Commentary

Checkpoints inhibitors in first line therapy of metastatic non-small cell lung cancer patients

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Lung cancer is still the leader cause of mortality due to cancer worldwide (1,2). Five-year overall survival (OS) in unresectable and metastatic non-small cell lung cancer (NSCLC) patients (stage IIIB/IV) is less than 5%, regardless of the number of cytotoxic chemotherapy lines given (3). NSCLC is characterized for having different genetic and epigenetic alterations, where high rates of somatic mutations generate a variety of tumor specific antigens that enhance immunogenicity (4). Cancer is the result of the failure of different immunological mechanisms that attempt to eliminate cancer antigens that finally escape the immune system allowing tumor growth (5). Immunotherapy in a very short period of time not only became a reality but also achieved the most spectacular results ever in different types of cancer including NSCLC patients.

CTLA-4 was the first checkpoint targeted for cancer therapy. CTLA-4 is constitutively expressed in regulatory T Cells (Tregs) but only upregulated in conventional T cells after activation. The main role of this checkpoint is to maintain the self-tolerance (6). Anti-CTLA-4 antibodies limit the interaction between CTLA-4 and its receptor allowing the maintenance of the antitumor immune response. Ipilimumab was the first checkpoint inhibitor ever approved for cancer treatment, achieving unexpected prolonged OS in metastatic and melanoma patients (7). A phase 2 clinical trial with three arms in treatment naïve stage IIIB/IV NSCLC patients compared carboplatin/paclitaxel with the combination ipilimumab, either as concurrent (CT) or as a phased treatment (PT) was done. The primary end point of this clinical trial was immune-related progression free survival (irPFS) and it was reached only for the PT (HR: 0.72; P=0.05). OS was 8.3 months for the control arm, 9.7 months for the CT (HR: 0.99; P=0.48) and 12.2 months for PT (HR: 0.87; P=0,23). Subgroup analysis showed a trend of benefit for irPFS for squamous histology (SQCC) when compared with non-squamous histology (Non-SQCC) (8,9). Another anti CTLA-4 antibody, tremelimumab, was tested against placebo in a phase 2 trial for metastatic NSCLC. The primary end point: PFS was not reached and objective response rate (ORR) was only 4% (10). There is not a validated biomarker for response to anti CTLA-4 treatment. Pretreatment levels of VEGF have been associated with OS in melanoma patients treated with ipilimumab (11); however there is not strong data that supports the use of any biomarker as prognosis of outcome in NSCLC patients under treatment with an anti CTLA-4 antibody.

Cell death protein—programmed 1 molecule (PD-1) is expressed in different immune-related cells such as T and B lymphocytes, natural killer cells, and myeloid derived suppressor cells. Its main function is to limit the activity of T cells in peripheral tissues. NSCLC and other cancer cells express high levels of a ligand for PD-1 (PD-L1) suggesting that PD-1/PD-L1 pathway activation is a major mechanism used by cancer tumors to avoid immune surveillance (12). Anti-PD-1 drugs have been the most important developed immunotherapy treatment against NSCLC patients in the current times. The first anti PD-1 antibody in obtaining

approval for metastatic NSCLC was nivolumab, a fully human immunoglobulin G4 (IgG4) monoclonal antibody specific for human PD-1 (13). The phase 1 clinical trial, CA 209-003 included 122 NSCLC patients (73 non-SQCC, 47 SQCC and 2 unknown). Eighty five percent of the patients had received at least two prior lines of treatment. Forty two samples were analyzed for PD-L1 expression, none of the 17 patients that had no expression for PD-L1 in their tumors achieved an ORR, but 36% of the patients that had positive PD-L1 expression had ORR (14). An updated publication based in the expansion cohort focused in NSCLC showed a median OS of 9.9 months with PFS of 2, 3 months, 1-year survival 42%, 2-year survival 24% and 3-year survival 18% respectively. The reported ORR was 17% (15).

Checkmate 063 was a single arm phase 2 trial that evaluated nivolumab treatment every 2 weeks in SQCC metastatic patients that had received at least two previous lines of treatment. The ORR was achieved in 14.5% of the patients with a median duration of response (MDR) not reached. One-year PFS was 20%, 1-year OS was 40.8% and median OS 8.2 months (16). With a cut off of 5% (PD-L1 expression higher or lower than 5%), partial responses (PR) and stable disease (SD) were seen in the 24% and in the 24% of patients with PD-L1 expression higher than 5% and in the 14% and 20% of patients with PD-L1 expression lower than 5% respectively. Checkmate 017 was a phase 3 trial comparing nivolumab and docetaxel, focused in SQCC patients stage IIIB/IV that had failed to a first line platinum doublet. The primary end point of this study was OS and it was positive (9.2 months for nivolumab *vs.* 6 months for docetaxel). ORR and MDR were higher for nivolumab arm. PD-L1 expression was evaluated by an immunohistochemical (IHC) assay, Dako North America from rabbit monoclonal antihuman (Clone 28-8, Epitonics). There were three pre-specified levels: 1%, 5% and 10%, any positive staining with at least 1% of expression was considered positive and authors concluded that PD-L1 expression was neither prognostic nor predictive of benefit for nivolumab treated patients (17). Despite this comment when analyzing the graphics of this publication, it is possible to observe that patients with PD-L1 expression of at least 10% have a greater benefit when compared with 5% and 1% PD-L1 expression subgroups, something similar is observed when compared the 5% PD-L1 expression subgroup have a greater benefit that the 1% PD-L1 expression.

FDA approved nivolumab in March 2015 for SQCC that had failed to a first line of chemotherapy platin-based doublet. In October 2015, nivolumab was approved too by FDA for non-SQCC pretreated patients based on the results of Checkmate 057, a phase 3 trial with similar design, primary and secondary end points than Checkmate 017 and that compared nivolumab and Docetaxel in non-SQCC. Median OS was 12.2 months for nivolumab and 9.4 months for docetaxel arm. PD-L1 expression was predictive of outcome for all the end points. Current and former smokers and KRAS mutated patients also had a greater benefit if used nivolumab (18). Update of 2-year overall survival in Checkmate 017 was 23% for nivolumab *vs.* 8% for docetaxel SQCC treated patients. Two-year OS for non-SQCC NSCLC patients from Checkmate 057 was 29% for nivolumab and 16% for docetaxel respectively (19).

We review here Checkmate 012 that is a multi-arm phase 1 trial that assesses nivolumab in the first line of treatment in NSCLC patients as monotherapy or in combination with standard chemotherapy, bevacizumab, erlotinib or ipilimumab. Preliminary results from the nivolumab plus standard chemotherapy arm have shown promising results in special when combining nivolumab 5 mg/kg with carboplatin/paclitaxel doublet arm that achieves a 2-year survival of 62% (20). Now the results from Checkmate 012 nivolumab monotherapy arm have been recently published (21). Grade 3–4 toxicity was reported in the 19% of patients. Reported ORR was 23%, 28% in PD-L1 positive expression and 14% in PD-L1 negative expression patients. Median OS was 19.4 months, and 12 and 18 months OS was 73% and 58% respectively (21). Checkmate 012 has also assessed the combination of nivolumab plus ipilimumab in different schedules. Depending of the dose ORR ranged between 13% and 39%, DCR ranged between 50% and 74%, grade 3–4 toxicities in some of the arms ranged between 33% and 37%. When analyzing one of the arms of this part of this trial, patients with PD-L1 expression greater than 50% achieved response rate of 50–92% (22).

This data is promissory about the opportunity to move nivolumab to the front line however we needed phase III data and in that regard unpublished data from Checkmate 026 has just been presented at ESMO. This was a phase 3 clinical trial that compared head to head nivolumab and standard chemotherapy in the first line of metastatic NSCLC patients that have a PD-L1 expression of 1% or greater. The primary end point of the trial was PFS in patients that have a PD-L1 expression of 5% or greater. Unexpectedly, results from this trial showed a lower PFS (4.2 months) for nivolumab compared with chemotherapy (PFS 5.9 months) (23). The reasons of these disappointed results are under revision but probably might be related

with the chosen cut off point for PD-L1 expression in tumor cells (TCs) that could theoretically show a real positive impact in the treated population. On top of that things are more complicated for nivolumab, we have already data from pembrolizumab being successful for NSCLC not only for second line but for front line as we can see with the data from Keynote 001/012/021 and especially 024 that got the front line approval (24-30).

Pembrolizumab is a selective IgG4 kappa isotype monoclonal antibody against PD-1 that binds PD-1 and blocks PD-1, PD-L1/PD-L2 pathway (24). Keynote 001 trial was a phase 1 study that included metastatic or advanced NSCLC patients and was assigned to multiple expansion cohorts. PD-L1 expression was assessed by IHC 22C3 antibody. Grade 3 or higher toxicity was reported in the 9.5% of patients. The ORR was 19.4% for all the patients, 18% for previous treated and 24.8% for untreated patients. ORR was also higher in current and former smokers (22.5%) when compared with never smokers (10.3%). Patients with PD-L1 expression of >50% achieved an ORR of 45.2% when compared with lower PD-L1 expression. Median OS was 9.3 and 16.2 months for previous treated and for untreated patients respectively (25). In patients with PD-L1 expression of 1–49% the median OS was 11.3 months in previous treated patients and 22.1% in untreated patients. These results were better in patients with PD-L1 expression of 50% or higher with a median OS of 15.4 months in previous treated patients and still not reached for untreated patients (26). Based on these results FDA approved pembrolizumab as treatment for metastatic NSCLC patients that failed to a first line and that express PD-L1 in TCs. Keynote 010 was an open label phase 2–3 trial that compared pembrolizumab in two different doses with docetaxel in NSCLC patients that failed to at least one prior line of platinum doublet based chemotherapy and that expressed at least 1% of PD-L1 in TCs. Primary end points were OS and PFS in the total population and in the population that expresses PD-L1 50% or higher. Median OS was 10.4 months for the pembrolizumab 2 mg/kg arm, 12.7 months for the pembrolizumab 10 mg/kg arm and 8.5 months for the docetaxel arm. Patients treated with pembrolizumab that expressed PD-L1 50% or higher achieved a median OS of 14.9 months in 2 mg/kg arm and 17.3 months for the 10 mg/kg arm. ORR was also higher in the pembrolizumab arms when compared with docetaxel (27). An update of this trial showed a greater benefit in OS, PFS and ORR in patients with PD-L1 expression of 75% or higher (28).

Recently, two publications have shown the efficacy of pembrolizumab: Keynote 021 is a phase 2 multicohort study for stage IIIB/IV non-SQCC patients that combined pembrolizumab with carboplatin/pemetrexed doublet and compared this combination with the doublet without pembrolizumab and it was stratified by PD-L1 status (≥1% or <1%). The primary end point was ORR that was 55% for the study arm and 29% for the chemotherapy arm (P=0.0016); 17% of the patients treated with chemotherapy alone but only 3% of the study arm had PD as the best response. In the pembrolizumab plus chemotherapy arm no differences in ORR were seen when comparing PD-L1 with 1% or greater or less than 1%, however greater ORR were observed in patients that expressed PD-L1 higher than 50%. PFS was higher for the combination arm than for chemotherapy alone arm (13 *vs*. 8.9 months; P=0102). No significant differences in OS were reported at 1-year follow-up. Toxicity grade 3 or greater was similar in both groups (29). Of great impact have been the results from Keynote 024, this is a phase 3 trial for NSCLC metastatic patients with a PD-L1 expression of at least 50% that compared pembrolizumab with a platinum based doublet as a first line of treatment. The primary end point was PFS that was 10.3 months in the pembrolizumab arm and 6 months in the chemotherapy arm (HR: 0.5; P<0,001). One-year overall survival was 70% in the pembrolizumab arm and 54% in the chemotherapy arm. This significant benefit was observed despite that there was crossover of 50% of patients from chemotherapy to pembrolizumab (HR: 0.6). ORR was also higher for the pembrolizumab arm when compared with chemotherapy arm (45% and 28% respectively; P=0.0011) (30).

Why the different results from Checkmate 026 and Keynote 024? It's hard to know if we believe that both agents are similar then the answer maybe is in the PD-L1 testing and the accuracy or reliability of the antibodies? Before we go there we also have to remember that more checkpoint inhibitors are making their way to the clinic because there is another strategy to fight lung cancer with immunotherapy that is the PD-L1 blockade by using monoclonal antibodies too (31). Durvalumab for example is a human IgG1 that selectively blocks PD-L1. In a phase 1–2 trial in NSCLC metastatic patients the ORR for durvalumab was 14% in the global population and 23% in patients that expressed PD-L1 (32). Also, durvalumab, in combination with an anti-CTLA-4 antibody, tremelimumab, achieved 17% of ORR including 5% of responses in patients with negative PD-L1 expression (33). Atezolizumab, is another

human IgG1 monoclonal antibody against PD-L1. The phase 2 clinical trial BIRCH assessed the safety and efficacy of atezolizumab in NSCLC patients that express PD-L1. PD-L1 status was assessed by an IHC assay developed by Roche Diagnostics that measures TCs and tumor infiltrating immune cells (ICs). Eligible patients for this trial were who had TC 2/3 or IC 2/3. The primary end point was ORR. Patients that scored TC3/IC3 had higher ORR than patients that presented TC2/3 or IC 2/3 in the first line (26% *vs*. 19%), second line (24% *vs*. 17%) and third line or further of treatment (27% *vs*. 17%) (34). POPLAR trial was a phase 2 study that compared atezolizumab *vs*. docetaxel in local advanced or metastatic NSCLC that progressed after a first line of treatment, regardless of the PD-L1 status. A recent update of POPLAR trial shows a further separation of curves with improve in OS when atezolizumab is compared with docetaxel (ITT median OS 12.6 months *vs*. 9.7 months (P=0.011); TC3 or IC3 median overall survival not reached *vs*. 11.1 months (P=0.033). By histology median OS favors atezolizumab for both squamous and non-squamous patients over docetaxel (35). FDA approved in October 2016 atezolizumab as a second line of treatment for metastatic NSCLC that failed to a first line platinum based doublet chemotherapy, becoming the first anti PD-L1 antibody to get approval in this group of patients. Avelumab, another anti PD-L1 drug is under assessment in a phase 3 clinical trial for metastatic NSCLC that had disease progression after a platin base doublet.

Going back to the current differences among checkpoint inhibitor results there are several questions that have not been answered or that do not have a clear explanation yet, most of them related with the PD-1 expression and with the outcomes in clinical trials that assess anti PD-1 and anti PD-L1 drugs. More complicated is to try to compare different trials that used different assays to measure PD-L1 expression. The blueprint proposal for companion diagnostic comparability is trying to resolve this issue making a call to the pharmaceutical companies that are involved with these types of drugs, in order to homogenize a common biomarker or a common assay to evaluate PD-1 expression in a useful manner to all patients regardless of any eventual selective drug to be used (36). Despite of the lack of a mechanism to compare those different trials because the diversity of PD-1 assays there are some conclusions than can be done: there are disparities in results according to PD-1 expression and outcomes in clinical trials when combining an anti PD-1 drug with chemotherapy or with an anti CTLA-4 drug. It has been demonstrated that immunotherapy has action in PD-1 negative patients but not in the magnitude of PD-1 positive patients, however this activity is not limited to only PD-1 positive patients. Probably the release of antigens due to tumor necrosis that underwent chemotherapy activates immune system and enhances the power of immunotherapy? Also outcomes in combining an anti PD-1 with an anti CTLA-4 might be increased by synergism of different immune-response mechanisms. In melanoma patients that have been treated with nivolumab in combination with ipilimumab it has been observed that the greater impact in PFS has been observed in patients that not express PD-1 in their TCs. This issue must be reviewed in NSCLC in order to select better patients and treatments.

Also two anti-PD-1 and one anti-PD-L1 antibodies have been approved for second line NSCLC metastatic patients as monotherapy treatment. Pembrolizumab and atezolizumab have clearly demonstrated benefit in patients that express PD-1 in the tumors. Both treatments have a correlation in their outcomes depending of the PD-1 expression. Nivolumab got approval regardless if the positive or negative PD-1 expression, nevertheless it seems to be a trend to better outcomes depending of the PD-1 expression.

Finally in the first line of treatment for NSCLC metastatic patients nivolumab failed in its primary end point (PFS in patients that expressed 5% PD-1 or greater in TCs). There is not a clear answer for this negative result, however, probably the correct cut off point for PD-1 expression was missed without discard that the IHC assay to assess PD-1 could be overestimated? Pembrolizumab was approved for first line NSCLC metastatic patients with high PD-1 expression on October 24, 2016 becoming the first immunotherapy drug to be ever approved as monotherapy for NSCLC. The trial that lead to this approval had a design that selected a restricted population that demonstrated the importance of PD-1 as a prognostic biomarker when pembrolizumab is used. I know that we are opening more questions than answers but there is many more to come in the short-term in the following months in the field of immunotherapy for NSCLC.

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Footnote

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