 (PD-1/PD-L1) axis and antibodies in development. T-cells interact with tumor cells in peripheral tissues. Tumor cells can present antigen to the T-cell receptor, resulting in a stimulatory signal to the T cell (+). Tumor cells may also express PD-L1, which interacts with PD-1 on activated T-cells, and results in inhibition (-) of the antitumor T-cell response

rash (29%), decreased appetite (26%), constipation (21%), arthralgia (20%) and diarrhea (20%). Severe immune-mediated side effects involving healthy organs were not common. Unlike cytotoxic T-lymphocyte-associated antigen-4 antibodies, the PD-1/programmed cell death ligand 1 (PD-L1) antibodies aim to potentiate the antitumor T-cell response at a tumor-specific level, by impairing the interaction of the inhibitory receptor PD-1 on T cells with PD-L1 expressed on tumor cells [Figure 1].^{6]} These antibodies bring immunotherapy to the forefront and indicate that immune-modulation will be a key component of therapeutic strategies from now on, because of this PD-1/PD-L1 antibodies are considered “drug of the year.”^{17]}

Food and Drug Administration granted the breakthrough therapy designation for pembrolizumab in early 2013 based on preliminary evidence of clinical activity in patients with advanced melanoma, previously untreated with or refractory to ipilimumab. The recommended dose of pembrolizumab is 2 mg/kg administered as an intravenous infusion over 30 min every 3 weeks until disease progression or unacceptable toxicity. While there is still a long path to travel to find the cure for metastatic melanoma, drug targeting the PD-1 pathway represents a significant step forward.

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