

# Consolidation of immunotherapy becomes new standard of care in unresectable stage III non-small cell lung cancer

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Stage III non-small cell lung cancer (NSCLC) accounts for one-third of NSCLC patients. Stage IIIA is considered resectable, but most of stage IIIA/B patients are unresectable, leading to chemoradiotherapy being standard of care. The median overall survival remains poor with less than 15% of 5-year overall survival after chemoradiotherapy. During the last decades, a number of large randomized clinical trials such as incorporation of surgery, different chemotherapy regimen for chemoradiation (1), consolidation of chemotherapy after chemoradiotherapy (2), increased dose of radiation therapy (3), addition of biologic therapy and immunotherapy with vaccine (4) have been conducted to improve clinical outcomes in patients with unresectable stage III NSCLC, however, no significant improvement of outcome has been observed so far.

During the last few years, immune checkpoint inhibitors, PD-1 or PD-L1 inhibitors, as novel immunotherapy has had a significant impact on the NSCLC treatment paradigm (5,6). Chemotherapy and radiotherapy can lead to tumor cells death, followed by the release of immunogenic antigen, resulting in enhancing antigen presentation and adaptive immune responses (7). Based on this hypothesis along with anecdotal observation, so-called “abscopal effect”, the combination of immune checkpoint inhibitors and radiotherapy has become increasing interest to improve the efficacy of radiotherapy.

In this issue of *the New England Journal of Medicine*,

Antonia and colleagues (8) reported the results of the large randomized phase 3 PACIFIC trial, which evaluated the role of durvalumab, an anti-PD-L1 antibody as consolidation therapy after chemoradiotherapy in unresectable stage III NSCLC. In this study, a total of 731 patients were randomized at 2:1 ratio to be treated with durvalumab at a dose of 10 mg/kg or placebo every 2 weeks for 12 months.

This study demonstrated that consolidation of durvalumab significantly improved progression-free survival (PFS) compared to placebo arm (16.8 months for the durvalumab arm *vs.* 5.6 months in the placebo arm), with 0.52 of hazard ratio (95% confidence interval: 0.42–0.65), leading to 11 months of difference in PFS with 48% reduction of disease progression risk. Considering only 8–9 months of PFS with standard chemoradiotherapy in unresectable stage III NSCLC, these results are quite remarkable. Of note, this benefit was observed regardless of stage (IIIA *vs.* IIIB), histology (squamous *vs.* non-squamous), PD-L1 expression status, or smoking status (smoker *vs.* never-smoker) except EGFR mutation status. In terms of adverse events, more treatment-related adverse events were associated with the durvalumab arm (68%) compared to 53% in the placebo arm. And the incidence of immune-mediated adverse events was more common in the durvalumab arm (24%) compared to the placebo arm (8%). However, it is of note that there was no significant increase of grade 3/4 severe pneumonitis between the durvalumab

arm and the placebo arm (3.4% *vs.* 2.6%). Moreover, the discontinuation rate due to pneumonitis between two arms is quite comparable (6.3% for the durvalumab arm *vs.* 4.3% for the placebo arm). In general, a slight increase of toxicity was observed in the durvalumab arm, however, severe toxicity was similar between groups.

Until now, PACIFIC is one of the largest studies addressing the role of immune checkpoint inhibitors as consolidation therapy after chemoradiotherapy in unresectable NSCLC and demonstrated clinically meaningful benefit. Overall survival data are still immature, however, the magnitude of benefit in terms of PFS might be enough to support the consolidation therapy with durvalumab as a new standard care for unresectable NSCLC patients who do not progress on chemoradiotherapy.

Several issues still remained to be elucidated. In PACIFIC study, patients received 12 months of durvalumab after chemoradiotherapy, thus the duration of therapy should be further evaluated. Durvalumab was given after chemoradiotherapy, where all the adverse events related to chemoradiation have been resolved. However, it is unknown whether concurrent administration of immune checkpoint inhibitors with chemoradiation compared to sequential approach can improve more clinical outcome or increase toxicity. Given the encouraging results with PACIFIC study, incorporation of immune checkpoint inhibitors can be applied to the earlier stage of NSCLC such as resectable N2 disease or stage I–II disease. To address this issue, several studies are currently undergoing as neoadjuvant setting or adjuvant setting. Considering significant prolongation of PFS with durvalumab after concurrent chemoradiotherapy (CTRT) in locally advanced NSCLC from PACIFIC study, the role of surgery in locally advanced NSCLC, especially N2 disease might be challenging. In line with this issue, the association between the burden of lymph node metastasis and efficacy of immune check point inhibitor should be further evaluated. Finally, further research to identify predictive biomarkers for the selection of patients who will most likely to benefit from immune checkpoint inhibitors should be warranted.

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### Footnote

*Conflicts of Interest:* The author has no conflicts of interest to declare.

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