Editorial

PACIFIC trial: new perspectives for immunotherapy in lung cancer

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Lung cancer still represents the most frequent cause of cancer-related mortality worldwide and 85% of all lung neoplastic disease are classified as non-small-cell lung cancer (NSCLC) (1); approximately one third of NSCLC are locally advanced disease at diagnosis (2). Actually, the standard-of-care for unresectable or inoperable stage IIIA and IIIB disease for patients with good performance status consists of platinum-based doublet chemotherapy (CT) concurrent with 60 Gy of radiotherapy (RT) administered daily over 6 weeks followed by possible further two cycles of consolidative CT (2). The supportive evidence for the use of concomitant chemoradiotherapy (CT/RT) is rooted in many clinical trials, with evidence of better results of concurrent CT/RT compared to either modality of administration of CT and RT, alone or sequential (3). The 5-year overall survival (OS) rate is 15–35% for stage IIIA and 5–10% for stage IIIB (4). Although survival outcomes are poor, notable is that a subset of the patients are potentially curable.

Immunotherapy has recently emerged as a promising therapeutic strategy for NSCLC, including immune checkpoint inhibitors, dendritic cell and peptide vaccines, adoptive T-cell transfer, oncolytic viruses and cytokine therapy. To evade host immune surveillance, cancer cells induce the inhibition of the immune system function through inhibitor pathways such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) or programmed-cell death 1 (PD-1) and its ligand (PD-L1). Thus, the immune response mediated by tumor-infiltrating lymphocytes is blocked, allowing the tumor cells proliferation (5). In 2015, two immune checkpoint inhibitors targeting PD-1, nivolumab and pembrolizumab, were approved for second-line treatment of advanced NSCLC. In 2016, the PD-L1-inhibitor atezolizumab received approval for the same indication. In 2016, pembrolizumab was approved by the Food and Drug Administration (FDA) in the first-line setting as a monotherapy for patients with NSCLC whose tumors have high PD-L1 expression (tumor proportion score TPS ≥50%) and in combination with CT (pemetrexed-carboplatin) for the treatment of patients affected by metastatic non-squamous NSCLC, regardless of PD-L1 expression levels.

Durvalumab (MEDI4736) is a selective, high-affinity, engineered human immunoglobulin IgG1 kappa monoclonal antibody that blocks the interaction of PD-L1 with PD-1 (IC_{50} 0.1 nM) and CD80 (IC_{50} 0.04 nM); as results of the blockade of PD-L1/PD-1 and PD-L1/CD80 interactions, the immune response is significantly reduced (6). Actually, durvalumab is approved in other oncological fields than lung cancer, in particular for the treatment of patients with locally advanced or metastatic urothelial carcinoma with disease progression during or following platinum-containing CT or within 12 months of neoadjuvant/adjuvant treatment. Regarding lung cancer, in a phase I/II study of durvalumab monotherapy (NCT01693562, "ATLANTIC") (7), encouraging durable antitumor activity was observed in patients affected by advanced pretreated NSCLC, together with a manageable toxicity profile [grade (G) 3/4 adverse events (AEs) in 8% of patients, AEs leading to discontinuation in 5%]. Confirmed

objective response rates (ORRs) with durvalumab 10 mg/kg every 2 weeks (q2w) were higher in patients with PD-L1 TPS ≥25% tumors [27%; 95% confidence interval (CI), 18.2–38.2] versus tumors with PD-L1 TPS <25% (5%; 95% CI, 1.8–12.2). A phase Ib study combining durvalumab with tremelimumab in patients with advanced NSCLC (NCT02000947) (8) demonstrated antitumor activity regardless of PD-L1 status, including in patients with PD-L1 TPS 0. In the combined durvalumab 10 to 20 mg/kg q4w or q2w plus tremelimumab 1 mg/kg patient cohort, 30% of patients had G3/G4 drug-related AEs, and 16% discontinued treatment owing to drug-related AEs. Confirmed ORRs were 2 of 9 (22%; 95% CI, 3–60) in patients with PD-L1 TPS ≥25% tumors versus 4 of 14 (29%; 95% CI, 8–58) in patients with PD-L1 TPS <25%. In the subpopulation of patients with PD-L1 negative tumors (0% staining), confirmed ORR was 4 of 10 (40%; 95% CI, 12–74). From these data, the durvalumab 20 mg/kg plus tremelimumab 1 mg/kg dose was selected for the ongoing phase III trials both in first-line setting (NCT02453282, "MYSTIC") and in further therapeutic lines (NCT02352948, "ARCTIC") (9).

The "PACIFIC" trial (NCT02125461) (10) was a randomized, double-blind, phase 3 study comparing consolidation therapy with durvalumab versus placebo in patients with stage III, locally advanced, unresectable NSCLC that had not progressed after the standard treatment for stage III NSCLC (platinum-based CT/RT). A previous analysis (11) was performed to assess preliminary safety and efficacy of durvalumab in combination with RT in an expansion cohort of patients included in a phase 1/2 trial (12); 5 patients (50%) reported an irradiation-related AE G1/G2 and one patient had two G2 AEs. The most frequently reported AE (3/6) was G2 mucositis; there was no G3 or more RT-related AEs. All AEs were transient, lasted less than one week, and were manageable by standard guidelines. On 10/15 in-field (IF) evaluable lesions, the ORR was 60%. Authors concluded that in the small data set of patients concurrent palliative RT with durvalumab was well tolerated. In the "PACIFIC" trial patients were randomly assigned, in a 2:1 ratio, to receive durvalumab (at a dose of 10 mg/kg intravenously) or placebo q2w for up to 12 months; durvalumab administration started 1 to 42 days after the conclusion of CT/RT. The coprimary endpoints were PFS and OS; the secondary endpoints were 12- and 18-month PFS rates, ORR, duration of response, time to death or distance metastasis and safety. A total of 713 patients were randomized, 709 received consolidation therapy; of them 473 patients (66.7%) received durvalumab and 236 (33.3%) received placebo. The study met first primary endpoint, with a median PFS of 16.8 months (95% CI, 13.0–18.1) versus 5.6 months (95% CI, 4.6–7.8) with durvalumab and placebo respectively [hazard ratio (HR): 0.52, 95% CI, 0.42–0.65; P<0.001]; OS results were not yet available at the time of this ad interim analysis. The 12-month PFS rate was 55.9% versus 35.3%, and the 18-month PFS rate was 44.2% versus 27.0%. The ORR was 28.4% versus 16.0% (P<0.001) with durvalumab and placebo respectively, and also the median duration of response was longer (72.8% versus 46.8% of the patients had an ongoing response at 18 months). The median time to death or distant metastasis was 23.2 versus 14.6 months (P<0.001) with durvalumab and with placebo respectively. G3/G4 AEs occurred in 29.9% and 26.1% of patients who received durvalumab and placebo respectively; the most common G3/G4 AE was pneumonia (4.4% and 3.8%, respectively). Discontinuation of the study drug because of toxicity occurred in a total of 15.4% of patients in the durvalumab group and 9.8% of those in the placebo group; the most frequent AEs leading to discontinuation of treatment were pneumonitis or radiation pneumonitis (in 6.3% and 4.3% respectively) and pneumonia (in 1.1% and 1.3% respectively). Immuno-mediated AEs of any grade were reported in 24.2% of patients treated with durvalumab and 8.1% of patients who received placebo; G3/G4 immune-mediated AEs were reported in 3.4% and 2.6% of patients respectively. The most frequent immune-related AEs were pneumonitis (in 10.7% and 8.1% respectively) and hypothyroidism (in 9.3% and 1.3% respectively). In conclusion, PFS was significantly longer with durvalumab than with placebo and safety was similar between the groups.

Association of immunotherapy with the well-established regimen of CT/RT as standard treatment could potentially improve therapeutic outcomes for unresectable NSCLC. While NSCLC is typically considered relatively non-immunogenic, RT may induce some tumor modifications with consequent increased tumor immunogenicity (13). It's well known than RT may induce tumor cell death through DNA damage. Moreover, radiation therapy effects are mediated also by the immune system, with the induction of tumor cell death in the radiation field (14). With regard to combining radiation and immunotherapy, two different topics have to be assessed: first, the immunological effects of radiation for itself; second, the effects of combination therapy (immunotherapy and radiation therapy) on local

disease control (radiosensitizing immunotherapy) and on systemic disease control (abscopal effect) (15).

Regarding the first topic, the upregulation of the major histocompatibility complex (MHC) class I represents one of the most important way by which radiation can enhance immune responses and consequently the efficacy of any immunotherapy. Another mechanism of RT-related improved immune response is the increase in the release of HMGB1 and in the surface expression of calreticulin. Both HMGB1 and calreticulin are essential for the antigen-specific T immune response and are also involved in dendritic cell activation. Furthermore, radiation induces upregulation of FAS, a programmed cell death inductor, and the binding with its ligand (FAS-L), expressed by nearby immune cells. It was also reported the increase of the lymphocytes tumor-infiltrate after irradiation; radiation therapy induces changes in the vascular endothelium and consequently this infiltrate is generated by increased immune cell extravasation; furthermore, radiation increases expression of chemokine like E-selectin and ICAM, with consequently enhanced immune-cell migration and invasion. Radiation therapy may also have a regulatory effect on the expression of immune checkpoint ligands, such as PD-L1, on the surface of tumor cells through γ-interferon derived from CD8 T cells. Treg cells tumor infiltrate can also be increased after radiation, through increased TGF-β secretion; one of the function of the Treg cells is downregulating cells for adaptive and induced immune response; increased Treg cells in tumor microenvironment represents a counterbalance to radiation-induced immune activation.

Regarding the second topic, it was demonstrated that combination of radiation and a checkpoint blockade immunotherapy induces a significant increase in locoregional tumor control, with a synergistic effect in this setting, both with anti-CTLA-4 and anti-PD-1 antibodies (radiosensitizing immunotherapy) (16,17). In particular, it was demonstrated an increase of the PD-L1 levels in the tumor microenvironment after tumor irradiation in mice, with consequent increased tumor sensitivity to a PD-L1 inhibitor added to irradiation; in this effect is also involved a reduction of tumor-infiltrating myeloid suppressor cells and increase in TNF-α released form CD8 T cells. Many murine studies using combination therapy between radiation and immune checkpoint inhibitors have shown that it is possible to achieve also a distant and persistent disease control, which probably is also immune-mediated. The mechanism of this phenomenon, defined as abscopal effect, is unknown, but preclinical models suggest that it results from immunogenic cell death induced by local RT and results in improvement of systemic immune function (15).

Combination of immunotherapy with RT and CT/RT could represent a new treatment option for clinicians; consequently, it will be mandatory to evaluate also timing, radiation doses, fractionation and safety among these combined therapies. Concomitant administration of immune-checkpoint inhibitors and radiation seems to be better than starting checkpoint blockade immunotherapy after the end of radiation therapy; single fraction radiation seems to be better than multiple fractions (18) and hypofractionated radiation (5–20 Gy per fraction) is thought to be better than conventionally fractionated schemes of 1.8–2.2 Gy fractions (16,17).

The "PACIFIC" trial evaluates the activity and safety of durvalumab administered after combined CT/RT treatment was completed in patients affected by stage III NSCLC. In this case immunotherapy administered sequentially to CT/RT improves significantly local disease control; this sequential therapy could represent a potential new treatment option in the context of clear unmet clinical need. This combination could potentially induce protective anti-tumor immune response and contribute to eliminate unknown possible micro-metastases, with consequently an improved local and distant relapse-free survival, a sort of "virtual abscopal effect". In this trial durvalumab reduces the incidence of new distant metastases, with also a lower incidence of new brain metastasis, although 14-month follow-up is a relative short time follow-up and many patients can still develop metastasis and disease progression in the next future. Data on OS were immature at the time of the analysis. As stage III is a potential curable disease status, OS data will be of great value and relevance to assess the real efficacy of immunotherapy in this field. However, most likely the significant PFS will translate into significant OS; moreover, the improvement in all secondary endpoints for patients treated with durvalumab support its clinical benefit as well.

As previously reported, in the "PACIFIC" trial the coprimary endpoint of PFS was met, with a difference of 11 months among patients treated with durvalumab and placebo. PFS in the placebo group was 5.6 months (95% CI, 4.6–7.8); it seems to be worse than expected and reported in other clinical trials in the same setting (2). The reason for this discrepancy remains unclear, because baseline characteristics of patients were well balanced in the two groups and inclusion criteria were definitively comparable

with other trials.

The longer PFS was accomplished in a biomarker-independent population. PD-L1 expression analysis was performed retrospectively with a cut-off of TPS 25% in only 63.3% of the total enrolled patients: PD-L1 TPS ≥25% on tumor cells occurred in 22.3% of patients, while PD-L1 TPS <25% occurred in 41% of the patients; 36.7% of the total enrolled patients in both groups had unknown PD-L1 status. Epidermal growth factor receptor (EGFR) mutations were observed in 6.0% of the patients, whereas 67.3% of patients were EGFR-negative or wild type (WT); 26.6% of the total enrolled patients in both groups had unknown EGFR status. No significant survival differences ($P<0.05$) were noted for patients based either on PD-L1 expression or EGFR mutation status. Regarding PD-L1 expression analysis, just a cut-off of TPS 25% was used; data with higher (50%) or lower (1%, 10%) cut-offs are not available. At present, there are no validated biomarkers to identify some subpopulation with higher probability to respond to the combination of immunotherapy and RT, but immunologic surrogates for immune response such as tumor infiltrating immune cell phenotypes, antibody titers, cytokine profiles and changes in the peripheral blood immune cells are actively investigated (19).

A potential limitation to the association of immunotherapy and RT could be related to toxicity, especially concerning chest irradiation and the risk of immune-related pneumonitis. In 915 patients treated with anti-PD-1/PD-L1 antibodies a previous study showed that about 5% of patients developed pneumonitis; moreover, the clinical presentation of RT-induced and immunotherapy induced pneumonitis is similar, with dry cough, fever, dyspnea and tachycardia. As reported in the "PACIFIC" trial, the safety profile of durvalumab is not different from what is well known for other immune checkpoint inhibitors and from what is known in patients with advanced disease treated with durvalumab as monotherapy. The incidences of AE of any cause, including pneumonitis, as reported in this trial with both durvalumab and placebo, is not different from what is expected after definitive CT/RT and is not alarming. A quality of life analysis of the "PACIFIC" trial presented at the International Association for the Study of Lung Cancer (IASLC) 18th World Conference on Lung Cancer (WCLC) (20) showed that patients treated with durvalumab did not experience worsening of symptoms, function or health-related quality of life, which was similar to patients who received placebo. These results strongly support the use of durvalumab in this disease setting, as the health benefits are significant and the treatment option is tolerable. The design of the study doesn't permit to evaluate the safety profile of durvalumab when administered concurrent with CT/RT.

It is worth highlighting the heterogeneity of the intention-to-treat population included in the "PACIFIC" trial, particularly regarding disease stage, doses of prior used RT, type and schedule of CT. Three hundred and seventy-seven patients (52.9%) had stage IIIA disease, while 319 patients (44.7%) had stage IIIB disease. Doses of previous chest RT were included in a range between 54 and 74 Gy, although the majority of patients (92.4%) received a dose of RT between 54 and 66 Gy. The final RT dose for each patient was established based on investigator or radiologist assessment, with doses sometimes different from the inclusion criteria of the trial (54 to 66 Gy, mean dose to the lung less than 20 Gy, V20 less than 35%). Patients could have received previous CT in more than one context, such as in adjuvant setting or induction setting; prior definitive CT regimens included combination of cisplatin or carboplatin with etoposide, vinorelbine, docetaxel, paclitaxel, pemetrexed, nab-paclitaxel and vinblastine; just 13 patients received monotherapy with cisplatin or carboplatin. Furthermore, after a protocol amendment, the period of time between the completion of the last radiation dose and the randomization was 1 to 42 days (initially the interval was 1 to 14 days); consequently, the time of the first durvalumab administration could be very changeable among different patients. Despite this heterogeneity, in fact representative of the clinical practice in this setting, the difference in PFS in favor of durvalumab arm was shown across all pre-specified subpopulation, as defined according to baseline patient demographic and clinical-pathological characteristics.

Actually, there are many ongoing clinical trials evaluating the combination treatment of immunotherapy and RT; in particularly, three ongoing clinical trials with similar design incorporating immunotherapy after definitive chemoradiation for inoperable NSCLC, one with consolidation pembrolizumab following chemoradiation (NCT02343952) and two with consolidation nivolumab following chemoradiation (NCT02434081 and NCT02768558) (9). Furthermore, there is one ongoing trial of concurrent treatment with pembrolizumab, paclitaxel, carboplatin and RT in treating patients with stages II–IIIB NSCLC (NCT02621398). It will be interesting to evaluate the safety profile of the concomitant administration of CT/

RT and immunotherapy and to verify data about emerging validated biomarkers, such as PD-L1 expression levels, to identify patients with higher probability to respond to the combination of immunotherapy and RT in this setting as well.

In conclusion, the "PACIFIC" trial demonstrates the efficacy and safety of the use of CT/RT combined with sequential durvalumab and the radiosensitizing role of immunotherapy as a definitive treatment modality for stage III NSCLC, as curable disease. Further clinical studies are ongoing and are warranted to investigate potential mechanisms driving the interaction between CT/RT and immunotherapy, the right duration and timing of immunotherapy, the best regimen of chemoradiation to combine it with and potential biomarkers to identify patients with higher probability to respond to the combination of immunotherapy and RT.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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