Review Article

Non-small cell lung cancer PDL1 >50%—should we go single or combo?

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Abstract: Recent years have witnessed a revolution in the era of immune checkpoint inhibitors (ICIs). It has greatly impacted the oncological field and especially advanced non-small cell lung cancer (NSCLC) treatment. Here, we summarized the 3 main treatment protocols for a specific population of NSCLC with strong PD-L1 staining (PD-L1 ≥50%); which include ICI (e.g., pembrolizumab) monotherapy, ICI in combination with chemotherapy or combination ICIs. To date, it is uncertain whether there is a therapeutic difference amongst the PD-L1 TPS ≥50% group in comparison to other PD-L1 subdivisions. The findings reviewed here show that the combination ICI with chemotherapy yields the best response rate in comparison to other treatment protocols. Crucially, this treatment protocol is highly suggested for patients with high disease burden, especially for those with liver or brain involvement.

Keywords: Immune checkpoint inhibitors (ICI); PD-L1; combination therapy; non-small cell lung cancer (NSCLC); KEYNOTE

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Introduction

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies which function through blocking the inhibitory immune-surveillance of tumor cells pathways. Most common pathways include programmed death-1 (PD-1) on T-cells, programmed death ligand-1 (PD-L1) on tumor cells, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) on activated T-cells (1).

ICIs (e.g., pembrolizumab) have become a major landscape treatment in advanced non-small cell lung cancer (NSCLC) (2). Recently, it represents the novel standard of care, either as monotherapy, in patients with PD-L1 tumor proportions score (TPS) expression ≥50%, or in combination with doublet platinum-based chemotherapy, regardless of histology and PD-L1 expression levels. These treatment standards have shown survival benefit, and safe manageable adverse events profile compared to standard chemotherapy as summarized in *Table 1*.

Recently FDA has approved the combined therapy of nivolumab with ipilimumab for NSCLC (10). Although the therapeutic options are increasing, there is still an unmet need for biomarkers to lead a better drug selection and particularly for the PDL1 >50% cohort, which may have significant benefit from any of those regimens.

Currently, there are two main biomarkers to predict response to ICIs; TPS for PD-L1 immunohistochemistry (IHC) and tumor mutation burden (TMB) (11,12). Here,

Table 1 Outcome summary of NSCLC clinical trials with PD-L1 status ≥50%

First line treatment	Study (phase III)	NSCLC histology	PD-L1 status	Overall survival/response rate	Reference
Single immunotherapy	KEYNOTE 024: Cohort A: pembrolizumab; Cohort B: chemotherapy	Squamous/ non-squamous	TPS ≥50%	6 months survival rate: 80.2% *vs.* 72.4% (HR 0.6; P=0.005)	(3,4)
				3 years survival rare: 43.7% *vs.* 24.9% (HR 0.49)	
				Median OS: 30 *vs.* 14.2 months (HR 0.63)	
				ORR: 44.8% *vs.* 27.8%	
	KEYNOTE 042: Cohort A: pembrolizumab; Cohort B: chemotherapy	Squamous/ non-squamous	TPS ≥50%	2-year survival rate: 45% *vs.* 30%	(5)
				Median OS: 20 *vs.* 12.2 months (HR 0.69; P=0.0003)	
				ORR: 39% *vs.* 32%	
Combination chemo-immunotherapy	KEYNOTE 189: Cohort A: chemotherapy + pembrolizumab; Cohort B: chemotherapy + placebo	Non squamous	TPS ≥50%	1-year survival rate: 73% *vs.* 48% (HR, 0.42)	(6-8)
				2-year survival rate: 51.9% *vs.* 39.4% (HR 0.59)	
				Median OS: NR (20.4 months–NE)	
				ORR: 61.4% *vs.* 22.9%	
	KEYNOTE 407: Cohort A: Chemotherapy + pembrolizumab; Cohort B: chemotherapy + placebo	Squamous	TPS ≥50%	1-year survival rate: 63.4% *vs.* 51.0% (HR 0.64; P<0.0008)	(9)
				Median OS: NR (11.3–NE)	
				ORR: 60.3% *vs.* 32.9%	
Combination immunotherapy	CHECKMATE 227: Cohort A: nivolumab + ipilimumab; Cohort B: nivolumab; Cohort C: chemotherapy	Squamous/ non-squamous	TPS ≥50%	1-year survival rate: 67% *vs.* 61% *vs.*54%	(10)
				2-year survival rate: 48% *vs.* 42% *vs.* 36%	
				Median OS: 21.2 *vs.* 18.1 *vs.* 14 months, cohort A, B, C, respectively. (HR 0.79 cohort A *vs.* C)	
				ORR: 44.4% *vs.* 36.9% *vs.* 35.4%	

NSCLC, non-small cell lung cancer; TPS, tumor proportion score; OS, overall survival; PFS, progression free survival; ORR, objective response rate; HR, hazard ratio; NR, not reached; NE, not estimated.

we will discuss the updated data for single *vs.* combinational therapy for the specific population of NSCLC with strong PD-L1 staining.

Single immunotherapy as first-line treatment of advanced NSCLC, PD-L1 expression ≥50%

There are two-phase III trials that have confirmed the benefit of immunotherapy as single agent in comparison to doublet platinum chemotherapy, in advanced NSCLC with PD-L1 expression ≥50%.

KEYNOTE-024 is a multicenter; phase III trial, which enrolled 305 patients with advanced NSCLC PD-L1 TPS ≥50% (3). These patients were randomized to receive standard platinum chemotherapy (4-6 cycles) versus pembrolizumab 200 mg every 3 weeks. After a median 11.2 months, it was concluded that all the results favored pembrolizumab, including progression-free survival PFS (HR 0.50; P<0.001), overall survival OS (HR 0.60; P=0.005) and objective response rate (ORR 44.8% *vs.* 27.8%) compared to standard chemotherapy. Moreover, a further updated analysis of KEYNOTE-024 after median follow-up of more than 3 years has shown the effectiveness of pembrolizumab with median OS of 30 months compared to 14 months (HR 0.63) in standard chemotherapy in spite of cross-over design of the study (4).

The second multicenter phase III trial (KEYNOTE-042) enrolled 1,274 patients with advanced NSCLC subdivided in 3 different cohorts according to PD-L1; TPS ≥1%, ≥20% and ≥50% (5). The patients were randomized to receive pembrolizumab 200 mg every 3 weeks *vs.* platinum-based chemotherapy. After median follow-up of 13 months,

the trial demonstrated a significant improvement in OS (20 *vs.* 12.2 months) in PD-L1 TPS ≥50% subgroup (N=300) who were treated with pembrolizumab compared to standard chemotherapy (HR 0.69; P=0.0003). Meanwhile, in patients with PD-L1 TPS ranging 1–49% no significant OS improvement has been observed (17 *vs.* 12 months) compared to chemotherapy arm (HR 0.92).

Based on these two groundbreaking trials, pembrolizumab monotherapy is considered a standard first-line option for patients with advanced NSCLC and PD-L1 TPS ≥50%.

Combination immuno-chemotherapy as first-line treatment of advanced NSCLC, PD-L1 expression ≥50%

Following the approval of pembrolizumab for NSCLC with strong PD-L1 expression, as discussed above, two additional positive clinical trials lead to a preferred regimen of combination of chemotherapy with pembrolizumab over chemotherapy alone in all NSCLC who are negative for EGFR and ALK, unrelated to PD-L1 status. Unfortunately, there is no study comparing the benefit of adding chemotherapy to pembrolizumab for the strong PD-L1 sub-population.

KEYNOTE-189 trial enrolled 616 metastatic non-squamous NSCLC patients, who were randomized 2:1 to receive pemetrexed and platinum-based therapy plus either pembrolizumab (200 mg every 3 weeks for 4 cycles) or placebo (6). This was followed by pembrolizumab or placebo for up to a total of 35 cycles plus pemetrexed maintenance therapy. The patients were stratified according to PD-L1 expression (TPS ≥1% *vs.* <1%). Furthermore, patients within TPS ≥1% group were further equally divided to TPS 1–49% and ≥50% subgroups. The trial concluded that the benefit of the pembrolizumab combination therapy is superior in all PD-L1 subgroups compared to standard chemotherapy. Furthermore, an estimated 1-year OS in intended to treat patients was 69% *vs.* 49% in the pembrolizumab combination therapy *vs.* chemotherapy group (HR 0.49; P<0.001), with median PFS of 8.8 *vs.* 4.9 months (HR 0.52; P<0.001), respectively. Moreover, within TPS ≥50% subgroup (N=202), the combination therapy in comparison to chemotherapy alone, had a 1-year OS rate of 73% compared with 48% (HR 0.42) and an ORR (61.4% *vs.* 22.9%), Respectively.

An updated analysis of KEYNOTE189 after median follow-up of 19 months, showed that all the results preferred combination therapy with median OS (22 *vs.* 10 months) and PFS (9 *vs.* 4.9 months) which was found to be statistically significant (P<0.00001) compared to the chemotherapy arm. importantly, the median OS within TPS ≥50% subgroup has not been reached (7,8).

The KEYNOTE-407 trial is similar in nature to KEYNOTE-189 trial described above with the main difference in the inclusion criteria of the study design including metastatic squamous NSCLC for KEYNOTE-407 and non-squamous NSCLC patients KEYNOTE-189 (9). The combination of chemotherapy plus pembrolizumab was associated with improved ORR (58.4% *vs.* 35.0%, P=0.0004) and improved median OS 16 *vs.* 11.3 months (HR 0.64, P=0.0008) compared to chemotherapy alone. The benefit in OS was seen across PD-L1 expression (TPS <1% HR 0.61, TPS 1%–49% HR 0.57). Moreover, the estimated 1-year survival rate among patients with a PD-L1 TPS ≥50%, was 63.4% *vs.* 51.0% (HR 0.64), improved ORR (60.3% *vs.* 32.9%, P=0.0004) and the median OS was not reached in the pembrolizumab-combination group *vs.* chemotherapy group.

Based on the results from KEYNOTE-189 and KEYNOTE-407 trials, the benefit of combination chemo-immunotherapy as first-line therapy in both metastatic squamous and non-squamous NSCLC is shown regardless of PD-L1 expression. In addition, the TPS ≥50% subgroups exhibit a more potent therapeutic response across these trials.

It is still uncertain whether there is a therapeutic difference amongst the PD-L1 TPS ≥50% group in comparison to other PD-L1 subdivisions. None of these trials provides a direct comparison between chemotherapy plus ICIs *vs.* ICI monotherapy.

Combination immunotherapy as first-line treatment of advanced NSCLC, PD-L1 expression ≥50% and high TMB

TMB is another predictive biomarker for response to ICI by enhancing tumor immunogenicity. It is notable that this biomarker is independent of the predictive value of PD-L1 IHC (11).

The phase III trial CheckMate 227, enrolled 1,739 patients with advanced NSCLC who were randomized 1:1:1 according to PD-L1 expression. PD-L1 expression ≥1% group received nivolumab plus ipilimumab, nivolumab monotherapy or chemotherapy alone; and patients with PD-L1 expression <1% received nivolumab plus ipilimumab, nivolumab plus chemotherapy or chemotherapy alone. Interestingly, patients with high TMB, regardless of

PD-L1 expression who were treated by combination of nivolumab plus ipilimumab, had a longer PFS compared to chemotherapy (HR 0.58, P<0.001) and a median 1-year PFS (42.6% *vs.* 13.2%). Among low TMB patients no difference in PFS was observed.

Furthermore, for the analysis of patients with PD-L1 expression ≥50%, the median duration of response for nivolumab plus ipilimumab was 31.8 *vs.* 17.5 months for nivolumab monotherapy and 5.8 months for chemotherapy. The median OS in these three groups were 21.2 *vs.* 18.1 *vs.* 14 months, and the ORR 44.4% *vs.* 36.9% *vs.* 35.4% respectively. It will be interesting to know from the exploratory analysis what was the response in those patients with high TMB and PD-L1 expression ≥50%.

Discussion

ICI have become the main treatment option for advanced NSCLC patients. Better outcomes have been observed specially for patients with a strong expression of PD-L1. Here, we summarized the three main strategies of treatment for patients with advanced NSCLC and strongly positive expression of PD-L1 (more than 50%) in first line therapy, either as ICI monotherapy, in combination with chemotherapy or in combination with another ICIs (*Table 1*).

In the era of immunotherapy, a balance between hyperactivation of the immune system, exhaustion and development of immunosuppression must be taken into account (13-17). Identifying the best combination therapies may improve response rates and diminish toxicities (18,19). The aim of these combinations, is to enhance functionality of immune cells leading to tumor eradication, to modify the immune suppressive tumor microenvironment (TME), and to prevent further immune escape mechanisms (20). For an instance, preclinical findings of colon cancer suggested that a synergistic response were achieved by adding chemotherapy to immunotherapy inducing tumor infiltration by activated PD-1, CD8+ T cells (21). Furthermore, it has been shown that certain chemotherapeutic agents can promote anti-tumor immune responses by enhancing proinflammatory cytokines and release neo-antigens from tumor cells which augment the efficacy of immunotherapy (22,23).

The current unmet need is to explore the best therapeutic regimen for the population of strong PD-L1 staining. We speculate that further factors associated with the host, may support a better decision for optimal treatment. For example, disease burden, liver involvement, brain disease and functionality of the immune system. As shown, from exploratory analysis of KEYNOTE-189 trial demonstrate a significant better outcome with doubled the median OS in patients with liver involvement (12.6 *vs.* 6.6 months, HR 0.62) and brain metastasis (19.2 *vs.* 7.5 months, HR 0.41) treated with combination chemotherapy plus pembrolizumab *vs.* chemotherapy alone, respectively (24). Furthermore, in the summarized *Table 1*. we noticed that patients with advanced NSCLC, TPS PD-L1 ≥50% treated with combination chemo-immunotherapy achieved a better objective response rate (ORR) approximately 60%, while almost similar ORR was observed in those treated with ICI single agent and combination ICIs around 40%. Therefore, combination chemotherapy with ICI is suggested for patients with high disease burden in order to accomplish a quicker response to treatment.

Conclusions

Combination of ICI with platinum-based chemotherapy in NSCLC, PD-L1 TPS >50% represents the new standard of care. Crucially, this is a highly suggested treatment protocol for patients with high disease burden, especially for those with liver or brain involvement. The addition of chemotherapy to ICI may enhance the immunogenicity of the tumor cells leading to improvement of the therapeutic efficacy by reprograming the immune suppressive TME resulting in better patients' outcomes. Further studies are suggested in this field.

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