Editorial

# Immunotherapy after chemoradiotherapy in stage III non-small cell lung cancer: a new standard of care?

**Anna W. Chalmers, Shiven B. Patel, Wallace Akerley**

Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA

*Correspondence to:* Anna W. Chalmers. Huntsman Cancer Institute, University of Utah, 2000 Circle of Hope Drive, Salt Lake City, UT 84103, USA. Email: anna.chalmers@hci.utah.edu.

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Stage III non-small cell lung cancer (NSCLC) remains a clinical challenge with only modest improvements in treatment over two decades and a plateau in survival. Despite aggressive treatment with concurrent chemotherapy and radiation, only 15% of patients survive 5 years (1). However, the addition of immunotherapy may improve upon this dismal prognosis. An interim analysis of a recent phase III trial (PACIFIC) adding durvalumab after chemoradiotherapy for stage III NSCLC showed a striking improvement in progression free survival (PFS) (2). Durvalumab is a monoclonal antibody that blocks programmed death ligand 1 (PD-L1), thus allowing T cell activation and antitumor response. In the trial, patients were minimally selected and were eligible if they had not progressed after two or more cycles of platinum-based chemoradiotherapy. A total of 713 patients were randomized (2:1) to durvalumab (10 mg/kg) every 2 weeks versus placebo for up to 12 months. The trial met one of its primary end points with an improvement of PFS of 16.8 (95% CI: 13.0–18.1) months with durvalumab versus 5.6 (95% CI: 4.6–7.8) months with placebo [stratified hazard ratio 0.52 (95% CI: 0.42–0.65); P<0.001]. It should be clarified that the PFS of 5.6 months is actually similar to other chemoradiotherapy studies which describe a PFS of 11 months; the PFS was calculated from the time of randomization after completion of chemoradiotherapy in the PACIFIC study rather than upon initiation of chemoradiotherapy (3). The benefit was observed regardless of tumor histology or PD-L1 status. The overall survival (OS) data is not yet mature.

Historically, prior attempts to increase OS have led to our current treatment paradigm of concurrent chemotherapy and radiation for stage III NSCLC. Concurrent treatment has more toxicity than sequential chemotherapy and radiation, but has a greater response rate and survival (4-6). Further attempts to improve on concurrent treatment have failed to improve OS, though some have improved tolerance. Adding consolidative chemotherapy has not been shown to increase survival rates and greater radiation doses led to decreased survival (3,7,8). As the overwhelming majority of these patients ultimately die of systemic disease and multiple randomized trials of inhibitors of the programmed death 1 (PD1) pathway have shown improved survival in patients with metastatic disease, the addition of immunotherapy was a rationale next consideration. In this setting, does immunotherapy dominantly has an additive effect, delaying inevitable relapse, or a synergistic effect with chemotherapy, radiation or both, boosting long-term cure rates?

Radiation therapy (RT) may promote tumor immunogenicity (9). Early initiation of immunotherapy after RT may exploit ionizing radiation-induced tumor antigen presentation which can them prime and activate T cells (9). RT can also trigger release of chemokines that attract T cells to the tumor site and induce an overexpression of cell surface apoptosis antigen triggers on

the tumor cell, further activating T cell mediated tumor response (10). Additionally, RT increases tumor expression of PD-L1 in mouse models, with combined RT plus anti-PD-L1 together reducing accumulation of tumor-infiltrating myeloid-derived suppressor cells (11).

Clinical data suggesting the synergy of radiotherapy and immunotherapy exists as well. The concept of the abscopal effect where radiotherapy to one site of disease leads to responses in another site has been well described and thought to be due to radiation induced immune activation (12). Also noteworthy is a secondary analysis of patients treated in the metastatic setting with pembrolizumab found those who had previous radiation had superior progression-free and OS compared to those who did not (4.4 and 10.7 *vs.* 2.1 and 5.3 months) (13). Therefore, the addition of a checkpoint inhibitor after radiation in NSCLC may augment both the cancer kill within the radiation field and lead to a systemic abscopal effect.

The improvement in PFS seen in PACIFIC trial could reflect the above mechanisms, though an impressive and worthy outcome regardless of etiology. Patterns of relapse (whether or not within radiation field) and mature survival data will provide support for subsequent hypotheses. Most important, is when and at what time duration the plateau of the survival curve develops since the goal of this treatment is intended to cure.

The investigators must be commended for their "all-comers" trial design. The main exclusionary criteria were limited to patients unable to complete conventional chemoradiotherapy, which supports extrapolation of the findings to the general population. As such, it allowed patients to participate with epidermal growth factor receptor (EGFR) mutations and non-smokers, both increasing in frequency in the lung cancer population and known to have lower response rate to immunotherapy (14,15). Of note improvement in PFS was observed in never-smokers, but less so in the EGFR subgroup, raising the possibility that their mechanisms of relative resistance may be different.

Regardless of the durvalumab interaction with chemotherapy, radiation, both or neither, the improvement noted in PFS, duration of response, and the time to death or metastatic relapse is commendable. Given these results and minimal side effects, the addition of durvalumab should be considered for use in all patients with unresectable stage III NSCLC who complete conventional chemoradiotherapy. While OS, a pre-specified co-primary endpoint, is not yet available, its primary benefit will be to help define which patients benefit most and refine hypotheses. Even if only modest survival benefits are seen, a tripling of PFS remains a worthy benefit for these patients who largely die of metastatic disease.

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## Footnote

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

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