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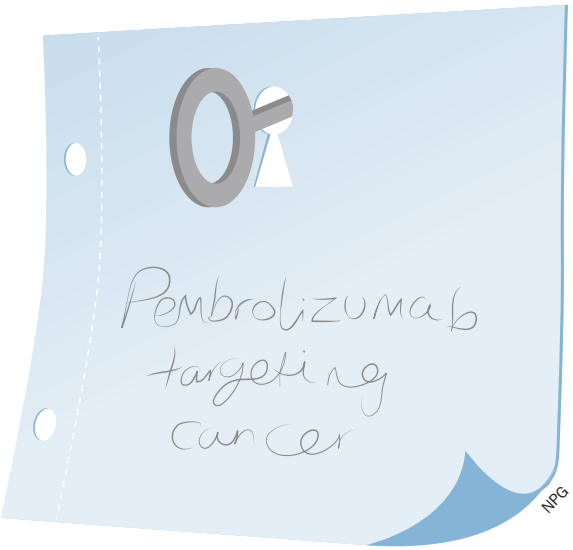
IMMUNOTHERAPY

Pembrolizumab—is the writing on the wall for cancer?



It cannot have escaped the attention of any clinical oncologist that immunotherapy has transformed the treatment landscape for patients with metastatic melanoma. Although attempts at harnessing the immune system to fight cancer have been ongoing for decades, it is only recently that inhibitors targeting programmed cell death protein 1 (PD-1) receptor and its ligand, PD-L1, have led to significant and, in some cases, durable improvements in clinical outcomes. Now, two pivotal studies, one in patients with melanoma (KEYNOTE-006) and the other (KEYNOTE-001) in patients with non-small-cell lung cancer (NSCLC) have proven the efficacy of the anti-PD1 antibody pembrolizumab.

Since 2011, the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) blocking agent ipilimumab has been shown to be more effective than classic cytotoxic-based treatment for patients with metastatic melanoma. Ipilimumab was recently approved for this category of patients; however, this immunotherapeutic drug benefits only 15–20% of patients and is associated with grade 3–4 adverse events in more than 20% of patients. KEYNOTE-006, led by Caroline Robert, was initiated to examine whether pembrolizumab, which has shown very promising results in a phase I study, was more effective than ipilimumab in patients with metastatic melanoma. Since September 2014, pembrolizumab has been approved for patients previously treated with ipilimumab but who did not response to this anti-CTLA-4 immunotherapy.

The open-label controlled KEYNOTE-006 study adopted a classic 1:1:1 randomization approach that evaluated two distinct doses of pembrolizumab (10 mg/kg every 2 weeks or every 3 weeks) versus ipilimumab in patients who had not received ipilimumab or any anti-PD1 treatment. Patients who were eligible for enrolment included those who were pretreated with BRAF-targeted agents if they had *BRAF*-mutant melanoma. As Robert highlights: "The results were clear and showed a significant benefit for both pembrolizumab doses compared with ipilimumab in terms of overall survival as well as progression-free survival (PFS). The response rate was also increased with pembrolizumab: 33.7% and 32.9% for the 2-weekly and 3-weekly doses, respectively, compared with 11.9% for ipilimumab. Moreover, pembrolizumab was less toxic than ipilimumab."

In NSCLC, a cohort study of 38 patients treated with pembrolizumab showed that most responses occurred in patients with tumours that showed the highest degree of PD-L1 staining. Therefore, in the KEYNOTE-001 trial, the protocol was amended to evaluate the role of pembrolizumab in 495 patients with advanced-stage NSCLC with high levels of PD-L1 expression. The researchers adopted a training set and a validation set model, in which the level of PD-L1 expression could identify those patients most likely to benefit from pembrolizumab. The group, led by Edward Garon, selected PD-L1 membrane staining in at least half of the tumour cells as the cut-off criterion for selection, and evaluated this in an independent set of patients. Garon explains: "we adopted this approach recognizing that we could not validate a biomarker in a setting in which we allowed the clinical data to inform the selection of the biomarker. The predictive utility of the biomarker could only be determined in an independent data set."

The objective response rate was 19.4% and the median duration of response was 12.5 months. Fewer than 10% of patients experienced grade 3 or greater immune-related adverse events. "This was the first time that the predictive role of the level of PD-L1 expression was assessed in an independent validation set," states Garon. Importantly, these data indicate that in previously treated patients with ≥50% of their tumour showing membranous PD-L1 staining, pembrolizumab seems a better option than cytotoxic chemotherapy. Crucially, among all patients with such a level of PD-L1 staining, at a median follow up of 10.9 months, the median overall survival was not reached.

Garon puts these data in context: "recognizing the limitation of the small sample size, the data on pembrolizumab in previously untreated patients who had membranous PD-L1 staining in at least half of their tumour cells was incredibly good." He comments on future planned studies in the NSCLC population: "In untreated patients, pembrolizumab will be compared to standard-of-care cytotoxic chemotherapy in the KEYNOTE-024 clinical trial. For patients with lower levels of PD-L1 staining, the relative benefit of pembrolizumab as opposed to cytotoxic chemotherapy is being evaluated in the KEYNOTE-010 study."

Ultimately, these trial data indicate that pembrolizumab could be soon approved as first-line treatment for patients with advanced melanoma, and this agent shows promise for the treatment of NSCLC.

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Original articles Robert, C. *et al*. Pembrolizumab versus ipilumumab in advanced melanoma. *N. Engl. J. Med*. doi:10.1056/NEJMoa1503093 | Garon, E. B. *et al*. Pembrolizumab for the treatment of non-small-cell lung cancer. *N. Engl. J. Med*. doi:10.1056/NEJMoa1501824