



# Advances in immunotherapy for stage III non-small cell lung cancer: moving immune checkpoint inhibitors to the front lines concurrently with chemoradiotherapy?

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Lung cancer is a leading cause of cancer-associated death worldwide. Non-small cell lung cancer (NSCLC) accounts for more than 80% of all lung cancer cases. Among all cases of NSCLC, approximately two-thirds are advanced and inoperable at the time of diagnosis. Although concurrent chemoradiotherapy (cCRT), the standard treatment for patients with inoperable, locally advanced NSCLC (1), is potentially curative, the 5-year overall survival (OS) rate has reached a plateau around 20%, despite considerable attempts to improve treatment results by intensification of conformal radiation therapy and enhanced chemotherapy with induction or consolidation.

Recently, PD-1 or PD-L1 immune checkpoint inhibitors (ICIs) have shown exceptional efficacy in patients with advanced NSCLC, and preclinical and early phase clinical studies suggest that radiation therapy and chemotherapy work synergistically with ICIs to develop antitumor immunity (2,3), that has led to testing of ICIs in patients with stage III NSCLC through clinical trials. The randomized phase 3 PACIFIC study demonstrated outstanding increases in median progression-free survival (PFS) and OS after consolidation therapy using durvalumab, a PD-L1 inhibitor, after cCRT, compared with the outcomes of cCRT alone (4,5). The PACIFIC data encourage the usage of consolidative durvalumab immunotherapy after completion of cCRT in patients with stage III inoperable NSCLC based on an acceptable safety

profile and significantly improved OS. The PACIFIC study raised query concerning the timing between cCRT and ICIs therapy. Additional durvalumab decreased progression, regardless of when it was started, but greater decrement was observed if durvalumab was started within 2 weeks of radiation therapy [hazard ratio (HR) =0.39; 95% confidence interval (CI) =0.26–0.58] instead of >2 weeks after radiation therapy (HR =0.63; 95% CI =0.49–0.80), implying a critical window for initiating PD-L1 blockade. This confirms the findings of reported studies that recognized enhanced results in patients treated with concurrent immune therapy or in close proximity to radiotherapy (6). Additionally, considering the potential of chemotherapy to synergize with ICIs, as shown by the KEYNOTE-021 trial (7), adding platinum-based chemotherapy to immunotherapy could enhance responses. Recently, trials involving ICIs initiated immunotherapy at various time points, and their collective outcomes may clarify the ideal timing between cCRT and ICIs.

Jabbour *et al.* conducted a phase 1, nonrandomized, controlled trial of cCRT [weekly carboplatin and paclitaxel plus 60 Gy of radiation (2 Gy per day)] with concurrent PD-1 blockade using pembrolizumab (8). The evaluated dose cohorts included full-dose pembrolizumab (200 mg intravenously every 3 weeks) 2–6 weeks after cCRT (cohort 1), reduced-dose pembrolizumab (100 mg intravenously every 3 weeks) starting on day 29 of cCRT

**Table 1** Ongoing trials combining immunotherapy and chemoradiotherapy concurrently in stage III non-small cell lung cancer (trials identified in ClinicalTrials.gov)

NCT No.	Study phase	Number	Immunotherapy	Treatment
NCT03519971 (PACIFIC 2)	III	328	Durvalumab	Durvalumab plus concurrent chemoradiation → durvalumab
			Placebo	Placebo plus concurrent chemoradiation → placebo
NCT04026412 (CheckMate 73L)	III	1,400	Nivolumab, nivolumab + ipilimumab	Nivolumab plus concurrent chemoradiation → Nivolumab + ipilimumab
			Nivolumab	Nivolumab plus concurrent chemoradiation → Nivolumab
			Durvalumab	Concurrent chemoradiation → Durvalumab
NCT03840902	II	350	M7824	M7824 plus concurrent chemoradiation → M7824
			Durvalumab	Placebo plus concurrent chemoradiation → Durvalumab

(cohort 2), full-dose pembrolizumab starting on day 29 of cCRT (cohort 3), reduced-dose pembrolizumab starting on day 1 of cCRT (cohort 4), and full-dose pembrolizumab starting on day 1 of cCRT (cohort 5). A safety expansion cohort of six patients was planned based on the maximum tolerated dose of pembrolizumab. Dose-limiting toxicity was defined as pneumonitis of at least grade 4 during the first cycle of pembrolizumab treatment. Among the 21 patients included in the analysis, no dose-limiting toxic effects were observed in any cohort. One case of grade 5 pneumonitis occurred in the safety expansion cohort with the cohort 5 regimen. Immune-related adverse events of at least grade 3 occurred in four patients (18%). PD-1 inhibition and cCRT for stage III NSCLC was tolerable with an 18% rate of grade 3 or greater immune-related adverse events, including grades 3 and 5 pneumonitis, grade 3 interstitial nephritis, and type 1 diabetes. The overall rate of pneumonitis of at least grade 2 was 33%, and in the PACIFIC study, any-grade pneumonitis and radiation pneumonitis occurred in 33.9% and 24.8% of patients, respectively. The PACIFIC study enrolled patients after cCRT and excluded those with preexisting pneumonitis of at least grade 2 caused by cCRT, in contrast to the study by Jabbour *et al.*, in which patients were registered before cCRT. In this study, grade 3 pneumonitis and grade 5 pneumonitis occurred in one patient each (5%). In the PACIFIC study, the percentages of grades 3 or 4 pneumonitis and radiation-induced pneumonitis were 3.4% and 2.6%, respectively.

In patients who had been treated at least a dose of pembrolizumab (n=21), the median PFS was 18.7 months (95% CI =11.8–29.4) and the 6- and 12-month PFS rates were 81.0% (95% CI =64.1–97.7) and 69.7% (95%

CI =49.3–90.2), respectively. The median PFS for patients who received at least two doses of pembrolizumab (n=19) was 21.0 months (95% CI =15.3 to infinity). The results suggested that combined treatment with PD-1 inhibitors and cCRT for stage III NSCLC is tolerable, with promising a PFS rate of 69.7% at 12 months. Although they observed an increased rate of pneumonitis, this adverse event responded to high-dose corticosteroid treatment in most patients. Adding pembrolizumab to cCRT in the definitive management of locally advanced NSCLC is feasible and generally well tolerated. They suggested that first-line therapy with PD-1 inhibition and cCRT for stage III NSCLC appears tolerable and suitable for evaluation in phase 2 and 3 clinical trials.

According to the phase 1 trial results, adding concurrent pembrolizumab to cCRT may represent a candidate first-line treatment regimen for stage III NSCLC. There is an ongoing phase 2 trial of pembrolizumab in combination with cCRT (9). In addition, two studies, DETERRED (NCT02525757) and NICOLAS (NCT02434081), assessed atezolizumab or nivolumab administration concurrently with cCRT (10,11). A phase 2 trial (WJOG11619L) investigating the effect and safety of durvalumab with concurrent radiation and a phase 2 study (TORIG1937) evaluating those of durvalumab provided immediately after the completion of cCRT are both in progress in Japan, but their findings will require confirmation through randomized trials. A number of randomized trials in NSCLC are currently in the planning phase or actively recruiting patients to assess the efficacy of radiation plus concurrent immunotherapy. The trials, described in ClinicalTrials.gov, are presented in *Table 1*. The PACIFIC 2 study (NCT03519971), an

international phase 3 trial, is currently investigating the efficacy and safety of durvalumab administered concurrently with platinum-based cCRT in patients with inoperable stage 3 NSCLC. Furthermore, CheckMate 73L, a randomized phase 3 trial comparing nivolumab plus cCRT followed by nivolumab/ipilimumab or nivolumab and cCRT followed by nivolumab versus cCRT followed by durvalumab in patients with previously untreated, inoperable NSCLC, is ongoing. This study's primary purpose is to evaluate the potency of nivolumab plus cCRT followed by nivolumab plus ipilimumab versus cCRT followed by durvalumab in patients with inoperable stage III NSCLC. A double-blind, randomized study of M7824 with cCRT followed by M7824 versus cCRT plus placebo followed by durvalumab in patients with inoperable stage III NSCLC is also ongoing. M7824 is a bifunctional fusion protein comprising a monoclonal antibody against PD-L1 fused to the extracellular domain of transforming growth factor- $\beta$  (TGF- $\beta$ ) receptor II that works as a trap for all three TGF- $\beta$  isoforms. Reportedly, M7824 specifically, simultaneously, and efficiently binds TGF- $\beta$  and PD-L1 (12); concurrent blocking of the TGF- $\beta$  and PD-L1 pathways by M7824 demonstrates effective and superior antitumor activity relative to monotherapies; and primary resistance to ICIs therapy is overcome by the selective inhibition of TGF- $\beta$ 1 activation through the alteration of the tumor immune landscape (13).

How should oncologists select from several available ICIs and cCRT combination regimens in clinical trials? So far, there is no evidence to provide responses to these questions because no comparative studies combining ICIs and cCRT have been conducted and some issues remain to be addressed. The first issue is regarding whether the antitumor effects and safety of PD-1 or PD-L1 inhibitors are similar. The selection of a proper ICI among PD-L1, PD-1, and cytotoxic T-lymphocyte antigen 4 inhibitors for use with cCRT may be important. The second issue is when to initiate radiotherapy. The optimal timing of ICI therapy relative to cCRT remains to be investigated. Other questions include proper selection of the combination chemoradiation regimens and the optimal ICI modality for concurrent therapy with cCRT. To answer the questions, optimal treatment strategies for stage III NSCLC is under investigation in several trials. In addition, some adequate biomarkers for identification of the subset of patients with stage III NSCLC who may most benefit from ICI therapy combined with cCRT are necessary. Depending on the outcomes of the ongoing studies, new combination

treatments involving cCRT and ICIs will be developed, although further investigations will be needed to preserve efficacy and reduce toxicity.

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## Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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