Lung Cancer: Targets and Therapy

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REVIEW

Immunotherapy for Stage III NSCLC: Durvalumab and Beyond

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Abstract: Immunocheckpoint inhibitors (ICIs) have altered the treatment landscape of a wide range of malignancies, including non–small cell lung cancer (NSCLC). This class of agents inhibits the interaction between PD1 and PDL1, and was shown to be efficacious in the landmark PACIFIC trial with 1 year of maintenance durvalumab (anti-PDL1 antibody). This trial demonstrated that its use as a consolidation treatment given after definitive chemoradiotherapy improved progression free survival and overall survival compared to standard-of-care treatment. In this review, we discuss both clinical trial and real-world data that have been published since PACIFIC that support the use of durvalumab for stage III unresectable NSCLC. In addition, we highlight specific populations that may require special considerations for the use of durvalumab in this setting, such as oncogene-addicted NSCLC, the toxicity of immunotherapy, and future directions in ICI research in stage III NSCLC.

Keywords: lung cancer, immunotherapy, durvalumab

Background

Non–small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide, and approximately a third of patients have locally advanced disease at diagnosis.[1,2] Treatment options for NSCLC vary depending on the stage at diagnosis, but recent advances in genomic profiling, targeted therapy, and cancer immunotherapy have resulted in an expansion of treatment options and improved disease outcomes.[3]

One area that has revolutionized the treatment of advanced NSCLC is the use of immunocheckpoint inhibitors (ICIs), highlighting the dynamic relationship between immunology and oncology. Tumor cells often downregulate expression of proteins involved in immunosurveillance, shielding cancer cells from protective immunoresponses.[4] Multiple targets of immunosuppressive pathways have been developed, facilitating the activation of immunomediated destruction of tumor cells.[5] One pathway includes PD1 and PDL1 targets. When PDL1 binds to PD1, it induces T-cell signaling that results in apoptosis and anergy, and it is this interaction that has been utilized to reinvigorate an antitumor T-cell response.[6–8] In recent years, a number of monoclonal antibodies targeting this interaction have demonstrated efficacy, including pembrolizumab, nivolumab, and cemiplimab targeting PD1, and atezolizumab, avelumab, and durvalumab targeting PDL1. These drugs have been shown to be efficacious in a wide range of malignancies, both in early and advanced disease, including lung cancer, melanoma, renal-cell carcinoma, Hodgkin's lymphoma, cutaneous squamous-cell carcinoma, urothelial cancer, and

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metastatic Merkel-cell carcinoma.[9–17] The incorporation of ICIs into the treatment landscape for advanced NSCLC has changed how we treat this disease in the last 5–8 years.[18,19] In the US, there are now more than five standard treatment options that incorporate immunotherapy in the first-line treatment of advanced NSCLC,[19–24] and their use has expanded to earlier-stage NSCLC.

Stage III NSCLC is a heterogeneous disease that is treated with a multimodality approach, incorporating chemotherapy, radiotherapy, and surgical resection in selected cases.[25] In patients with unresectable locally advanced (stage III) NSCLC, the standard of care has been definitive chemoradiotherapy since the early 2000s, with a platinum-based doublet-chemotherapy regimen in combination with concurrent radiotherapy (RT).[26] A phase III clinical trial demonstrated that a combination of concurrent cisplatin, etoposide, and chest radiotherapy resulted in a benefit in median OS of 15 months, with 3- and 5-year survival of 17% and 15%, respectively.[27] This approach of combination chemoradiotherapy with carboplatin, pemetrexed, and thoracic radiotherapy consolidated the data available on cisplatin and etoposide, increasing chemotherapy treatment options.[27,28] The incidence of neutropenia was similar in both studies (35% vs 42%), with fatigue, dehydration, and anemia the most common adverse events (AEs) noted.[28] The delivery of concurrent versus sequential chemoradiotherapy has been associated with a higher incidence of both hematological and nonhematological toxicity, notably esophagitis, but it has proven significantly effective in sustaining survival outcomes and became a standard of care >10 years ago.[29] With concurrent treatment in one study, median progression-free survival (PFS) was 8 months and 5-year survival <20%.[30]

More recently, several studies have explored the use of immunotherapy after definitive chemoradiotherapy for stage III NSCLC. This "consolidation treatment" is delivered with the intent of reducing recurrence, and is administered after completion of chemoradiotherapy.[31] In this narrative review, we highlight clinical trial and real-world data that support the use of immunotherapy for stage III NSCLC, in particular durvalumab, populations that may require special consideration such as oncogene-addicted NSCLC, the toxicity of immunotherapy for stage III NSCLC, and future directions.

Immunotherapy for Stage III NSCLC

A landmark study, the PACIFIC trial, published in 2017, assessed the potential benefit of durvalumab as consolidation treatment after completion of concurrent chemoradiotherapy in unresectable stage III NSCLC.[26] This trial included 713 patients, randomly assigned to receive either durvalumab or placebo, commencing 1–42 days after combined chemoradiotherapy at a 2:1 ratio. Durvalumab was administered as an intravenous infusion every 2 weeks at 10 mg/kg. This phase III study demonstrated a benefit in both PFS (16.8 months vs 5.6 months, $P<0.001$) and overall survival (OS) (23.2 months vs 14.6 months, $P<0.001$) compared with placebo.[26] Patients who received maintenance durvalumab also demonstrated prolonged median time to death or distant metastases in favour of durvalumab (28.3 months versus 16.2 months) and lower incidence of brain metastases (6.3% vs 11.8%) compared with placebo.[32]

Recently, a 4-year update on survival outcomes in the PACIFIC trial demonstrated that 49.6% of patients who received durvalumab remained alive at 4 years compared with 36.3% who received a placebo, with 35.5% of patients who received durvalumab alive with no disease progression versus 19.5% who received a placebo.[33] Five-year survival outcomes were published this year at ASCO, showing 42.9% of patients who received durvalumab remained alive at 5 years and approximately a third remained alive and free of disease progression[34]

Real-World Data on Durvalumab for Stage III NSCLC

While clinical trial data demonstrate an impressive benefit for durvalumab in stage III NSCLC in the maintenance setting, other studies have examined whether this approach yields favorable outcomes in a real-world setting. Three retrospective studies in this area have shown patients with increased expression of PDL1 were more likely to receive durvalumab and showed improved PFS and OS in more heterogeneous patient cohorts compared to the PACIFIC trial.[35–37]

In the first of these three studies, a retrospective analysis conducted in Germany including 437 patients with stage III NSCLC, patients were treated with platinum-based chemoradiotherapy followed by durvalumab as per the PACIFIC regimen, and 50.3% were eligible to receive durvalumab.[35,38] Reasons for inability to receive durvalumab included insufficient response to chemoradiotherapy based on RECIST[38] (32.4% of patients), PDL1 positivity <1% (22.3% of patients), grade 2 or higher radiation pneumonitis (12.6%), and 3.5% due to prior autoimmune disease, mainly rheumatoid arthritis.[35] Those with higher

PDL1 expression (≥50%) were more likely to receive durvalumab (OR 2.4, P=0.006).[35]

Other retrospective studies have assessed survival outcomes in patients who received chemoradiotherapy alone compared with those who also received durvalumab consolidation treatment. A multicenter retrospective analysis of 147 patients found that PFS and 12-month OS was higher in patients who received durvalumab consolidation, but was specific to patients with PDL1 expression ≥50%.[36] Notably, pneumonitis incidence was similar in both groups, yet those who developed grade 2+ pneumonitis had lower 12-month OS, regardless of treatment group.[36]

A retrospective study in Germany covering 56 centers and 126 patients assessed PFS, OS, and safety outcomes for durvalumab in patients with stage III NSCLC, including those with poorer performance status and autoimmune disease.[37] In this study, 71.2% of patients had PDL1 expression >1%, slightly higher than the PACIFIC trial,[37] and 54% completed 12 months of durvalumab consolidation treatment. Patients assessed in this analysis demonstrated a median PFS of 20.1 months with durvalumab, while 12- and 24-month OS was 78.6% and 66.0%, respectively.[37] The incidence of both intrathoracic and extrathoracic metastases, including brain metastases, was lower in the durvalumab group. With further subgroup analysis, younger patients, female patients, and those with a good performance status showed improved PFS, again demonstrating the efficacy of durvalumab consolidation treatment.[37]

Separately, a prospective study of 26 patients with PDL1-positive unresectable stage III NSCLC showed impressive efficacy for durvalumab consolidation treatment, with 12-month PFS of 62% and 12-month OS of 100%.[39] This study differed in terms of including patients that had received concurrent or sequential chemoradiotherapy, and it included one patient with stage IV disease. At the time of publication, a number of participants in this study were still receiving durvalumab, with a median follow-up of 20.6 months.[39] Taken together, these data support the PACIFIC data, but also identify that in real-world settings there are particular considerations, including tumor PDL1 expression, comorbidities, and autoimmune disease history, that may limit or curtail the use of durvalumab.

Other Immunotherapeutic Approaches for Stage III NSCLC

The efficacy of consolidation treatment with ICIs, specifically PD1 or PDL1 blockade, has been assessed when given sequentially after a platinum-based doublet in stage III resectable NSCLC, and due to significant improvements in both PFS and OS, further research into optimal timing of this blockade has taken place. A pilot study of 21 patients with resectable NSCLC in 2018 investigated administering a PD1 blockade with nivolumab prior to surgery, and showed a major pathological response of 45%.[40] Delivery of two doses of nivolumab prior to surgery did not delay surgery, with few AEs.[40] The NADIM trial also investigated the use of neoadjuvant nivolumab in stage IIIa resectable NSCLC, and showed 77.1% 24-month PFS and 90% OS.[41] The addition of nivolumab to chemotherapy did not result in a significantly higher incidence of AEs, and there was no delay to planned surgery.[41] The phase II NEOSTAR trial of 44 patients investigated the use of neoadjuvant PD1 blockade with nivolumab alone or in combination with ipilimumab prior to surgery in resectable NSCLC. The use of combination ICIs resulted in a higher pathological complete-response rate (38% vs 10%), indicating neoadjuvant ICIs, alone or in combination, can improve survival in advanced NSCLC.[42]

The use of concurrent ICIs with chemoradiation in stage III unresectable NSCLC in the KEYNOTE-799 trial evaluated response rate as per RECIST criteria and incidence of grade 3 or higher pneumonitis with the addition of pembrolizumab in comparison to standard-of-care treatment.[38] Although median OS and PFS were not reached after 1 year of follow-up, there was an objective response rate of 70% in standard-of-care treatment with and without pembrolizumab, with an incidence of 8% of grade 3 or higher pneumonitis demonstrating tolerable side effects of combination treatment.[43] An additional phase II trial assessed the use of consolidation pembrolizumab in unresectable stage III NSCLC in 93 patients.[44] Although the primary end point of time to metastatic disease or death was not reached, OS estimates of 80.5% at 12 months and 68.7% at 24 months indicated promising results with consolidation PD1 blockade.[44]

Atezolizumab is currently in a phase II trial (AFT-16, NCT03102242) assessing PDL1 blockage both before and after definitive chemoradiotherapy in stage III unresectable NSCLC, with four cycles being administered prior to platinum doublet chemotherapy, followed by 1 year of adjuvant atezolizumab therapy.[45] Although secondary end points are awaited, initial results show it has been well tolerated, with a disease-control rate of 82.4% for patients with PDL1-negative tumors and 90.9% for PDL1-positive tumors.[45] These studies emphasize the tolerability of

combined neoadjuvant treatment in resectable NSCLC, and current data suggest improved disease-response rates.

The use of consolidation durvalumab has been assessed in resectable NSCLC. The SAKK 16/14 trial on 67 patients with resectable stage IIIA NSCLC investigated the role of preoperative chemotherapy and durvalumab, followed by consolidation treatment for up to 1 year.[46] This single-arm phase II trial did not reach median event-free survival or OS at 28 months, but did demonstrate safety or presurgical ICI use and 1-year event-free survival of 73%.[46]

Immunotherapy in Stage III Oncogene-Addicted NSCLC

Since the PACIFIC trial, a number of studies have focused on investigating the efficacy of durvalumab in particular subsets of patients with NSCLC who may have differential responses to immunotherapy, such as *EGFR*-mutant NSCLC. A multicenter retrospective analysis of 37 patients investigating its use in *EGFR*-mutated stage III NSCLC, failed to show PFS or OS benefit in this subgroup (10.3 vs 6.9 months, P=0.993).[47] When durvalumab consolidation therapy was compared to consolidation treatment with EGFR tyrosine-kinase inhibitors (TKI), the survival benefit was significantly longer in the EGFR tyrosine-kinase inhibitor–treatment subgroup (P=0.023) highlighting that it may not offer survival benefits in tumors with different genomic features.[47] This was confirmed in a study evaluating durvalumab efficacy in *ERBB2*/*EGFR*-mutant stage III NSCLC, again demonstrating shorter PFS than the *ERBB2*/*EGFR* wild-type cohort.[48]

Toxicity of Immunotherapy in Stage III NSCLC

Durvalumab consolidation treatment has demonstrated improved PFS and OS compared to placebo; however, it has not come without immunorelated toxicities. ICIs can affect multiple organ systems.[49] The most common AEs of any grade in those receiving anti-PDL1 treatment are fatigue, gastrointestinal (bloody diarrhea, abdominal pain, hepatitis, and jaundice), endocrine (altered thyroid function and hypocalcemia), peripheral neuropathy, and dermatological irAEs.[50–53] The most common AE is skin rash, reported by up to 40% of patients, but severe dermatological AEs are rarely reported, even in those receiving combined immunotherapy.[54,55] Respiratory AEs, such as pneumonitis, are the most common cause of immunorelated deaths, and have been reported 7–23 months after commencing treatment.[56] The incidence of pneumonitis in clinical trials compared to real-world settings appears to vary quite significantly (3%–5% versus 19%, respectively) and may be multifactorial, related to patient selection, pharmacovigilance, and increased awareness of AEs.[57]

Pneumonitis is of particular interest in stage III NSCLC, as these patients are also at high risk of developing radiation pneumonitis due to the temporal proximity of chemotherapy, radiation treatment, and consolidation with durvalumab.[58,59] Differentiating between radiation pneumonitis and immunorelated pneumonitis can be difficult clinically due to timing of onset and overlapping symptoms, and thus the comparison of morphology on CT imaging has become increasingly important. The distribution of changes, extent of lung involvement, presence of ground-glass opacity, consolidation, fibrosis, acute respiratory distress syndrome, and the presence of sharp borders around the edge of the affected areas are all taken into consideration.[60] Radiation pneumonitis classically displays unilateral involvement, smaller areas confined to the radiation field, and sharp borders, whereas immunorelated pneumonitis tends to be bilateral with a larger area involved, and is less likely to display sharp borders.[60] Immunomediated pneumonitis is considered a diagnosis of exclusion, and workup to rule out other etiologies, including infection, should take place, with input from respiratory physicians as needed.[61]

The management of immunomediated pneumonitis includes corticosteroid therapy, holding or delaying treatment, or permanently discontinuing treatment in severe cases, according to the Common Terminology Criteria for Adverse Events grade of pneumonitis.[56,62] Patients who develop pneumonitis that does not clinically improve with corticosteroids may need rescue therapy with additional immunosuppressive agents, including infliximab, mycophenolate mofetil, or intravenous immunoglobulin.[62]

There is an increased incidence of severe pneumonitis, both radiation- and immunorelated, in patients with poorer performance status, worse lung function, prior respiratory disease, and smoking history.[59,63] Pulmonary function testing is not routinely performed prior to commencement of ICI treatment, but is used as part of the diagnosis of pneumonitis, commonly demonstrating a restrictive pattern and significantly decreased diffusion capacity of the lungs for carbon monoxide.[64] The development of a standardized patient assessment prior to commencement

of ICIs in patients with preexisting lung disease would identify those with poor lung function who may need heightened monitoring for AEs during their treatment course.[65–67]

The PACIFIC trial reported that 29.9% of patients who received durvalumab and 26.1% of those in the placebo group had grade 3 or 4 AEs, most commonly pneumonia.[26] Overall, 15.4% of patients who received durvalumab discontinued treatment secondary to AEs compared to 9.8% of patients in the placebo group.[26] The most frequent AE resulting in cessation of consolidation treatment was pneumonitis. Other commonly reported AEs included diarrhea, rash, and pruritus. Immunomediated AEs of any grade in the durvalumab group were approximately triple those in the placebo group (24.2% vs 8.1%).[26] Similar AE incidence was reported in follow-up studies.

Follow-up analysis of the PACIFIC trial data reported grade 3 or 4 AEs in 30.5% of the durvalumab group versus 26.1% of the placebo group, again reporting pneumonitis as the most common AE, with 4.8% of patients in the durvalumab group discontinuing treatment due to this compared to 2.6% of the placebo group.[32] Respiratory AEs remained the most common AE in other studies, but some reported a lower incidence of pneumonitis — as low as 15% compared to 23% in the PACIFIC trial.[37] The rate of AEs were higher in patients with a history of autoimmune disease, with one study reporting 78% of patients with a known diagnosis of autoimmune disease having an AE of any grade. Despite a higher incidence of AEs in this subgroup, it did not significantly affect PFS or OS.[37]

Cost of Durvalumab for Stage III NSCLC

Since publication of the PACIFIC trial, the importance of access to durvalumab for stage III NSCLC has been increasingly emphasized. Regulatory agencies in the US, Canada, Australia, Japan, Singapore, and India have approved durvalumab consolidation treatment in unresectable stage III NSCLC. Controversially, the European Medicines Agency (EMA) approved its use only in patients whose NSCLCs have PDL1 expression ≥1%. Multiple studies have demonstrated the cost-effectiveness of durvalumab, and although funding varies across different countries, the overall conclusion is that durvalumab consolidation treatment is cost-effective compared to combined chemoradiotherapy alone, accentuating the importance of increased access.[68–70] Cost-effectiveness analysis has shown no consolidation therapy resulted in a mean cost of US $185,944 and mean quality-adjusted life-years of 2.34. Durvalumab consolidation increased quality-adjusted life-years to 2.57, with an increase in mean cost to $201,563.[68] A retrospective study carried out in Japan in 2019 of 81 patients with unresectable stage III NSCLC found 70% would be eligible to receive durvalumab consolidation therapy based on PACIFIC criteria.[71] Since approval by the EMA in 2018, its administration has risen annually, and now approximately 50% of eligible patients with stage III NSCLC are gaining access to durvalumab.[72] A retrospective review of 82 patients in Japan with unresectable stage III NSCLC highlighted that although some patients may meet eligibility criteria for durvalumab therapy initially, this status may change after they undergo chemoradiotherapy, so initial eligibility for treatment may not coincide with real-world administration rates.[73]

Discussion

The use of ICIs has altered the landscape of anticancer treatment in diagnoses with previously poor outcomes. Anti-PDL1 maintenance treatment with durvalumab after combined chemoradiotherapy improves both PFS and OS in unresectable stage III NSCLC. This was first demonstrated in the PACIFIC trial, but multiple studies published after this have consolidated these results in the last 4 years in real-world settings. In this review, we have highlighted the prospective and real-world data in support of durvalumab maintenance in stage III NSCLC, other immunotherapeutic approaches for stage III NSCLC, such as neoadjuvant immunotherapy, immunotherapy for those with oncogene-addicted NSCLCs, and immunotherapy toxicity that is of particular interest in stage III NSCLC.

Our review has also highlighted several controversial issues in the use of immunotherapy for stage III NSCLC. Although the PACIFIC trial did not select for PDL1 status in its inclusion criteria and its access in the US and other countries did not select for it, a division developed when the EMA approval process required a PDL1 status ≥1%. PACIFIC trial criteria also specified a World Health Organization performance status of 0 or 1 and excluded patients with a history of any autoimmune disease.[26] However, stage III NSCLC can be considered a broad spectrum of disease, and subsequent studies have noted that a large proportion of patients with this disease have a performance status >1 when commencing treatment, highlighting that the patients enrolled in the original study may not fully represent a real-world population.[37]

Subsequent real-world studies have included a broader range of patients, including those with autoimmune disease and a performance status >1, confirming durvalumab benefits in more heterogeneous and real-world patient cohorts.[37] While the PACIFIC trial did not specify tumor analysis, follow-up studies have also demonstrated reduced efficacy of durvalumab in patients with *EGFR*-mutant NSCLCs.[47]

An open question in stage III NSCLC that remains unaddressed is the optimal duration of ICI therapy. Multiple trials have assessed continuing treatment for varying durations: until disease progression, unacceptable toxicity, or fixed duration of 1 or 2 years. Three trials assessing nivolumab — CA-209-003, Checkmate-153, and Checkmate-017/057 — varied from up to 2 years' treatment, 1 year versus continuous, and continuous treatment, respectively.[74–76] Current evidence suggests that continuing ICIs beyond 1 year can improve outcomes, including PFS and OS, up to 5 years compared to continuing docetaxel.[76] Pembrolizumab-treatment duration in Keynote-001 and Keynote-010 was either continuous or up to 2 years, respectively. In Keynote-001, continuous treatment showed an OS of 25% at 5 years in both treatment-naïve and previously treated advanced NSCLC.[77] Keynote-010 showed similar data: patients treated with 2 years of pembrolizumab showed increased OS, and a second course of pembrolizumab after disease progression provided significant disease control.[78] Atezolizumab duration in the OAK trial was continuous, and follow-up data after 2 years demonstrated a survival benefit compared to docetaxel.[79] All three ICIs here — nivolumab, pembrolizumab, and atezolizumab — work via the PD1–PDL1 pathway, and with the addition of durvalumab as a new consolidation therapy, further research into the optimum duration of treatment is required.

Lastly, as more patients survive from stage III NSCLC after durvalumab and live beyond 5 years, patients may enter an era of "survivorship" after NSCLC. Current issues of survivorship in lung cancer include but are not limited to physical symptoms, psychological distress and socioeconomic issues secondary to cost of treatment, and time spent out of work.[80] There may be unique issues related to survivorship after immunotherapy, such as the management of long-term immunotoxiciy, eg, hypothyroidism and pneumonitis.[81] A retrospective review of 159 patients who received nivolumab, pembrolizumab, or atezolizumab identified almost 40% of patients developed new or worsening AEs after 6 months of treatment.[81] This emphasizes the need to ascertain optimal treatment duration to increase PFS and OS, but limit the incidence of long-term toxicity. The development of a multidisciplinary immunorelated toxicity team has been shown to be beneficial and feasible in the acute management of ICI toxicity, and perhaps this approach with long-term survival is also required.[82] A study encompassing the importance of a multidisciplinary-team approach to survivorship issues post–ICI treatment used a 1-hour webcast available on demand for physicians to increase awareness of AEs, a resource that encompasses both medical and psychological long-term effects, including quality-of-life parameters.[83,84]

Advanced NSCLC has long been a diagnosis associated with poor outcomes, high symptom burden, and limited treatment options. The advent of immunotherapy, and in this case durvalumab consolidation treatment in stage III unresectable NSCLC, has been shown to improve survival significantly, providing hope to both clinicians and patients about the changing landscape of lung cancer management.

Disclosure

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