FEATURE

# Immunotherapy in the treatment of stage III NSCLC

## Towards a new standard of care

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Approximately one-third of patients with non-small cell lung cancer (NSCLC) are diagnosed with stage III disease, where cancer is locally advanced and not amenable to curative surgical treatment.[1] The current standard of care involves combining radiation therapy (RT) with chemotherapy. Despite a great number of trials with new agents, doses and combinations, this standard of care has not changed in decades and the 5-year survival remains low. The PACIFIC trial results have shown improved survival with the addition of immunotherapy to the standard of care. In this article, we will look at this development in context. First, we will describe results achieved with the current standard of care; second, we will look at strategies tried in recent years to improve outcomes. We will then explore some of the research that led to the PACIFIC trial, showing an additive effect between RT, chemotherapy and immunotherapy. Finally, we will present the key results of the PACIFIC trial and discuss the implications for the treatment of stage III NSCLC.

### THE STAGE III NSCLC POPULATION

Locally advanced NSCLC makes up about 30% of the NSCLC patient population. Current treatment guidelines involve a combination of RT and doublet platinum-based chemotherapy.[2,3] Stage III patients are considered to be at high risk of progression, so treatment planning should be expedited.[4] Patients considered for chemoradiotherapy should have adequate Eastern Cooperative Oncology Group (ECOG) performance status to avoid risk of serious complications from treatment.[5] Meta-analyses of more than 50 trials confirm the survival benefit of combined chemotherapy (cisplatin/etoposide) with radiotherapy over radiotherapy alone in this population.[6] Treatment given concurrently is associated with higher 5-year survival (around 20%) than sequential treatment.[7] There is significant variation in cure rates within the heterogeneous stage III population; with combined modality treatment, they range from 36% for stage IIIA to 13% with stage IIIC.[1]

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### EFFORTS TO IMPROVE SURVIVAL

A number of strategies have been attempted to improve survival in patients with stage III NSCLC. The benefit of surgery after chemoradiation was demonstrated in the pivotal Intergroup 0139 study.[8] Patients were randomized after chemotherapy+ radiation to either surgical resection or radiation boost. PFS was found to be superior in the surgical arm, with a median PFS of 12.8 versus 10.5 months in the patients randomized to radiation boost. The overall survival (OS) was not significantly different between the 2 arms, with a median OS of 23.6 months (surgical arm) versus 22.2 months (radiation boost). Both curves plateaued at approximately 25% at 5 years. Experience in the BC Cancer Lung Tumour Group has shown that carefully selected patients may benefit from surgery after completing chemoradiation therapy, achieving a median survival of over 3 years and a 5-year survival rate of 35%.[9] Other approaches have been less successful. Neither induction nor consolidation chemotherapy, given alongside chemoradiotherapy, has been found to improve outcomes.[10,11,12] As well, no form of targeted therapy has been shown to improve survival.[13] However, valuable insights have been gained along the way.

Over the past few years, the Radiation Therapy Oncology Group (RTOG) has tried different strategies to improve survival in patients with stage III NSCLC. One trial found that increasing the radiation dose from 60 Gy (the standard for more than 30 years[14] to 74 Gy, while also targeting it more precisely, resulted in median overall survival (OS) of 24 months,[15] compared to 17.1 months seen with the 60 Gy dose.[16] Another phase 2 trial (RTOG 0324) found that concurrent treatment with chemoradiation and cetuximab, an anti-epidermal growth factor receptor (EGFR) antibody, showed median survival of 22.7 months.

These results led to the RTOG 0617 trial,[17] which looked at the benefit of adding cetuximab to chemoradiotherapy and increasing the dose of radiation. The study randomly assigned patients to 1 of 4 treatment groups: standard-dose radiotherapy + concurrent chemotherapy, with or without the addition of cetuximab; and high-dose radiotherapy + concurrent chemotherapy, with or without the addition of cetuximab. The outcome of interest was OS. The authors concluded that 74 Gy radiation given in 2 Gy fractions with concurrent chemotherapy was not better than 60 Gy plus concurrent chemotherapy, and in fact might potentially be harmful. The addition of cetuximab to concurrent chemoradiation and consolidation treatment provided no benefit in OS for these patients. The authors identified 2 potential contributors to worse-than-expected

results from higher-dose radiotherapy: it may have made it more difficult for patients to complete chemotherapy; as well, heart toxicity may have been worse at the high dose.

## BACKGROUND TO THE COMBINATION OF CHEMORADIATION AND IMMUNOTHERAPY

While immunotherapy has long been seen as a promising way to specifically attack cancer cells, early studies noted the persistence of malignancies after immunotherapy, and associated this with a lack of T-cell function and limited infiltration of immune cells into the tumour tissue.[18] In a 2005 study in mice, Lugade et al[19] investigated whether combining immunotherapy with other treatments that increase inflammation at the tumour site might provide the necessary signals to overcome both shortcomings by increasing T-cell generation and their recruitment into tumours. Results suggested that localized radiation could increase both the generation of antitumour immune effector cells and their trafficking to the tumour site.[19] RT causes tumour cell destruction, leaving a large amount of tumour antigen in the form of necrotic and apoptotic tumour cells and debris, which can stimulate an immune response.[20,21,22] Both the exposure of neoantigen and changes induced in the tumour microenvironment were seen to increase immune cell infiltration and retention.

The dosage and timing of RT may influence its impact on immunotherapy. Treating patients with a series of fractioned doses limits toxicity but may be detrimental to immunotherapy because it causes repeated damage to immune cells within tumours and may compromise their ability to develop systemic protection when supported by immunotherapy.[19] Sublethal doses of radiation have been associated with the upregulation of several classes of molecules on tumour cells that could potentially influence the immune system. A similar impact on immune response is seen with many standard chemotherapy regimens. These observations support the notion that radiation and/or chemotherapy may be used to improve antitumour responses.[24]

Clinical trials demonstrated that programmed death ligand 1 (PD-L1) or programmed cell death protein 1 (PD-1) antagonistic antibodies can elicit responses in 15% to 25% of patients, depending on the tumour type, and that the presence of PD-L1 may be a biomarker for success of the treatment.[25]

Deng et al (2014), in a study of antitumour immunogenicity in mice, demonstrated that PD-L1 was upregulated in the tumour microenvironment after irradiation (IR), providing a potential target for immunotherapy. They observed that IR and anti–PD-L1 synergistically reduced the local accumulation of tumour-infiltrating myeloid-derived suppressor cells (MDSCs) and altered the tumour immune microenvironment. Local upregulation of the PD-L1/PD-1 axis following IR was therefore involved in limiting the expression of antitumour immunity and facilitating relapse. The authors suggested that the concept of inducing PD-L1 expression with IR, and subsequently blocking PD-L1, might prove to be a potent anticancer therapy. Findings from this study further suggested that anti–PD-L1 treatment not only improves the effects of IR on the primary tumour, but also delays or stops the growth of distant tumours.[26]

## THE PACIFIC TRIAL

The PACIFIC phase 3 study[27] was the first trial of immunotherapy with curative intent in stage III NSCLC. It compared the anti–PD-L1 antibody durvalumab as consolidation therapy with placebo in patients with stage III NSCLC who did not have disease progression after 2 or more cycles of platinum-based chemoradiotherapy. Of 713 patients who underwent randomization, 709 received consolidation therapy (473 received durvalumab and 236 received placebo).

Median progression-free survival (PFS) from randomization was 16.8 months (95% CI: 13.0 to 18.1) with durvalumab versus 5.6 months (95% CI, 4.6 to 7.8) with placebo (stratified hazard ratio for disease progression or death, 0.52; 95% CI, 0.42 to 0.65; P<0.001). Response rates were 28.4% with durvalumab vs 16.0% with placebo (P<0.001), and median duration of response was longer: 72.8% vs 46.8% of patients had ongoing response at 18 months. At 12 months, 55.9% of patients on durvalumab were progression-free vs 35.3% for patients on placebo. Median time to death or distant metastasis was 23.2 months with durvalumab vs 14.6 months with placebo (P<0.001).

Grade 3 or 4 adverse events were not significantly more common with durvalumab than placebo (29.9% vs 26.1%). A total of 15.4% of patients in the durvalumab group and 9.8% of those in the placebo group discontinued the study drug because of adverse events. Symptomatic grade 3 or 4 pneumonitis rates were low and similar between durvalumab (3.4%) and placebo (2.6%), providing assurance that immunotherapy can be given safely after chemoradiation.

All subgroups in the trial benefited from durvalumab except for possibly the small number of patients with EGFR-mutated tumours, where the confidence interval crossed one. Tumour PD-L1 expression was not predictive of outcome, although there was a trend toward longer PFS

with higher PD-L1 expression.

These results were greeted as a turning point in the way stage III NSCLC is treated, with immunotherapy representing a significant step forward in the eradication of this deadly disease. Further trials are anticipated or underway to assess different dosing and treatment duration protocols with durvalumab.

Based on the PACIFIC study results, the US Food and Drug Administration (FDA) approved durvalumab in February 2018, with breakthrough designation for the treatment of patients with unresectable stage III NSCLC whose disease has not progressed following concurrent platinum-based chemotherapy and RT. We eagerly await Canadian regulatory bodies to follow suit.

Stage III patients with inoperable disease have a new standard of care, being combined radiation with chemotherapy, followed by 12 months of durvalumab immunotherapy.

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