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PACIFIC: An Ocean of Hope in Patients With Stage III Unresectable Non–Small Cell Lung Cancer

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Lung cancer is the leading cause of cancer-related death worldwide.¹ In 2012, an estimated 1.8 million new lung cancer cases were diagnosed.¹ Non–small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases, and approximately 40% of these patients present with stage III disease.² For patients whose disease is deemed unresectable, concurrent chemoradiation (CRT) is the standard of care. A phase II study (SWOG 9010) conducted by Albain et al³ was the first landmark trial showing the feasibility of the cisplatin/etoposide combination with radiotherapy in patients with locally advanced NSCLC. Concurrent CRT treatment is superior to a sequential approach, but has the disadvantage of increased toxicity.⁴ Up to 10% of patients receiving concurrent CRT will have early treatment-related mortality.⁵ Despite this intense therapy with curative intent, median survival is approximately 18 to 28 months and only approximately 15% of these patients are alive at 5 years.^{4,5} Unfortunately, no major advances have been made in this group of patients for many years. The use of a higher dose of radiation does not improve survival and is associated with inferior outcomes. Additionally, no role for targeted therapy with CRT has been proven.

Antonia et al⁶ recently reported the results of the phase III PACIFIC trial, which evaluated the role of durvalumab (a selective monoclonal antibody against programmed death-ligand 1 [PD-L1]) as consolidation therapy in patients with stage III, locally advanced, unresectable NSCLC that had not progressed after concurrent CRT therapy. The study used a fixed time frame for randomization, and immunotherapy was started without significant delay. A total of 709 patients were randomly assigned in a 2:1 fashion to receive either durvalumab (n=473) or placebo (n=236) every 2 weeks for up to 12 months. The study revealed significant improvement in progression-free survival (PFS) with durvalumab: 16.8 months (95% CI, 13.0–18.1) versus 5.6 months (95% CI, 4.6–7.8) in the placebo arm. The benefit was seen irrespective of sex, smoking status, PD-L1 expression, and tumor histology type. Additionally, the development of new lesions was lower in the durvalumab arm (20.4% vs 32.1%).

The brain is a common metastatic site for NSCLC, and has been historically associated with decreased survival and poor quality of life. The rate of new brain lesions in the PACIFIC trial was almost halved with durvalumab (5.5% vs 11.0%). Although the overall survival (OS) data are yet to mature, a PFS benefit of almost a year and a significant decrease in the occurrence of new lesions, including brain lesions, provide reasons to consider durvalumab as a new standard of care.

Various platinum-based chemotherapy regimens can be used for concurrent CRT, including cisplatin/etoposide, carboplatin/paclitaxel, cisplatin/vinblastine, and, for nonsquamous pathology, carboplatin or cisplatin with pemetrexed.⁷ The carboplatin/paclitaxel regimen is given weekly with radiation therapy, at carboplatin dosed to an area under the curve (AUC) of 2 and paclitaxel dosed at 45 to 50 mg/m², followed by 2 additional cycles of full-dose chemotherapy (carboplatin, AUC=6 and paclitaxel, 200 mg/m²).⁸ Should treating oncologists therefore omit these 2 additional full-dose chemotherapy cycles when using this regimen? The authors of the PACIFIC trial do not comment on this issue. Also, can these data be extrapolated to the subset of pa-

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tients with M1b disease, who are treated locally with surgical resection or stereotactic radiosurgery? These questions remain unanswered by this trial and warrant further study.

Concurrent CRT is a highly toxic regimen associated with significant risk of lung toxicity.⁵ Symptomatic pneumonitis can occur in up to 15% to 40% of patients. The risk is higher in patients who are elderly (>65 years of age) and those receiving a carboplatin with paclitaxel chemotherapy regimen, higher total dose of radiation, or larger lung volume of radiation.⁹ Autoimmune pneumonitis is a concerning potential side effect of checkpoint immunotherapy agents. The PACIFIC trial demonstrated a slight increase in rates of pneumonitis in the durvalumab arm compared with the standard arm (pneumonitis of any grade, 33.9% vs 24.8%; grade ≥ 3 pneumonitis, 3.4% vs 2.6%; pneumonia any grade, 13.1% vs 7.7%; grade ≥ 3 pneumonia, 4.4% vs 3.8%; and severe pneumonitis leading to discontinuation, 6.3% vs 4.3%). Durvalumab appears to be safe, even from a postmarketing surveillance standpoint. It has been on the market since May 2017, after it received FDA approval in patients with urothelial carcinoma, with no new concerning immune-related adverse events reported.

Immunotherapy has not been associated with superior outcomes in patients with *ALK*-rearranged and *EGFR*-mutated NSCLC in the metastatic setting.^{10,11} The PACIFIC trial echoed this finding in stage III *EGFR*-mutated NSCLC, with no difference seen in disease progression or death between durvalumab and placebo (hazard ratio, 0.76; 95% CI, 0.35–1.64). Of note, only 43 patients were available for analysis, and the results were not statistically significant. Clinical trials of erlotinib or crizotinib with CRT in patients with stage III NSCLC are ongoing (ClinicalTrials.gov identifier: NCT01822496). Another area of research is combining targeted small molecule agents with immunotherapy. A study using ensartinib, an *ALK* inhibitor, and durvalumab in patients with *ALK*-rearranged NSCLC is underway (ClinicalTrials.gov identifier: NCT02898116).

Molecular biomarkers can provide important information on patient selection for specific therapy in NSCLC. In the PACIFIC trial, durvalumab offered a PFS benefit regardless of PD-L1 expression level. NSCLC with high tumor mutation burden has a higher likelihood of response to immunotherapy.¹² Although currently not incorporated in standard practice, checking for tumor mutation burden through comprehensive genomic profiling as a predictive biomarker for verifying response to immunotherapy may be a future strategy. Given these exciting PACIFIC trial data in the locally advanced setting, it will be interesting to see whether this benefit extends to earlier stage disease.

IONESCO is a phase II trial exploring durvalumab as neoadjuvant immunotherapy in early-stage lung cancer (stage I–IIIA). A study of the effectiveness of durvalumab in early-stage NSCLC is also planned using stereotactic body radiation therapy (ClinicalTrials.gov identifier: NCT02904954). The European Thoracic Oncology Platform is recruiting patients to investigate the tolerability and efficacy of nivolumab when added to concurrent CRT in patients with locally advanced NSCLC in the NICOLAS trial. RTOG 3505 is a multicenter phase III, double-blind, placebo-controlled clinical trial assessing the role of nivolumab as maintenance therapy in patients with unresectable NSCLC after receiving concurrent CRT.¹³ Additionally, a phase II study will incorporate atezolizumab as neoadjuvant immunotherapy before standard CRT with carboplatin and paclitaxel followed by 1 year of atezolizumab maintenance therapy in patients with unresectable stage IIIA/B NSCLC (ClinicalTrials.gov identifier: NCT03102242). Hopefully these trials will add value to the role checkpoint immunotherapy agents can play in treating patients with NSCLC.

In summary, durvalumab offered significant PFS benefit over placebo for patients with stage III unresectable NSCLC, at the expense of slightly increased toxicity. OS data are not yet mature, but a PFS benefit of almost 12 months is convincing enough

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to consider it a new standard of care. This is an exciting time in thoracic oncology, because various trials are underway to better show the optimal therapeutic strategy for immunotherapy in early-stage NSCLC.

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