Editorial Commentary

The role of anti-PD-1/PD-L1 monotherapy as first-line treatment of metastatic NSCLC without targetable mutations and PD-L1 TPS 1–49%

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Introduction

The use of immunotherapy with monoclonal antibodies (mABs) against programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) has revolutionized treatment in non-small cell lung cancer (NSCLC). Pembrolizumab, nivolumab, and atezolizumab were initially approved by the FDA for treatment of NSCLC in the second-line setting based on improvements in overall survival (OS) compared to docetaxel, as summarized in *Table 1*. Notably, patients with NSCLC with molecular alterations in *EGFR* and *ALK* were permitted to enroll in these trials if their tumors had progressed on prior tyrosine kinase inhibitor therapy; however, OS benefit was not seen in these patients based on subgroup analyses (1-4).

FDA approval for the anti-PD-L1 agent pembrolizumab in NSCLC was based on the Phase II/III KEYNOTE-010 study, which randomized patients with previously treated advanced NSCLC and PD-L1 expression via tumor proportion score (TPS) ≥1% to pembrolizumab at low dose (2 mg/kg), pembrolizumab at high dose (10 mg/kg) or docetaxel (3). Pooled OS at 3.5 years of patients receiving either dose of pembrolizumab and with PD-L1 TPS ≥1% was 11.8 months, compared to 8.4 months among patients who received chemotherapy [hazard ratio (HR) 0.69, 95% CI: 0.60 to 0.80]. Median OS was particularly higher in patients with PD-L1 TPS ≥50%, with median OS 16.9 months in this population (5).

Based on the success of immunotherapy in the second-line setting, use of checkpoint inhibitors were subsequently evaluated in the front-line setting, both as single agents and in combination with chemotherapy. KEYNOTE-024 evaluated the role of pembrolizumab monotherapy in the first-line setting for patients with metastatic NSCLC, PD-L1 TPS ≥50% expression and lacking *EGFR* or *ALK* activating mutations (6). Based on the results of this study which showed a significantly greater objective response rate (ORR), greater PFS as well as improved median OS (*Table 1*) in patients receiving pembrolizumab monotherapy versus cytotoxic chemotherapy (7), single-agent pembrolizumab received FDA approval for first-line therapy for patients with NSCLC and PD-L1 TPS ≥50%. Similarly, atezolizumab as a single-agent has also been approved for treatment of NSCLC with PD-L1 TPS ≥50% or tumor-infiltrating immune cells ≥10% of tumor area, based on results of IMpower110 showing improved OS relative to platinum based chemotherapy (*Table 1*) (8).

Furthermore, multiple studies have led to the approval of front-line chemotherapy plus immunotherapy combination regimens in patients with NSCLC without activating mutations. In KEYNOTE-189, pembrolizumab in combination with platinum/pemetrexed resulted in improved ORR, improved median PFS, and improved median OS compared to platinum/pemetrexed in non-squamous NSCLC regardless of PD-L1 TPS (*Table 1*) (9,10). Similarly, results from IMpower150 showed that the regimen of ABCP (atezolizumab, bevacizumab, carboplatin, paclitaxel) also had improved PFS and improved OS regardless of PD-L1 staining compared to carboplatin, paclitaxel and bevacizumab (*Table 1*) (11). Patients with squamous NSCLC were evaluated in KEYNOTE-407, where pembrolizumab in combination with platinum/taxane also showed improved median PFS and median

Table 1 Immunotherapy clinical trials in non-small cell lung cancer (NSCLC)

Clinical trial	Enrollment group	Comparator	ORR	PFS	OS
CHECKMATE 017	Second-line; advanced, squamous NSCLC	Nivolumab *vs.* docetaxel	20% *vs.* 9%	3.5 *vs.* 2.8 months (HR 0.62, 95% CI: 0.47–0.81)	9.2 *vs.* 6.0 months (HR 0.59; 95% CI: 0.44–0.79)
CHECKMATE 057	Second-line; advanced, non-squamous NSCLC	Nivolumab *vs.* docetaxel	19% *vs.* 12%	2.3 *vs.* 4.2 months (HR 0.92, 95% CI: 0.77–1.1)	12.2 *vs.* 9.4 months (HR 0.73, 95% CI: 0.59–.89)
OAK	Second-line; advanced NSCLC	Atezolizumab *vs.* docetaxel	14% *vs.* 13%	2.8 *vs.* 4 months (HR 0.95, 95% CI: 0.82–1.10)	13.8 *vs.* 9.6 months (HR 0.73, 95% CI: 0.62–0.87)
KEYNOTE-010	Second-line; advanced NSCLC with PD-L1 ≥1%	Pembrolizumab (pooled 2 and 10 mg/kg) *vs.* docetaxel	18% *vs.* 9%	4.0 *vs.* 4.1 months (HR 0.83, 95% CI: 0.72–0.96)	11.8 *vs.* 8.4 months (HR 0.69, 95% CI: 0.60–0.80)
KEYNOTE-024	First-line; advanced NSCLC with PD-L1 ≥50%	Pembrolizumab *vs.* chemotherapy	45% *vs.* 28%	10.3 *vs.* 6 months (HR 0.50, 95% CI: 0.37–0.68)	30 *vs.* 14.2 months (HR 0.63, 95% CI: 0.47–0.86)
IMpower110	First-line; advanced NSCLC with PD-L1 ≥50% on Tumor Cells or ≥10% on Immune Cells	Atezolizumab *vs.* chemotherapy	38% *vs.* 29%	8.1 *vs.* 5.0 months (HR 0.63, 95% CI: 0.45–0.88)	20.2 *vs.* 13.1 months (HR 0.59, 95% CI: 0.40–0.89)
KEYNOTE-189	First-line; advanced non-squamous NSCLC	Pembrolizumab + chemotherapy *vs.* dhemotherapy	48% *vs.* 19%	9.0 *vs.* 4.9 months, (HR 0.48, 95% CI: 0.40–0.58)	22.0 *vs.* 10.7 months, HR 0.56, 95% CI: 0.45–0.70
IMpower150	First-line; advanced, non-squamous NSCLC	Atezolizumab + bevacizumab + chemotherapy (ABCP) *vs.* bevacizumab + chemotherapy (BCP)	64% *vs.* 48%	8.3 *vs.* 6.8 months (HR 0.62, 95% CI: 0.52–0.74)	19.2 *vs.* 14.7 months (HR 0.78 95% CI: 0.64–0.96)
KEYNOTE-407	First-line; advanced squamous NSCLC	Pembrolizumab + chemotherapy *vs.* chemotherapy	58% *vs.* 38%	6.5 *vs.* 4.8 months (HR 0.68, 95% CI: 0.45–0.70)	15.9 *vs.* 10.9 months (HR 0.64, 95% CI: 0.49–0.85)
CHECKMATE 9LA	First-line; advanced NSCLC	Nivolumab/ipilimumab + 2 cycles of chemotherapy *vs.* chemotherapy	38% *vs.* 25%	6.8 *vs.* 5.0 months (HR 0.70, 95% CI: 0.57–0.86)	15.6 *vs.* 10.9 months (HR 0.66, 95% CI: 0.55–0.88)

OS compared to platinum/taxane regardless of PD-L1 status (12). Lastly, in CheckMate-9LA, the combination of nivolumab and ipilimumab administered with two cycles of platinum-doublet chemotherapy was compared to four cycles of platinum-doublet chemotherapy and the 4-drug combination resulted in improved median PFS and improved median OS (13).

Based on the results of these studies, the recommended first-line therapy and regulatory approvals for first-line therapy in metastatic NSCLC without targetable mutations included pembrolizumab or atezolizumab monotherapy for patients with PD-L1 TPS ≥50%, as an alternative to combination chemotherapy and immunotherapy regardless of PD-L1 TPS. However, the findings from KEYNOTE-042 and the regulatory approval for pembrolizumab monotherapy resulted in lingering uncertainty regarding which patients are potentially appropriate for pembrolizumab monotherapy in the first-line setting for NSCLC in patients with *EGFR/ALK* wildtype tumors with PD-L1 expression 1–49%.

KEYNOTE-042

KEYNOTE-042 is an ongoing phase III trial of first-line therapy in patients with advanced, *EGFR/ALK* wild-type NSCLC and ≥1% PD-L1 expression (14). In this study, 1,274 patients were randomized to treatment with pembrolizumab monotherapy or platinum-doublet chemotherapy. Overall survival in patients with PD-L1 TPS ≥1 percent was found to be 17 months in those receiving pembrolizumab monotherapy versus 12 months in patients receiving chemotherapy (HR 0.81, 95% CI: 0.71–0.93).

In this study, the 599 patients with tumor PD-L1 TPS ≥50 percent appeared to have the greatest benefit, with OS of 20 months versus 12 months in the chemotherapy arm (HR 0.69, 95% CI: 0.56–0.85), mirroring the pattern of results seen in KEYNOTE-010. Given the stronger benefit in patients with PD-L1 TPS ≥50 percent, there is concern that the overall survival benefit seen in patients with PD-L1 TPS ≥1% is driven by the subgroup of patients with ≥50% PD-L1 TPS (15-17). This hypothesis is supported by an exploratory subgroup analysis of patients in KEYNOTE-042 with PD-L1 TPS between 1–49% which showed OS of 13.4 months in patients receiving pembrolizumab versus 12.1 months in those receiving chemotherapy (HR 0.92, 95% CI: 0.77–1.11) (14).

In part due to the aforementioned subgroup analysis, NCCN guidelines do not list pembrolizumab monotherapy as a preferred first-line regimen for NSCLC with *EGFR/ALK* wild-type and with PD-L1 TPS 1–49%, rather, the addition of chemotherapy is recommended (18). However, there may be reasons to consider immunotherapy alone as an initial therapy when taking into account baseline patient comorbidities and performance status (PS), tumor burden, and predictive markers beyond PD-L1.

Patients ineligible for chemotherapy

When choosing between single-agent immunotherapy or combination immunotherapy with chemotherapy in the first-line setting for advanced NSCLC, the presence of certain baseline comorbidities in a patient may favor the avoidance of chemotherapy. For example, patients with calculated creatinine clearance of less than 50 were excluded from KEYNOTE-189, which evaluated the use of pembrolizumab in combination with pemetrexed and platinum in non-squamous NSCLC, (9). Notably, pemetrexed administration is not recommended for patients with calculated creatinine clearance less than 45, whereas no dose adjustments are required for baseline renal dysfunction in patients receiving pembrolizumab alone. Moreover, in KEYNOTE-407, which evaluated pembrolizumab in combination with platinum and taxane for squamous NSCLC, peripheral neuropathy was seen in 16% of patients, alopecia in 36% of patients, and anemia in 52% of patients (12). Given that none of these adverse events are seen to a significant degree in patients receiving pembrolizumab monotherapy (14), single-agent immunotherapy may be a preferred agent in patients with these baseline comorbidities or who wish to avoid alopecia.

Further, up to 30–40% of patients with NSCLC have an ECOG PS of 2; however, the majority of clinical trials that have led to first-line therapy approvals, including KEYNOTE-042, have only included patients with ECOG PS 0-1 (19). Platinum-based chemotherapy is not routinely recommended for patients with PS 2 or worse, but in the "real world" these patients are often offered treatment if improvement in their disease burden could lead to functional improvement. However, it is unknown whether the data from patients with PS 0 or 1 can be extrapolated to those with a worse PS.

In an effort to address this question, the PePS2 trial was a UK-based, single-arm, phase 2 clinical trial evaluating the use of pembrolizumab in patients with NSCLC and PS of 2 (20). Patients were stratified by both PD-L1 TPS (<1%, 1–49%, and ≥50%) and line of therapy. Outcomes from PePS2 showed durable clinical benefit (DCB), defined as stable disease or better at 18 weeks after initiation of therapy, in 40.5% of patients with PD-L1 TPS 1–49% receiving first-line pembrolizumab, compared to 44.6% in patients with PD-L1 TPS 50–100% receiving first-line pembrolizumab. Toxicity in this trial, defined as treatment-related dose delay or treatment discontinuation due to adverse event, had an incidence of 28%, reflecting the feasibility of pembrolizumab administration in this group of patients. Further, grade 3 or higher AEs related to pembrolizumab were found to be 15%, comparable to that seen in KEYNOTE-042, in which 18% of patients had grade 3 or higher AEs.

Thus, the available evidence suggests that it would be reasonable to consider pembrolizumab monotherapy in NSCLC with TPS PD-L1 1–49% if PS and baseline comorbidities such as renal dysfunction, cytopenias, or peripheral neuropathy preclude tolerance or administration of platinum-based chemotherapy in combination with immunotherapy.

Burden of disease

When looking at the details of the overall survival curves in KEYNOTE-042, there appears to be a heterogenous response to pembrolizumab, both among the PD-L1 TPS 1% or greater population, as well as within the exploratory analysis of PD-L1 TPS1–49% population. Specifically, within both populations, the overall survival curves cross approximately 7 months after the initiation of therapy. This suggests that a subset of patients receiving pembrolizumab appear to do poorly as compared to those receiving chemotherapy upfront, while another subset of patients may have better long-term results with pembrolizumab in the front-line setting (17). Similar results with crossing of the overall survival curves at around 6 months were noted in the MYSTIC trial comparing durvalumab to chemotherapy in the first-line setting (21). However, these results were not seen in the aforementioned trials of front-line combination chemotherapy with immunotherapy (9,11,12), suggesting that a subgroup of patients, such as those with significant tumor or symptom burden, do benefit from the incorporation of chemotherapy upfront with immunotherapy.

Thus, when selecting a patient for upfront pembrolizumab monotherapy, one must also consider the burden of disease and how well any progression of disease may be tolerated For example, patients with minimal disease burden may be able to tolerate some degree of progression of disease, for which chemotherapy can then be considered. Given that some patients will have durable response to single-agent immunotherapy—KEYNOTE-001 showed that patients with tumor PD-L1 TPS 1–49% had 5 year OS of 15%—single-agent immunotherapy may allow for the chance of a durable response without ever having side effects from combination chemotherapy with immunotherapy (22).

Predictors of response beyond PD-L1

Moreover, relying solely on PD-L1 as a predictor of response to immunotherapy can be misleading. For example, while the FDA approval for single-agent pembrolizumab in the first-line setting specifically excludes those with *EGFR* and *ALK* alterations, we agree with the NCCN guidelines and preferentially choose first-line targeted therapy for those with molecular alterations in *ROS1*, *BRAF*, *MET* exon 14, *RET* or *NTRK*, regardless of the tumor PD-L1 status (18). Another consideration when using a specific PD-L1 expression cutoff to determine therapy is the heterogeneity of expression within the tumor and, subsequently, in biopsy specimens (23); in one study by Ilie *et al.*, there was a discordance rate of 48% for PD-L1 expression between lung biopsies and matched resected tumors; in all cases, the biopsy specimens had underestimated the PD-L1 status that was observed on the whole tissue sample (24).

Further, it is notable that in KEYNOTE-042, subgroup analyses of overall survival showed benefit in former smokers, but not in never smokers or current smokers. While not specifically evaluated in patients with TPS 1–49%, this OS benefit for smokers was present across all PD-L1 subgroups (TPS ≥50%, TPS ≥20%, and TPS ≥1%).

Thus, there can be significant limitations if relying only on PD-L1 expression as a biomarker of response to immunotherapy. As such, utilizing a strict cutoff of PD-L1 TPS 50% or greater may result in fewer patients being considered eligible to benefit from pembrolizumab monotherapy. Thus, consideration of the source of the biopsy specimen, as well as other predictive factors such as smoking status, may increase the number of patients who could potentially be considered for and receive the benefits of pembrolizumab monotherapy.

Incorporating into clinical practice

Because the FDA approved options for metastatic NSCLC without a targetable mutation and PD-L1 TPS 1–49% include both histology-specific platinum-based doublet with immunotherapy, and single agent immunotherapy alone, either can be considered for this patient subgroup. When considering the use of single-agent pembrolizumab as first-line therapy for NSCLC with PD-L1 TPS 1–49%, there is no head-to-head comparison of pembrolizumab monotherapy to combination therapy with chemotherapy and immunotherapy. However, based on cross-trial comparisons of ORR and PFS in NSCLC with PD-L1 TPS 1–49%, we concede that combination therapy with chemotherapy and immunotherapy is the preferred regimen for the majority of patients (15-17).

However, there are multiple reasons to consider pembrolizumab alone in this patient population. As we have discussed, certain patients may have baseline comorbidities such as renal dysfunction that precludes the use of pemetrexed. For patients with squamous NSCLC being considered for taxanes, certain side effects such as cytopenias, alopecia, or peripheral neuropathy may wish to be avoided, and single-agent pembrolizumab may be a reasonable alternative in this subset of patients.

Furthermore, we sometimes consider a "hybrid" approach in which immunotherapy is initiated, with consideration of subsequent addition of chemotherapy depending on response and tolerability. This approach can be considered in patients with manageable disease burden, in whom an immediate response is not necessarily needed, and in whom there are concerns about the toxicities associated with combination chemotherapy with immunotherapy. As mentioned above, careful patient selection for the use of pembrolizumab monotherapy is important given a subset of patients with tumor PD-L1 TPS 1–49% may respond poorly to single-agent pembrolizumab in the front-line setting, as compared to chemotherapy. Because of this, we usually do scans after only 6 weeks of therapy to identify rapidly progressing patients. In patients for whom an immediate tumor response is needed, combination chemotherapy with immunotherapy would still be our preferred option.

Ultimately, regulatory approval of pembrolizumab monotherapy in the front-line setting for NSCLC with PD-L1 ≥1% has further expanded the growing options available to patients and providers. There is some concern that first-line pembrolizumab monotherapy for NSCLC with PD-L1 1–49% may be inferior to combination pembrolizumab with chemotherapy; however, this must be weighed against pembrolizumab's generally favorable tolerability. Further exploration of other predictive biomarkers of response to immunotherapy such as incorporating clinical characteristics such as smoking status, tumor mutational burden, and early biomarkers of response such as changes in ctDNA levels may also inform decision making in the future (25).

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