Editorial

Checkpoint inhibitors after chemoradiation: is it ready for prime time?

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Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related death in the United States (1). About a third of the patients diagnosed with NSCLC are diagnosed at a locally advanced stage (stage III). Despite concurrent chemoradiation, the outcome for patients diagnosed with locally advanced NSCLC is very poor with a 5-year survival of <20% (2-4). Recently a new class of drugs blocking the immune checkpoint pathways have revolutionized the treatment paradigm for many solid tumors (5). Immune checkpoint pathways serve a critical role in maintaining immune-homeostasis and inducing immune tolerance to self. Immune checkpoint pathways, particularly the programmed death-1 (PD-1) axis is often co-opted by cancer cells to evade the anti-tumor immune response (6-8). Several such drugs targeting the PD-1 axis are approved by the United States Food and Drug Administration (US-FDA) for treating patients with metastatic NSCLC. However, the response rates are modest and are lower than 50% even in patients expressing high levels of programmed death ligand 1 (PD-L1) (>50% TPS) (9-11). Several pre-clinical and clinical studies demonstrate the possible synergistic effect of radiation and immunotherapy (12-14). Tumor antigen presentation, immune recognition, and activation are the key steps involved in generating an effective anti-tumor immune response (5). Radiation can induce damage-associated molecular patterns (DAMPs), the release of tumor-specific antigens and enhance antigen presentation thus augmenting an anti-tumor immune response (in-situ vaccination) (12). In a large phase 1 trial of pembrolizumab (PD-1 inhibitor) patients with metastatic NSCLC patients (KEYNOTE-1) who had prior radiation had nearly two-fold improvement in both progression-free survival (PFS) and overall survival (OS) [PFS: hazard ratio (HR), 0.56; 95% CI, 0.34–0.91, P=0.019; mPFS 4.4 *vs.* 2.1 months] and (OS: HR, 0.58, 95% CI, 0.36–0.94, P=0.026; mOS 10.7 *vs.* 5.3 months) (14).

Durvalumab is a highly selective IgG1 monoclonal antibody with high affinity to PD-L1 which is a ligand of PD-1. Several early phase trials of durvalumab as a single agent and in combination demonstrate encouraging anti-tumor activity in metastatic NSCLC and larger confirmatory trials are ongoing (15,16).

Dr. Antonia *et al.* recently reported the interim results of the phase III double-blind randomized (PACIFIC) study evaluating the role of consolidation durvalumab for patients with locally advanced and unresectable NSCLC after definitive chemoradiation (17). This study included patients with stage IIIA and IIIB NSCLC patients who completed platinum-based chemotherapy with concurrent radiotherapy (54–66 Gy) and patients who did not progress after chemoradiation were randomized (2:1) to consolidation durvalumab (10 mg/kg every 2 weeks) or placebo for 1 year. The study had two co-primary end points of PFS and OS. At the time of the preplanned interim analysis, OS data of the study were yet to mature however, PFS in the durvalumab group was 16.8 months compared to 5.6 months in the placebo group. The HR for disease progression or death was 0.52 (95% CI, 0.42–0.65; P<0.001). The 1-year PFS rate was 55.9% (95% CI, 51.0–60.4) for patients treated with durvalumab compared to 35.3% (95% CI, 29.0–41.7) for patients receiving placebo. Patients in the durvalumab arm also had significantly higher objective response rate (ORR) than in the placebo arm (28.4% *vs.* 16.0%; P<0.001). The clinical benefit was seen across all patients independent of pre-specified sub-groups including in smoking status, EGFR status and pre-chemoradiation PD-L1 status (<25% and ≥25% tumor cell expression). Treatment related adverse events in the durvalumab compared to the placebo were 67.8% *vs.* 53.4%, respectively. All grade

Immune-related adverse events were seen in 24.2% of patients treated with durvalumab with 3.4% of them were grade 3 or 4. The most common adverse event resulting in treatment discontinuation was pneumonitis and was seen in 6.3% of patients in the durvalumab arm compared to 4.3% in the placebo arm. Grade 3 or 4 pneumonitis was seen in 3.4% *vs.* 2.6%, respectively.

Overall as expected treatment with durvalumab maintenance resulted in an increase in immune-related adverse events however the rates of grade 3/4 adverse events were modest and manageable. Updates on the OS from the PACIFIC study are highly anticipated, however, the magnitude of the PFS benefit (16.8 months for the durvalumab *vs.* 5.6 months in the control arm) is quite significant. The mPFS in the control arm was 5.6 months and was measured from the time of randomization after chemoradiation. This is comparable to other concurrent chemoradiation trials (2).

The benefit was seen in both patients with squamous and non-squamous NSCLC, and was independent of PD-L1 status. These data thus support the use of durvalumab consolidation therapy in all patients with unresectable stage III NSCLC. The National Comprehensive Cancer Network (NCCN) update (version 9) incorporated durvalumab consolidation treatment for stage III NSCLC following concurrent chemoradiation (level 2A evidence) (18).

Treatment with chemoradiation could result in improved immunogenicity of the tumor resulting from improved antigen presentation and amplification of tumor directed immune response by "in-situ vaccination" (12). The data from the PACIFIC trial further support the idea of combination/sequencing of immune-checkpoint inhibitors with chemotherapy and radiation with the intent to "immune-prime" tumors. There is increasing clinical evidence for an immune priming role of radiation. Recent post-hoc analysis of a large phase 1 trial of pembrolizumab in patients with stage IV NSCLC (KEYNOTE-1) there was a nearly doubling of OS in patients who had previous radiation (14). The optimal dose, radiation technique and sequencing of radiation with immunotherapy is still unclear and further evaluation in prospective trials is warranted. Several prospective clinical trials are currently ongoing to explore the additive benefit of radiation to immune-checkpoint therapy in metastatic NSCLC (NCT02444741, NCT03217071, NCT02658097, NCT03307759, NCT02492568, NCT02407171, and NCT02858869) (19).

Is durvalumab maintenance therapy ready for prime time on stage III NSCLC after chemoradiation? For patients with locally advanced NSCLC based on the PACIFIC study durvalumab is the new standard of care following chemoradiation for un-resectable NSCLC. OS data has not been presented yet however, with nearly three-fold improvement in the PFS and the durability of the responses seen in patients receiving durvalumab it is likely that this will translate to an OS benefit.

The role of surgery in stage IIIA NSCLC has been widely debated and the patterns of practice vary across institutions. The only randomized phase III study (Intergroup 0139 trial) that evaluated induction chemoradiation followed by surgery versus definitive chemoradiation demonstrated no survival advantage for doing surgery in resectable stage IIIA NSCLC (20). However, based on post-hoc analysis from the intergroup 0129 trial and several retrospective analyses patients with limited/non-bulky mediastinal (N2) and candidates for lobectomy could benefit from a trimodality approach (21). In some institutions with high surgical volumes and low operative mortality trimodality approach with induction chemotherapy followed by surgery has come to be the standard approach in managing "resectable" stage IIIA NSCLC. The PACIFIC trial does not address the role of immune-checkpoint inhibitors in the surgically resectable stage IIIA NSCLC patients. It could be plausible that patients undergoing chemoradiation followed by surgery could also benefit from maintenance durvalumab. However, considering that this patient population was not studied in the PACIFIC trial it may not be considered as a standard of care at this time. Considering the PACIFIC data, it would be even more important to be highly selective in offering a trimodality approach to patients with "resectable" stage IIIA NSCLC. Several trials incorporating checkpoint inhibitors in the management of early stage and locally advanced NSCLC are ongoing. Future trials particularly in locally advanced stage NSCLC should incorporate better patient selection strategies using biomarkers for selecting patients who could benefit most from immunotherapy. Identifying patients who could potentially benefit from a more aggressive surgical approach incorporating immunotherapy could lead to an improved chance of cure for these patients.

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Footnote

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