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Clinical Considerations for the Management of Advanced PD-L1 ≥50% Non-small Cell Lung Cancer In 2025: Should All Patients Be Treated the Same?

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Non-small Cell Lung Cancer with PD-L1 Tumour Proportion Score ≥50%

Despite advances in the treatment of non-small cell lung cancer (NSCLC) due to the advent of immunotherapy in the form of immune checkpoint inhibitors (ICI), NSCLC remains the leading cause of cancer-related death in Canada.[1] In addition, multiple first-line options exist for patients with NSCLC without a sensitizing mutation in epidermal growth factor receptor (*EGFR*) or anaplastic lymphoma kinase (*ALK*), but no head-to-head comparisons of first-line treatment regimens have been made in randomized controlled trials. The programmed cell death ligand 1 (PD-L1) tumour proportion score (TPS)—which is derived from immunohistochemistry analysis—emerged as an important biomarker early in the advent of ICI in NSCLC. Approximately 30% of patients with NSCLC have PD-L1 expression in at least 50% of the tumour.[1] This ≥50% threshold was established through retrospective biomarker analyses in pivotal trials, such as the KEYNOTE-001[2] and KEYNOTE-024 trials,[3] in which patients with higher PD-L1 expression demonstrated superior response rates and overall survival (OS) benefits with immunotherapy compared to chemotherapy. The KEYNOTE-001 trial first identified ≥50% PD-L1 expression as an optimal cut-off for predicting response to pembrolizumab (anti-programmed cell death protein 1 [PD-1] antibody), showing an objective response rate (ORR) of ~45% in this group. Subsequently, the KEYNOTE-024 trial confirmed that patients with PD-L1 ≥50% had significantly improved progression-free survival (PFS) and OS with pembrolizumab than those treated with chemotherapy (hazard ratio [HR] for PFS: 0.50, 95% confidence interval [CI]: 0.37–0.68). Similar findings from the IMpower110[4] (atezolizumab) and EMPOWER-Lung 1[5] trials (cemiplimab) reinforced ≥50% PD-L1 TPS as a clinically meaningful biomarker. As a result, ≥50% PD-L1 TPS became an actionable biomarker in regulatory approvals and treatment guidelines, guiding immunotherapy decisions in advanced NSCLC.

ICI Monotherapy

Randomized controlled trials have demonstrated that ICI monotherapy consisting of pembrolizumab, atezolizumab, or cemiplimab, is an excellent first-line treatment option for patients with high (≥50%) PD-L1 TPS NSCLC without an actionable driver. ICI demonstrated benefits in ORR, PFS, and OS compared to chemotherapy. The use of pembrolizumab in patients with a PD-L1 TPS ≥50% is supported by the Phase III KEYNOTE-024 trial, which randomized 305 treatment-naïve patients with advanced NSCLC to receive either pembrolizumab monotherapy or platinum-doublet chemotherapy.[6] Pembrolizumab significantly improved PFS compared to chemotherapy (median PFS: 10.3 vs. 6 months; HR: 0.50, 95% CI: 0.37–0.68) and had a higher ORR

(45% vs. 28%).[3] At 5 years of follow-up, pembrolizumab demonstrated improved OS compared to chemotherapy (median OS: 26.3 vs. 13.4 months; HR: 0.62, 95% CI: 0.48–0.81).[7] The addition of ipilimumab (anti-cytotoxic T lymphocyte-associated protein 4 [CTLA-4]) to pembrolizumab did not improve efficacy and increased toxicity.[8] Atezolizumab (anti-PD-L1) in this patient population was studied as part of the IMpower110 trial, which included 572 patients with treatment-naïve stage IV NSCLC with PD-L1 expression. This study demonstrated that among 205 patients with high PD-L1 expression, atezolizumab improved OS compared to platinum-based chemotherapy (20.2 vs. 13.1 months; HR: 0.59, 95% CI: 0.40–0.89).[9] Median PFS was also superior with atezolizumab (8.1 vs. 5.0 months; HR: 0.63, 95% CI: 0.45–0.88), and the ORR was higher (38% vs. 29%).[9] Lastly, cemiplimab (anti-PD-1), was evaluated in the EMPOWER-Lung 1 trial, which enrolled 565 patients with NSCLC and PD-L1 expression of at least 50%, and showed that cemiplimab improved OS compared to platinum-doublet chemotherapy at a 35-month follow-up (26.1 vs. 13.3 months; HR: 0.57, 95% CI: 0.46–0.71).[10] None of these regimens have been compared head-to-head, but pembrolizumab has the advantage of having approval to be administered every 6 weeks, which is preferred for some patients over the 3 week intervals which require more frequent visits to the hospital. Severe grade ≥3 adverse events in response to single agent anti-PD(L)-1 therapy occur in 10–30% of patients.[1]

ICI in Combination with Platinum-Doublet Chemotherapy

The KEYNOTE-189 trial enrolled 616 patients with metastatic non-squamous NSCLC, who were randomized to receive either a combination of pembrolizumab, pemetrexed, and platinum-based chemotherapy, or placebo plus pemetrexed and platinum-based chemotherapy.[11] Patients were stratified based on PD-L1 expression (TPS ≥1% vs. <1%), with further division of the PD-L1 ≥1% group into PD-L1 1–49% and ≥50% subgroups. The trial demonstrated superior outcomes for the pembrolizumab combination therapy in all PD-L1 subgroups compared to standard chemotherapy. In the TPS ≥50% subgroup (N=202), the pembrolizumab combination therapy resulted in a one-year OS rate of 73% vs. 48% for placebo plus chemotherapy (HR: 0.42), with an ORR of 61.4% vs. 22.9%. An updated analysis at 5 years of follow-up demonstrated continued OS benefit in the PD-L1 ≥50% subgroup (29.6 vs. 21.4 months, HR: 0.68).[12]

Similarly, the KEYNOTE-407 trial focused on metastatic squamous NSCLC and demonstrated improved outcomes with pembrolizumab and chemotherapy compared to chemotherapy alone.[13] The combination therapy resulted in an ORR of 58.4% vs. 35.0% (P=0.0004) and a median OS of 15.9 versus 11.3 months (HR: 0.64, P=0.0008). Among patients with a PD-L1 TPS ≥50%, the one-year survival rate was 63.4% versus 51.0% (HR: 0.64), with continued benefit at 5 years (23.3 vs. 8.3 months, HR: 0.68).[14] These findings from the KEYNOTE-189 and KEYNOTE-407 trials indicate that combination chemoimmunotherapy is effective as a first-line treatment for both metastatic squamous and non-squamous NSCLC, regardless of PD-L1 expression. Notably, the PD-L1 ≥50% subgroup exhibited a stronger therapeutic response across both trials. Nevertheless, the combination across all studies was associated with grade ≥3 adverse events in 50–70% of patients.[1]

Should all Patients with NSCLC with High PD-L1 Expression Be Treated the Same?

A direct comparison between ICI monotherapy and a combination of ICI with chemotherapy in patients with PD-L1-high NSCLC has not been conducted in a randomized controlled trial. However, indirect evidence from existing studies, retrospective studies, and meta-analyses provides insights into their relative efficacy.

A meta-analysis of 5 randomized trials indicated that the combination of pembrolizumab and chemotherapy led to superior ORR compared to pembrolizumab monotherapy (relative risk: 1.6, 95% CI: 1.2–2.2) and improved PFS (HR: 0.55, 95% CI: 0.32–0.97). However, there was not a statistically significant difference in OS between the two approaches (HR: 0.76, 95% CI: 0.51–1.14).[15]

Another analysis that included data from 12 trials, of which half evaluated chemoimmunotherapy and the other half immunotherapy monotherapy in patients with PD-L1 expression ≥50%, found that the median PFS was longer for chemoimmunotherapy than immunotherapy monotherapy (9.6 vs. 7.1 months, HR: 0.69, 95% CI: 0.55–0.87). Additionally, the ORR was higher in the chemoimmunotherapy

group (61% vs. 43%). While OS showed a trend toward improvement with chemoimmunotherapy (HR: 0.82), it did not reach statistical significance. Furthermore, among patients aged 75 years or older, there was a nonsignificant trend toward worsened survival with chemoimmunotherapy (HR: 1.7).[16]

Some clinicians consider the ORR and PFS advantage of adding chemotherapy to immunotherapy compelling, especially in patients with symptomatic disease, high disease burden, or rapidly progressive disease, while others argue that the absence of a clear OS benefit supports the use of immunotherapy alone in this selected patient population. The choice between these strategies may depend on patient-specific factors, including disease burden, comorbidities, and treatment goals. For those whose tumours have ≥50% PD-L1 TPS and a low risk of symptomatic decline if treatment is ineffective, either ICI monotherapy or chemoimmunotherapy are appropriate. Patients who value minimizing time and toxicity of treatment may choose immunotherapy monotherapy, while patients who value delayed time to progression may opt for chemoimmunotherapy.

Real-world retrospective data have also aimed to solve this conundrum—in a large analysis from Memorial Sloan Kettering and the Dana Farber Cancer Institute, our group retrospectively analyzed 866 patients treated with immunotherapy or chemoimmunotherapy in the first-line setting.[17] Relative to immunotherapy, and similar to previously shown results, chemoimmunotherapy was associated with improved ORR and PFS, but not OS, in the PD-L1 TPS ≥50% subgroup. Using propensity-adjusted analyses, only never-smokers in the PD-L1 TPS ≥50% subgroup derived a differential survival benefit from chemoimmunotherapy vs. immunotherapy. Among patients with very high PD-L1 TPS (≥90%), there were no differences in outcome between treatment groups, suggesting that immunotherapy alone may be sufficient in this subgroup. These results corroborated earlier findings by Perrol et al.[18]

Conclusions

The clinical trial results reviewed here highlight that the addition of chemotherapy to immunotherapy increases the probability of an initial response in a heterogeneous patient population with differential sensitivity to chemotherapy and immunotherapy. However, long-term benefit appears largely driven by whether PD-L1 blockade generates durable antitumour immunity. Retrospective data, which have inherent limitations, demonstrate that chemoimmunotherapy should be considered for never-smokers, even in the presence of high PD-L1 expression. It is possible that the advantage observed for chemoimmunotherapy in the never-smoker population with PD-L1 TPS ≥50%, might represent a subset of NSCLC, which, although it is genomically negative for drivers such as EGFR or ALK, may be a group of patients whose cancer has yet unidentified drivers, for which existing data suggests inferior immunotherapy response. For example, several studies have identified oncogenic fusions using RNA sequencing in patients without a driver alteration identified through targeted next-generation sequencing (NGS) methods, highlighting the importance of broad NGS profiling in the clinic. Lastly, emerging biomarkers, such as the gut microbiome,[19] and artificial intelligence (AI)-based analysis of pathology slides,[20] may further help tailor treatment decisions.

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