Lung cancer is the most commonly diagnosed cancer worldwide (excluding non-melanoma skin cancer), with 1.8 million new cases diagnosed in 2012. In addition, lung cancer gives the leading figure in mortality from oncological illnesses both in the United States and worldwide (1).

In the last few years, a better understanding of the mechanisms by which tumor cells are able to escape the immune system and proliferate, grow and spread, has provided us with promising potential targets that may be used to attack cancers. More specifically, all immune checkpoints modulating the immune response against cancer cells have the potential to become therapeutic targets for many tumor types. Two of those targets are the programmed cell death 1 (PD-1) and its ligand (PD-L1) (2).

PD-L1, mainly expressed in tumor cells, binds to PD-1, an immune inhibitory receptor expressed by cytotoxic T cells. This interaction between PD-1 and PD-L1 inhibits T-cell activation impeding any lethal action against tumor cells. During the inflammation or during the immune response, PD-1-PD-L1 interaction is essential to prevent autoimmunity (3). These immune checkpoints provide a gateway through which tumor cells can escape immune surveillance, proliferate and spread to distant sites.

In fact, among the numerous immunotherapeutic strategies currently under investigation, monoclonal antibodies targeting PD-1 or PD-L1, have provided the most relevant clinical results against non-small cell lung cancer (NSCLC). These antibodies that bind to PD-1 (nivolumab and pembrolizumab) and PD-L1 (atezolizumab) have already been Food and Drug Administration (FDA) approved for patients with metastatic NSCLC based on their survival advantage and their safety profile (4).

One of the last PD-L1 inhibitors to access the market is avelumab (MSB0010718C), a fully human immunoglobulin G1 (IgG1) monoclonal antibody that specifically binds PD-L1 and inhibits its binding to PD-1 (5). Earlier this year, the US FDA granted accelerated approval to avelumab for the treatment of patients 12 years and older with metastatic Merkel cell carcinoma (MCC) based on the results of a multicenter, international, prospective, single-group, open-label, phase 2 trial, conducted in stage IV MCC chemotherapy-refractory patients (6). In that trial, Kaufman et al. showed a 32% objective response rate (ORR) including eight complete responses with a tolerable profile.

Other clinical trial testing avelumab across more than 16 different tumor types, both as monotherapy and in combination is the JAVELIN Solid Tumor trial. This trial included a dose-escalation part (phase 1a), and a dose-expansion part (phase 1b) comprising 16 different cohorts. The phase 1a, dose-escalation, open-label, single-center trial assessed four doses of avelumab (1, 3, 10, and 20 mg/kg), with dose-level cohort expansions to provide safety, pharmacokinetics, and target occupancy data (7). Fifty-three previously treated patients with solid tumors...
were enrolled (4 patients at 1 mg/kg, 13 at 3 mg/kg, 15 at 10 mg/kg, and 21 at 20 mg/kg). Also in this trial, avelumab showed an acceptable toxicity profile up to 20 mg/kg and the maximum tolerated dose was not reached. In addition, initial efficacy results showed that avelumab is associated with early responses (within 6 weeks) and durable responses across a range of tumor types, including NSCLC. Partial responses in 4 of 53 patients (8%) were observed. Thirty additional patients (57%) had stable disease. Based on pharmacokinetics, target occupancy, and immunological analysis, the 10 mg/kg every 2 weeks dose was chosen for further development.

Within the phase 1b of the JAVELIN trial, the first dose-expansion cohort to be reported comprised 184 eligible patients with histologically or cytologically confirmed stage IIIB or IV NSCLC, with squamous or non-squamous histology, which had progressed after treatment with platinum-based doublet chemotherapy for metastatic disease (8). Noteworthy, this represents the largest cohort of patients studied in a phase 1 trial of avelumab. Patients received intravenous infusion of avelumab monotherapy 10 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The primary objective was to assess safety and tolerability. Remarkably, patient selection was not based on PD-L1 expression or expression of other biomarkers including EGFR or KRAS mutation or ALK translocation status.

Avelumab showed a manageable safety profile and promising clinical activity in this population of pretreated metastatic, or recurrent NSCLC patients. Regarding its tolerability profile, fatigue (25%) and infusion-related reactions (19%) were the most frequent grade ≥3 adverse events. Among the treatment-related adverse events classified as immune-related hypothyroidism was the most frequently reported (6%), all graded as 1 or 2 (8).

Interestingly enough, responses occurred irrespective of PD-L1 expression status and in squamous and non-squamous tumors. The ORR was 12% including one complete response and 25 partial responses and disease control rate (DCR) was 50%. Although median progression-free survival (PFS) was 11.6 weeks according to RECIST v1.1, according to immune-related response criteria PFS increased up to 17.6 weeks. Median overall survival (OS) was 8.4 months (8). In line with the results previously shown by the only PD-L1 inhibitor approved for NSCLC after platinum-based chemotherapy (9), atezolizumab (OAK trial), the proportion of patients who achieved an objective response outcome did not differ between patients with PD-L1-positive versus PD-L1-negative tumors at any prespecified PD-L1 expression level. No significant differences were shown in terms of OS depending on PD-L1 expression either. Although at most cutoff levels for PD-L1 expression PFS outcomes showed no significant differences between PD-L1-positive and PD-L1-negative tumors, PFS was significantly longer in those individuals with PD-L1-positive tumors than in those with PD-L1-negative tumors in an analysis based on a 1% cutoff for tumor cell staining (8).

Obviously, relevant population characteristics differences such as prior number of anticancer therapy lines received for advanced disease between the population treated in the JAVELIN trial (8) and the OAK trial (9), impede any indirect comparison of the OS results in both trials. In fact, patients in the OAK trial had received a maximum of two previous lines of therapy (including the locally advanced setting) in 25% of the cases, whereas, those in the JAVELIN trial had previously received two or more active lines of treatment in the 33% of the cases, only for advanced disease.

Regarding the differential value of avelumab compared with other PD-L1 or PD-1 inhibitors, two aspects of the mechanism of action of this drug deserve additional discussion. Noteworthy, while avelumab inhibits PD-L1-PD-1 interactions, it leaves the PD-L2-PD-1 pathway intact, an aspect that results critical for allowing continuity of PD-L2-mediated homeostasis (10). On the other hand, avelumab results unique among its class members due to its potential to use both, adaptive and innate immune mechanisms to attack tumor cells (5,11). In fact, avelumab has a wild-type IgG1 fragment (Fc) region, which enables the drug to engage with Fc-c receptors on natural killer cells and induce tumor-directed antibody-dependent cell-mediated cytotoxicity (ADCC) in vitro (11). PD-L1 blockade with avelumab therefore has the potential to both enhance tumor-specific effector T cell activity and induce ADCC-mediated lysis of tumor cells. This particular characteristic makes avelumab unique among anti-PD-L1 or anti-PD-1 antibodies approved or in advanced clinical development (12).

Moreover, anti-PD-1 IgG4 antibodies and other anti-PD-L1 IgG1 antibodies have been intentionally developed to overcome ADCC, based on a hypothesis about the potential for ADCC to deplete activated T cells (13). Importantly enough, several preclinical and clinical studies showed minimal changes in immune cell subsets with avelumab treatment (14,15).
Nevertheless, despite the interesting antitumor activity shown by avelumab in patients with advanced pretreated NSCLC patients, this novel anti-PD-L1 compound still has a long pathway to walk in order to demonstrate its potential clinical utility and own personality, for the first and second line scenario in advanced NSCLC. Interestingly enough, the field has turned even more competitive since durvalumab, another selective, high-affinity, human IgG1 monoclonal antibody that blocks PD-L1 binding to PD-1 and CD80, demonstrated a significantly longer median time to death or distant metastasis compared to placebo, when administered as adjuvant therapy after definitive chemoradiation for stage III, unresectable, NSCLC (16). That is other clinical niche in which avelumab will have to show its clinical efficacy and safety in order to be able to compete with durvalumab.

Finally, some crucial questions need to be answered before being able to select the best checkpoint inhibitor, for the right patient, in the proper clinical setting. In the absence of head to head comparisons between drugs elucidating the potential supremacy of one of them among the others, other critical aspects will need a satisfactory answer. The central nervous system penetration and brain metastasis response rate of the different checkpoint inhibitors, the best synergies between them and with other cytotoxic drugs and therapeutic strategies such as radiotherapy, and the most precise predictive biomarkers are relevant questions that warrant further investigation.

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Footnote

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