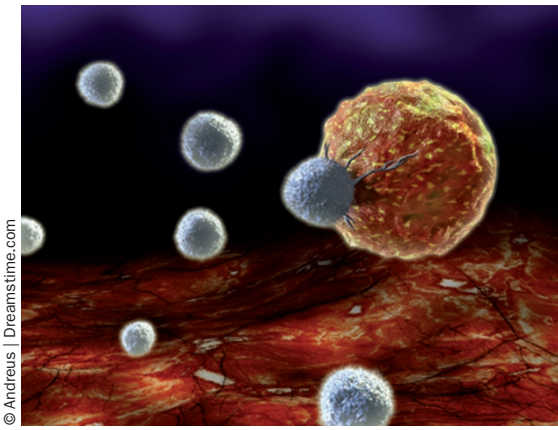
Nature Reviews Clinical Oncology **9**, 427 (2012); published online 19 June 2012; doi:10.1038/nrclinonc.2012.104

FROM ASCO—IMMUNOTHERAPY

Programming cancer cell death



© Andreus | Dreamstime.com

The development of a truly targeted anticancer therapy is the goal of many researchers. Harnessing endogenous immune responses to target the genetic and epigenetic changes that cancer cells harbour is one very promising avenue for this development. In studies presented at the ASCO annual meeting and published in the *New England Journal of Medicine* by Suzanne Topalian, Julie Brahmer and their colleagues, novel targeted immunotherapies have shown promise in early stage clinical trials.

The research builds on the success of ipilimumab, which targets the endogenous 'immune checkpoint' protein CTLA-4 and is an approved therapy for patients with advanced-stage melanoma. The novel therapies target the key immune checkpoint interaction between a T-cell co-inhibitory receptor called programmed death 1 (PD-1) and one of its immunosuppressive ligands, PD-L1. The drugs are both fully human IgG4-blocking antibodies, one is directed against PD-1 (BMS-936558) and the other is directed against PD-L1 (BMS-936559).

The first trial was a dose-escalation study of the drug that targets PD-1 in 296 patients with solid tumours who had advanced-stage disease. The tumour types included melanoma, non-small-cell lung cancer (NSCLC), renal cell cancer, castration-resistant prostate cancer and colorectal cancer. The majority of the patients were heavily pretreated with almost half of them receiving three or more therapies prior to enrolling on the trial. Patients received the antibody as an intravenous infusion (0.1–10 mg/kg) every 2 weeks of each 8-week treatment cycle, and could continue to get treatment for up to 2 years.

Antitumour activity was observed at all doses tested; however, the response was tumour-type specific. Although responses were seen in patients with NSCLC (14 out of 76 patients), melanoma (26 out of 94 patients) and renal cell cancer (9 out of 33 patients), no objective responses were reported in patients with colorectal cancer or castration-resistant prostate cancer.

"It's exciting to see this degree of antitumour activity from a single-agent among patients with a range of cancers that had progressed despite standard therapies," said Topalian. "We were especially surprised to see activity in nearly 20% of patients with lung cancer, who are historically unresponsive to immune-based therapies. These findings mark what is probably the strongest anti-lung cancer activity observed to date with any immunotherapy."

The maximum tolerated dose was not identified in the study and 86% of patients received 90% or more of the planned therapy. 5% of patients had to discontinue therapy because of treatment-related adverse events. In his discussion of the trial at ASCO, Giuseppe Giaccone noted that the therapy seems to be better tolerated that ipilimumab, but severe pneumonitis is of concern.

In a subset analysis, pre-treatment tumor biopsies from 42 patients were analysed for PD-L1 expression on the surface of the tumour cells using immunohistochemistry. 36% of those patients who tested positive for PD-L1 had an objective response, but no objective responses were seen in those who tested negative. Although these early results in a relatively small subset of patients warrant further study, this finding offers the tantalizing possibility of a predictive biomarker for this agent.

The second study assessed the PD-L1 targeting antibody in 207 patients with NSCLC, melanoma, colorectal cancer, pancreatic cancer, gastric cancer or breast cancer. Of the treated patients, 86% had received prior chemotherapy and 28% had received immunotherapy or biological therapy. Patients were treated with an intravenous infusion of the antibody (0.3, 1, 3 or 10 mg/kg) on days 1, 15 and 29 of each 6-week cycle for up to 16 cycles. Clinical activity was seen at all doses of 1 mg/kg or higher, and objective responses were seen in patients with melanoma (9 out of 52 patients), NSCLC (5 out of 49 patients), renal cell cancer (2 out of 17 patients) and ovarian cancer (1 out of 17 patients). As observed in the other study, the response in patients with NSCLC was unexpected and very promising. The maximum tolerated dose was also not reached in patients receiving the anti-PD-L1 antibody, and 6% of patients discontinued therapy because of treatment-related adverse effects.

Clearly, these two drugs would likely be efficacious in similar patient populations. Although they have not been compared directly, the authors did state that "the frequency of objective responses for anti-PD-L1 antibody appears to be somewhat lower than that observed for the anti-PD-1 antibody in initial trials." It remains to be seen how they will compare in further clinical trials—the results of which will be awaited with interest.

Rebecca Kirk

Original articles and abstracts Brahmer, J. R. *et al.* Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N. Engl. J. Med.* doi:10.1056/NEJMoa1200694 | Topalian, S. L. *et al.* Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N. Engl. J. Med.* doi:10.1056/NEJMoa1200690 | Topalian, S. L. *et al.* Anti-PD-1 (BMS-936558, MDX-1106) in patients with advanced solid tumors: clinical activity, safety, and a potential biomarker for response [abstract]. *J. Clin. Oncol.* **30** (Suppl.), CRA2509 (2012) | Brahmer, J. R. *et al.* Clinical activity and safety of anti-PD1 (BMS-936558, MDX-1106) in patients with advanced non-small-cell lung cancer (NSCLC) [abstract]. *J. Clin. Oncol.* **30** (Suppl.), a7509 (2012)