Editorial

# Avelumab: another active immune checkpoint inhibitor in non-small cell lung cancer

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Inhibitors of the immune checkpoints PD-1 and PD-L1 have changed the standard of care and clinical outcome of patients with many cancer types. For example, patients with advanced non-small cell lung cancer (NSCLC) were traditionally treated with chemotherapy with or without anti-angiogenic agents if their tumors did not carry actionable driver mutations. The use of immune checkpoint inhibitors provided additional options, in both the first-line and second-line settings, for these patients with clinically significant, often durable responses and prolonged survival. Nivolumab, an anti-PD-1 antibody, has been approved for both advanced non-squamous and squamous NSCLC in the second-line setting, after it demonstrated superior overall survival to docetaxel in large randomized phase 3 trials (1,2). Pembrolizumab, another anti-PD-1 antibody, has been approved for previously treated, PD-L1 positive, advanced NSCLC (3). The same applies to atezolizumab, an anti-PD-L1 monoclonal antibody (4). In addition, pembrolizumab also received regulatory approval as first-line therapy for PD-L1 positive NSCLC (5). The combination of pembrolizumab and carboplatin/pemetrexed as first-line therapy for non-squamous NSCLC has also demonstrated superior response rate and progression-free survival to chemotherapy alone, and is approved for use in the US (6).

Avelumab is a human immunoglobulin G1 anti-PD-L1 antibody. In addition to its inhibition of interaction between PD-L1 and its receptor PD-1, unlike other approved anti-PD1 or anti-PD-L1 antibodies, avelumab has an IgG1 Fc region which allows avelumab to engage with natural killer cells and induce antibody-dependent cell-mediated cytotoxicity *in vitro* (7). It was recently approved for patients with chemotherapy-refractory metastatic Merkel cell carcinoma (8). In a recent issue of *Lancet Oncology*, Gulley and colleagues reported a multicenter, open-label, phase 1b trial of avelumab for patients with previously treated metastatic or recurrent NSCLC (9). This was a dose-expansion cohort of a dose-escalation phase 1a trial (JAVELIN solid tumor) after avelumab demonstrated antitumor activity with an acceptable adverse event profile in patients with advanced solid tumors (10). A total of 184 patients with confirmed stage IIIB or IV NSCLC and ECOG performance status of 0 or 1 were enrolled in this study. Patients received 10 mg/kg avelumab administered intravenously every 2 weeks until disease progression or unacceptable toxicity. The dose of avelumab used in this study was chosen based on its pharmacokinetics, target occupancy, and immunological analysis, although maximum tolerated dose was not reached in the dose-escalation phase 1a trial (10). The primary endpoint of this study was toxicity and tolerability and secondary end points included response rates, progression-free survival, and overall survival.

The safety profile of avelumab in this study was comparable to other approved anti-PD-1 and anti-PD-L1 agents, except for infusion-related reactions, which were more common. The rate of any treatment-related adverse events and those attributed to immune-related causes from avelumab were 77% and 12%, respectively. These

were similar to pembrolizumab in the KEYNOTE-001 trial (11), nivolumab in its phase 1 dose-escalation cohort expansion trial (12), and atezolizumab in the phase 2 BIRCH trial (13) for patients with advanced NSCLC. Among these treatment-related adverse events, grades 3 to 5 toxicities were rare (12% of any event and 2% of immune-related event). However, infusion-related reactions of any grade were 21%. This rate is similar to what was seen in the Merkel cell carcinoma study (8), but is significantly higher than the 3% seen with pembrolizumab and 5% with nivolumab in the phase 1 setting for advanced NSCLC (11,12). Most of the infusion reactions occurred after the first two infusions and were mild to moderate in severity. They did not lead to treatment discontinuation with modern supportive care (9). This observation is perhaps due to the unique construct of avelumab which will be further characterized in large ongoing phase 3 trials.

In terms of efficacy, 22 (12%) of 184 patients had objective responses with one complete response and 50% of the patients achieved disease control. The majority of responding patients (83%) still had an ongoing response at the time of data analysis (9). Progression-free survival was 11.6 weeks and overall survival was 8.4 months. These results would appear to be inferior to those reported in previous large phase 3 trials of pembrolizumab, nivolumab, and atezolizumab in the same setting (1,4,7). However, patients enrolled in this study were more heavily pretreated with 33% of them having received two or more lines of therapy. More importantly, these efficacy results are comparable to those observed in early phase trials of other approved immune checkpoint inhibitors. For example, the overall response rate of advanced NSCLC to pembrolizumab was 18% in previously treated patients with median progression-free survival of 3 months and overall survival of 10.4 months (11). In the phase 1 trial of nivolumab in advanced NSCLC, the overall response rate was 17% with overall survival of 9.9 months (12).

Previous studies on anti-PD-1 and anti-PD-L1 antibodies in advanced NSCLC have attempted to select patients using predictive biomarkers to improve patient outcomes. Predictive biomarkers that have been studied include PD-L1 expression on either tumor cells or tumor-associated immune cells, and tumor mutational burden. Pembrolizumab, for example, was approved as a single agent for first- and second-line therapy only for patients whose advanced NSCLC has high PD-L1 expression on the tumor cells (3,5). In the present study, a novel anti-PD-L1 rabbit monoclonal antibody clone 73-10 was used to evaluate PD-L1 expression on tumor cells and tumor-associated immune cells. Patients were categorized into subgroups with a grading system composed of three different cutoff points 1%, 5%, or 25% for PD-L1 positivity of tumor cells and 10% cutoff for tumor-associated immune cells (9). Exploratory post-hoc subgroup analyses demonstrated essentially similar response rates and survival independent of patient characteristics, number of previous lines of therapy, PD-L1 expression on either tumor cells or tumor-associated immune cell. It is worth pointing out that 122 (86%) of the 142 evaluable patients had ≥1% PD-L1 expression on their tumor cells, significantly higher than approximately 50% reported in other studies (1,11). Perhaps, clone 73-10 is more sensitive compared to other analytically similar clones 22C3, 28-8, and SP263 (14). Thus, the heterogeneity of PD-L1 expression assays makes the interpretation of statistically significant longer median progression-free survival observed in the PD-L1 ≥1% group more difficult when compared across the studies (9).

In summary, this phase 1b dose-expansion trial of avelumab demonstrated its safety and efficacy in patients with previously treated advanced NSCLC. While it is hazardous to compare results across different clinical trials performed over different time periods, it is fair to say that the clinical results achieved with avelumab are similar to other checkpoint inhibitors. We await results from the ongoing phase 3 trials of avelumab compared with chemotherapy agents (NCT02395172, NCT02576574). It will be interesting to see if we can discern any differential activity of avelumab based on its associated antibody-dependent cell-mediated cytotoxicity. In addition to avelumab, another PD-L1 inhibitor, durvalumab is being studied in NSCLC. Regardless of their individual results, oncologists will not be able to come to any conclusions on relative toxicity and efficacy of these agents in the absence of head to head comparative trials. It is therefore incumbent on academic oncologists to start designing comparative trials to address issues such as comparative toxicity, efficacy and cost-effectiveness.

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## Footnote

*Conflicts of Interest*: The authors have no conflicts of interest

 

to declare.

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