Editorial

Second-line avelumab in platinum-treated non-small cell lung cancer patients: comment on the JAVELIN Lung 200 clinical trial

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Since the approval of nivolumab for the second line treatment of unresectable locally advanced (IIIB stage according to the current TNM staging system) or metastatic (IV stage according to the current TNM staging system) non-small cell lung cancer (NSCLC) (1) with progression on or after a platinum based chemotherapy in early 2015 (2), immunotherapy and specifically immune checkpoint inhibitors (ICIs) have revolutionized pulmonary oncology diagnostic and treatment algorithms and have become one of the most common drugs employed to treat this type of cancer.

In fact, according to the most recent ESMO and ASCO guidelines, three ICIs are approved for the treatment of nonsquamous or squamous-histology IIIB/IV stage NSCLC without any driver genes mutations (*EGFR/ALK/ROS1*): pembrolizumab, nivolumab and atezolizumab; more specifically, pembrolizumab should be used in monotherapy in a first-line setting for patients with a high PD-L1 expression (tumor proportion score ≥50%), or in a second-line setting after a first-line platinum-based chemotherapy for patients with a positive PD-L1 expression (TPS ≥1%), on the other hand, nivolumab or atezolizumab should be used in monotherapy in a second-line setting after a first-line platinum-based chemotherapy for patients with a positive (TPS ≥1%), negative or unknown PD-L1 expression (3,4).

These drugs exert their activity by blocking the PD-1-PD-L1 axis: PD-1 is a transmembrane receptor physiologically expressed on T-cells, while PD-L1 is a member of the B7 protein family, primarily expressed on APC, as a result of their binding, T-cells are inhibited (5); however, PD-L1 can also be expressed on cancer cells, that exploit this mechanism in order to avoid immunosurveillance (6). Therefore, by blocking PD-1 (nivolumab, pembrolizumab) or PD-L1 (atezolizumab), ICIs manage to prevent the immune inhibition and to enhance T cell-mediated tumor cells cytolysis (7).

Avelumab (MSB0010718C) is an anti PD-L1 (8) currently under investigation in different tumor types, NSCLC being one of them.

In a recent open-label phase III randomized trial (JAVELIN Lung 200), Barlesi *et al.* assessed the efficacy and safety of avelumab in patients with advanced NSCLC without any driver gene mutation that had already progressed on a first-line platinum-based chemotherapy. From March 2015 to January 2017, 792 patients were enrolled and randomly assigned (1:1) to receive either avelumab 10 mg/kg every two weeks (396 patients) or docetaxel 75 mg/m^2 every three weeks (396 patients), moreover, patients were stratified according to histology (squamous *vs.* nonsquamous) and most importantly to PD-L1 expression (≥1% *vs.* <1% of cancer cells), assessed with the PD-L1 IHC 73-10 pharmDx assay as a companion test, in addition, as a pre-planned exploratory analysis, PD-L1 positive patients were further stratified according to two higher PD-L1 expression cut-offs: ≥50% and ≥80%; overall survival (OS) was the primary endpoint, while progression free survival (PFS) and safety were among secondary endpoints (9).

As a result, Barlesi *et al.* found that median PFS didn't differ significantly between the treatment groups neither in the full analysis set population: 2.8 months in the avelumab group *vs.* 4.2 months in the docetaxel group (HR =1.16; P=0.95), nor in the primary analysis set population: 3.4 months in avelumab-treated patients *vs.* 4.1 months in docetaxel-treated patients (HR =1.01; P=0.53); similarly, median OS didn't differ significantly between the treatment groups neither in the full analysis set population: 10.5 months in the avelumab group *vs.* 9.9 months in the docetaxel group (HR =0.90; P=0.12), nor in the primary analysis set population: 11.4 months in avelumab-treated patients *vs.* 10.3 months in docetaxel-treated patients (HR =0.90; P=0.16).

However, in the subgroups of patients expressing PD-L1 in ≥50% or ≥80% of tumor cells, median PFS and median OS of avelumab-treated patients proved to be significantly longer than docetaxel-treated patients' ones; more specifically, with regard to the PD-L1 positive population at the ≥50% cut-off, median OS was 13.6 months in the avelumab group *vs.* 9.2 in the docetaxel group (HR =0.67; P=0.0053) and 17.1 in the avelumab group months *vs.* 9.3 months in the docetaxel group (HR =0.59; P=0.0022), with regard to the PD-L1 positive population at the ≥80% cut-off.

With respect to safety, avelumab was found to be associated with less treatment-related adverse events (TRAEs) when compared to docetaxel, in fact, TRAEs of any grade arose in 251 (64%) of all avelumab-treated patients, while they occurred in 313 (86%) of all docetaxel-treated patients, in a like manner, the number of grade 3/4 TRAEs was lower in avelumab-treated patients than docetaxel-treated ones: 10% *vs.* 49% and 2% *vs.* 22% of all treated patients, respectively. The most common any-grade TRAEs in the avelumab-treated population were infusion-related reaction and decreased appetite (17% and 9% of all treated patients, respectively), while the most common grade 3 or worse TRAEs were infusion-related reaction (2% of all treated patients) and increased lipase (1% of all treated patients), on the other hand, the most common any-grade TRAEs in the docetaxel-treated population were alopecia, anemia and decreased appetite (27%, 19% and 18% of all treated patients, respectively), while the most common grade 3 or worse TRAEs were neutropenia (14% of all treated patients), febrile neutropenia (10% of all treated patients) and decreased neutrophil count (10% of all treated patients).

On a side note, immune-related AEs arose in 17% of all avelumab-treated patients, rash, hypothyroidism and pneumonitis being the most common ones (6%, 5%, 2%, respectively); lastly, 28 (7%) patients in the avelumab group and 51 (14%) in the docetaxel group discontinued treatment due to TRAEs, while 16 (4%) avelumab-treated patients and 72 (20%) docetaxel-treated patients had to reduce the drug dosage due to TRAEs (9).

In the light of the above-mentioned data, the JAVELIN Lung 200 study didn't show any OS improvement when compared to docetaxel, thus failing to meet its primary endpoint and precluding, to date, its use in the second-line setting. In this regard, it is appropriate to analyze results from this trial in comparison with data from approved ICIs in the same setting: pembrolizumab, nivolumab and atezolizumab. In fact, all three of these drugs were compared to docetaxel in platinum-treated NSCLC-affected patients (KEYNOTE-010, CheckMate 017/057 and OAK trials, respectively), managing to show median OS improvements in PD-L1 positive patients (pembrolizumab) and both in PD-L1 negative and positive patients (nivolumab and atezolizumab), with a trend toward greater performances as PD-L1 expression level increases: median OS: 10.4 *vs.* 8.5 months (HR =0.71; P=0.0008), 9.2/12.2 *vs.* 6.0/9.4 months (HR =0.59/0.73; P<0.001/P=0.002) and 13.8 *vs.* 9.6 months (HR =0.73; P=0.0003), respectively (*Table 1*) (10-13).

One interesting point, that might have affected the Javelin Lung 200 clinical trial results, is related to the PD-L1 assessment performed using the PD-L1 IHC 73-10 pharmDx assay as a companion test, in fact, as discussed by the authors, the Blueprint Project evaluating the analytical performance of different PD-L1 assays has shown that the 73-10 assay has a higher sensitivity to detect PD-L1-positive tumor cells, with respect to other IHC PD-L1 assays, in particular with reference to 22C3 (Dako, Carpinteria, CA, USA) and SP142 (Ventana, Tucson, AZ, USA) assays (14). In addition, in a recent direct comparison of PD-L1 73-10 and 22C3 assays in NSCLC samples, 73-10 detected a higher proportion of PD-L1-positive tumors, in particular, using the 80% or greater cutoff it classified 24% of 148 commercial samples as PD-L1 positive, while 22C3 classified in the same way only 20% of these samples, moreover, adopting the 80% or greater cutoff for 73-10 and the 50% or greater cutoff for 22C3 the overlap percentage was 94%, emphasizing the differences between PD-L1 73-10 and 22C3 assays (15).

In conclusion, taking into account both clinical and IHC data, avelumab showed a favorable safety profile and

Table 1 II line immune checkpoint inhibitors in platinum-treated NSCLC patients

Trial	OS[†] (months)	HR	P value[§]
JAVELIN Lung 200, avelumab *vs.* docetaxel	10.5 *vs.* 9.9 (full analysis set population); 11.4 *vs.* 10.3 (primary analysis set population)	0.90 (full analysis set population); 0.90 (primary analysis set population)	0.12 (full analysis set population); 0.16 (primary analysis set population)
KEYNOTE-010, pembrolizumab *vs.* docetaxel	10.4 *vs.* 8.5	0.71	0.0008
CheckMate 017, nivolumab *vs.* docetaxel	9.2 *vs.* 6.0	0.59	<0.001
CheckMate 057, nivolumab *vs.* docetaxel	12.2 *vs.* 9.4	0.73	0.002
OAK, atezolizumab *vs.* docetaxel	13.8 *vs.* 9.6	0.73	0.0003

[†], Full analysis set population: all the patients assigned to avelumab or docetaxel; primary analysis set population: PD-L1 ≥1%; [§], P value: statistically significant results for P<0.05. NSCLC, non-small cell lung cancer; OS, overall survival; HR, hazard ratio.

clinical activity, especially at higher PD-L1 cutoffs (≥50% and ≥80% of tumor cells), in agreement with the already-mentioned trials in this same setting, supporting further investigation for its use in NSCLC-affected patients.

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