Editorial

Comments on the trial of cisplatin and etoposide plus thoracic radiotherapy followed by nivolumab or placebo for locally advanced non-small cell lung cancer (RTOG 3505)

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Radiotherapy (RT) induce lethal DNA damage to tumor cells and the concurrent chemoradiation (CCRT) is the standard treatment option for inoperable stage III non-small cell lung cancer (NSCLC) until now (1). The expectancy of 5-year survival, however, is less than 20–25%. Thus, some modification or addition of new treatment modality would be a reasonable approach to improve its cure rate.

Various modifications could be introduced to improve its survival rate by addition of other treatment modality, such as chemotherapy before or after CCRT. And the irradiation dosage could be intensified. However, the induction chemotherapy or consolidation chemotherapy with CCRT had no impact on survival (2,3). RTOG 0617 study did not show survival benefit with high dose conformal RT (4).

New successful treatment options have appeared. More than 60% of the patients with adenocarcinoma of the lung might have actionable mutations and those who could have received appropriate targeted therapies could survive longer (5). Maintenance gefitinib after CCRT and docetaxel consolidation did not improve survival in inoperable stage III NSCLC (6). The LOGIK0902/OLCSG0905 intergroup study is ongoing to see the effect of combining gefitinib with standard CCRT in EGFR-mutant advanced NSCLC (7).

Programmed cell death-1 (PD-1) is an immune check point and facilitates immune evasion. PD-1 or its ligand PD-L1 inhibitors are working at the effector phase of tumor immune response (8). Nivolumab is a fully humanized anti-PD-1 monoclonal IgG4 antibody and inhibits engagement of the receptor with PD-L1 and PD-L2 (9). This action abrogates inhibitory signal and augments host antitumor immune response. In Checkmate 017 trial, nivolumab showed better survival than docetaxel in patients with advanced squamous cell carcinoma of the lung who had disease progression during or after first-line chemotherapy (10). In Checkmate 057 study, it showed better survival than docetaxel in non-squamous cell carcinoma of the lung with PD-L1 ≥1% (HR=0.59). In patients with PD-L1<1%, there was no survival benefit (HR=0.9), but better tolerability (11). And for patients with advanced NSCLC and PD-L1 expression on at least 50% of tumor cells, first-line pembrolizumab, another PD-1 inhibitor was associated with significantly longer progression-free and overall survival than was platinum-based chemotherapy (12). Thus, the combination of PD-1 inhibitor and the standard CCRT should be explored to see better overall survival.

Many aspects could influence on the result of the combination of the standard CCRT and immune check point inhibitors. Synergism could be inferred through many preclinical and clinical evidences. Tumor antigen release during RT could facilitate the activity of dendrite cells (13,14). Moderate doses of RT such as 2 Gy × 5 could modulate macrophage from M2 to M1 phenotype (15). It was reported that T cell-mediated depletion of myeloid-derived suppressor cells was induced when combining anti-

PD-L1 antibody and RT (16). PD-L1 is a ligand for PD-1 to facilitate immune evasion and its up-regulation during RT looks to be a mechanism of adaptive resistance by tumor cells limiting the outcome (17). Therefore, RT combined with anti-PD-1 or anti-PD-L1 therapy has a potential to overcome this resistance and to improve the outcome further. And there were clinical reports called abscopal effect (18).

The RTOG 3505 trial consists of the standard CCRT followed by nivolumab versus placebo in the patients with locally advanced NSCLC (19). Stratification factors for nivolumab are ECOG (0 *vs.* 1), histology (squamous *vs.* non-squamous) and PD-L1 status (≥1% *vs.* <1% *vs.* not evaluable/undetermined). With 60 Gy of thoracic RT, the protocol employed cisplatin 50 mg/m^2 days 1, 8, 29, 36 and etoposide 50 mg/m^2 days 1–5, 29–33 (EP). Nivolumab 240 mg or placebo will be started 4–12 weeks after completion of CCRT and continued every 2 weeks for 1 year.

EP was chosen as the partner of thoracic RT, because it is a classic regimen and seems to have some advantages over weekly paclitaxel and carboplatin in terms of efficacy and toxicity. In a multicenter randomized phase III trial, EP produced superior survival to weekly paclitaxel and carboplatin (23.3 *vs.* 20.7 months, HR 0.76, P=0.095) and lesser incidence of grade ≥2 radiation pneumonitis (33.3% versus 18.9%, P=0.036) (20). And the weekly paclitaxel based regimen requires frequent use of steroid which could hinder immune stimulation.

Considering usual progression after CCRT within 12 months, the addition of nivolumab following CCRT would be a timely strategy, during when RT induced tumor antigenic stimulation still exists. And one merit of such immunotherapy would be the memory function of cytotoxic T cells. In advanced NSCLC patients who had been given 1–5 lines of prior systemic therapy and participated in CA209-303 study of nivolumab monotherapy, the 5-year survival rate was 16% (21). Through combining nivolumab, the cure rate of CCRT would be expected to improve. PACIFIC trial is a phase III randomized, multi-center trial of durvalumab, anti-PD-L1 antibody as sequential treatment in patients with locally advanced, unresectable Stage III NSCLC who had not progressed following standard CCRT. A planned interim analysis was reported on web site that it has already met a primary endpoint by showing statistically significant and clinically meaningful progression free survival in patients receiving durvalumab compared to placebo (22). It will be presented at coming ESMO 2017.

One thing important when considering the combinational treatment would be the summation of toxicities from each treatment modality. Of these, pneumonitis should be of most concern, because radiation pneumonitis and immune pneumonitis could happen and the symptoms and signs of two diseases are quite similar. Immune pneumonitis is a toxicity of variable onset clinically and it ranged from 9 days to 19.2 months (23). In a case report of 3 solid tumor patients who were previously irradiated in lung field, severe pneumonitis could be observed (24). Urgent evaluation and the initiation of steroids would be important. However, in the phase I dose escalation cohort expansion trial of nivolumab in the patients with NSCLC (n=129) who were heavily pretreated (including 58% of prior RT), grade 3–4 pneumonitis was reported in only 2.3%, although it was not reported the time interval between previous RT and nivolumab (25). Other immune mediated toxicities could also be problematic if radiation could potentiate the immune mediated toxicities.

Mode of RT could influence on immune system. It is reported in animal model that ablative radiation such as stereotaxic body radiation could induce strong T-cell response leading to tumor rejection. CD8$^+$ T cells could be activated during RT. However, concurrent chemotherapy or fractionated radiation could reduce RT induced anti-tumor immunity, ending up an early progression at both local and distant sites (26).

In the immunotherapy era, the anti-cancer treatment has been extended to the area of the tumor immune system and many results are quite encouraging. However, the adverse effects by those novel combinational treatments also should be kept in minds. RTOG 3505 trial which combines the standard CCRT with following nivolumab versus placebo for locally advanced NSCLC will give us the answers.

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Footnote

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

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