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Review Article

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Immunotherapy for Non-small Cell Lung Cancer: Current Landscape and Future Perspectives

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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
ABCP, atezolizumab, bevacizumab, carboplatin, and paclitaxel; AE, adverse event; CI, confidence interval; HPD, hyperprogressive disease; HR, hazard ratio; ICI, immune checkpoint inhibitor; irAE, immune-related

ABSTRACT

Immune checkpoint inhibitors (ICIs) have shown remarkable benefit in the treatment of patients with non-small-cell lung cancer (NSCLC) and have emerged as an effective treatment option even in the first-line setting. ICIs can block inhibitory pathways that restrain the immune response against cancer, restoring and sustaining antitumor immunity. Currently, there are 4 PD-1/PD-L1 blocking agents available in clinics, and immunotherapy-based regimen alone or in combination with chemotherapy is now preferred option. Combination trials assessing combination of ICIs with chemotherapy, targeted therapy and other immunotherapy are ongoing. Controversies remain regarding the use of ICIs in targetable oncogene-addicted subpopulations, but their initial treatment recommendations remained unchanged, with specific tyrosine kinase inhibitors as the choice. For the majority of patients without targetable driver oncogenes, deciding between therapeutic options can be difficult due to lack of direct cross-comparison studies. There are continuous efforts to find predictive biomarkers to find those who respond better to ICIs. PD-L1 protein expressions by immunohistochemistry and tumor mutational burden have emerged as most well-validated biomarkers in multiple clinical trials. However, there still is a need to improve patient selection, and to establish the most effective concurrent or sequential combination therapies in different NSCLC clinical settings. In this review, we will introduce currently used ICIs in NSCLC and analyze most recent trials, and finally discuss how, when and for whom ICIs can be used to provide promising avenues for lung cancer treatment.

Keywords: Non-small cell lung cancer; Immunotherapy; Programmed cell death protein 1

INTRODUCTION

Immune checkpoint proteins, such as PD-1 or CTLA-4 emerged as promising targets of immunotherapy, and have improved clinical outcomes of non-small-cell lung cancer (NSCLC) patients tremendously. Currently, the anti-PD-1 agent pembrolizumab is approved for use as first- and second-line therapy in patients with advanced NSCLC whose tumors express PD-L1 in immunohistochemistry analysis (1,2). Nivolumab (anti-PD-1) and atezolizumab (anti-PD-L1) are both indicated for use as second-line therapies regardless of PD-L1 expression (1,3). Durvalumab (anti-PD-L1) is approved as a maintenance therapy in patients

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adverse event; LAG-3, lymphocyte-activation gene-3; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression free survival; TIM-3, T cell immunoglobulin- and mucin-domain-containing module 3; TKI, tyrosine kinase inhibitor; TMB, tumor mutational burden

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with unresectable, stage 3 NSCLC whose disease has not progressed following concurrent platinum-based chemoradiotherapy (4). However, many issues are still not resolved regarding the biomarker status, choice in the first-line setting, immunotherapy in oncogene-addicted tumors, and how to combine immunotherapy with other agents.

NSCLC is a heterogeneous disease that is categorized into 2 broad histologic subtypes, adenocarcinoma and squamous cell carcinoma. Recent investigation of tumor immune microenvironment suggested that lung adenocarcinoma and squamous cell carcinoma show significant differences in immune landscape (5). Understanding the differences in immune microenvironment may suggest heterogeneous response to immunotherapy. Several microenvironmental factors differentially induce lung adenocarcinoma and squamous cell carcinoma immune subtypes, as well as immune checkpoint expression (6). For example, tumor-associated macrophages are key immune cells in lung squamous cell carcinoma, whereas regulatory B cells play immunosuppressive role in lung adenocarcinoma. In addition, the complexity of immune landscape of NSCLC arises from molecular subtype, oncogenic drivers, nonsynonymous mutational load, tumor aneuploidy, clonal heterogeneity and tumor evolution (7).

Tumor expression of PD-L1 has been most widely investigated as a predictive marker of response, but the sensitivity and specificity of this approach is modest (8,9). PD-L1 testing shows variable results because of the different Abs and cutoff values used (10), thus PD-L1 alone cannot accurately reflect the complexity of the tumor microenvironment involved in the response to immunotherapy. At the genomic level, tumor mutational burden (TMB) has been correlated with the clinical response to anti-PD-1 therapy and associated with favorable responses in smokers (11). The role of TMB as a marker predictive of response has been also evaluated in several clinical trials (CheckMate026, CheckMate568, CheckMate227) (12-14), which showed that patients with high TMB showed enhanced response to immunotherapy, regardless of PD-L1 expression. However, overall survival (OS) was not affected by TMB alone, and further understanding of the role of TMB as a biomarker is warranted before the integration into clinical practice.

Recent pivotal studies have assessed the role of immunotherapy in previously untreated metastatic NSCLCs in both squamous and nonsquamous histology, and 4 studies have shown an OS benefit from adding PD-1 or PD-L1 inhibitor to standard chemotherapy (KEYNOTE-189, IMpower150, IMpower130, KEYNOTE-407). Chemotherapy-sparing regimens such as PD-1 or PD-L1 inhibitor alone or in combination with a CTLA-4 inhibitor have also demonstrated a survival benefit in biomarker-selected, treatment-naïve NSCLC patients (KEYNOTE-024, KEYNOTE-042, and CheckMate227). Therefore, it is recommended that treatment-naïve, metastatic NSCLC patients receive 1st line treatment with immunotherapy, alone or in combination with chemotherapy. The only subsets of patients that should not receive first-line immunotherapy regimens are those with genomic-driven lung cancer, such as *EGFR*-mutant or *ALK*-positive NSCLC. First-line treatment with a tyrosine kinase inhibitor (TKI) is recommended, and guidelines for genomic testing in newly diagnosed metastatic NSCLC remain unchanged.

In this review, we focus on pivotal clinical trials (**Table 1**) which changed the treatment landscape in advanced, stage 4, NSCLC and discuss open issues on how to choose the best therapeutic strategy and to select patients for the different treatment options.

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Table 1. Pivotal studies of ICIs in advanced NSCLC

Study name	Phase	Histology, PD-L1	Line of treatment	Study design	Control arm outcome	Experimental arm outcome	Hazard ratio (95% Confidence interval, p value)
First-line ICI only							
KEYNOTE-024	III	NSCLC, PD-L1 TPS≥50%	Treatment-naïve	Pembrolizumab vs. chemotherapy	mOS 14.2 months	mOS 30.0 months	0.63 (0.47–0.86), p=0.002
KEYNOTE-042	III	NSCLC, PD-L1 TPS≥1%	Treatment-naïve	Pembrolizumab vs. chemotherapy	mOS 12.1 months	mOS 16.7 months	0.85 (0.71–0.93), p=0.0018
CheckMate026	III	NSCLC, PD-L1 TPS≥1%	Treatment-naïve	Nivolumab vs. chemotherapy	mOS 13.2 months	mOS 14.4 months	1.02 (0.80–1.30), p=NS
MYSTIC	III	NSCLC	Treatment-naïve	D vs. D+Tr vs. chemotherapy	mOS 12.9 months	mOS 16.3 months (D) mOS 11.9 months (D+Tr)	D vs. Chemotherapy: 0.76 (0.56–1.02). p=NS D+Tr vs. Chemotherapy: 0.85 (0.61–1.17), p=NS
First-line ICI+Chemotherapy combination							
KEYNOTE-189	III	Nonsquamous	Treatment-naïve	Pem/C±pembrolizumab vs. placebo	12-month OS 49.4%	12-month OS 69.2%	0.49 (0.38–0.64), p<0.001
IMpower150	III	Nonsquamous, including EGFR/ALK+	Treatment-naïve	B/Pac/C±atezolizumab	mOS 14.7 months	mOS 19.2 months	0.78 (0.64–0.96), p=0.02
IMpower132	III	Nonsquamous	Treatment-naïve	Pem/P±atezolizumab	mPFS 5.2 months	mPFS 7.6 months	0.60 (0.49–0.73), p<0.0001
KEYNOTE-407	III	Squamous	Treatment-naïve	T/C±pembrolizumab	mOS 11.3 months	mOS 15.9 months	0.64 (0.49–0.85), p<0.001
IMpower131	III	Squamous	Treatment-naïve	Nab/C±atezolizumab	mPFS 5.6 months	mPFS 6.3 months	0.715 (0.603–0.848), p=0.0001
Later-line ICI							
CheckMate017	III	Squamous	Second or later	Nivolumab vs. docetaxel	mOS 6.0 months	mOS 9.2 months	0.62 (0.47–0.80)
CheckMate057	III	Nonsquamous	Second or later	Nivolumab vs. docetaxel	mOS 12.2 months	mOS 9.5 months	0.75 (0.63–0.91)
KEYNOTE-010	II/III	NSCLC, PD-L1 TPS≥1%	Second or later	Pembrolizumab 2 mg/kg or 10 mg/kg vs. docetaxel	mOS 8.5 months	2 mg/kg: mOS 10.4 months 10 mg/kg: mOS 12.7 months	2 mg/kg: 0.71, p=0.0008 10 mg/kg: 0.61, p<0.0001
OAK	III	NSCLC	Second or later	Atezolizumab vs. docetaxel	mOS 9.6 months	mOS 13.8 months	0.73 (0.62–0.87), p=0.0003

ICI, immune checkpoint inhibitor; NSCLC, non-small-cell lung cancer; OS, overall survival; PFS, progression free survival.

EFFICACY OF KEY TRIALS

PD-1/PD-L1 inhibitor monotherapy in previously treated NSCLC

Three agents (nivolumab, pembrolizumab, atezolizumab) have been investigated for efficacy in phase III trials involving previously treated NSCLC patients.

In the open-label, randomized, phase III CheckMate017 trial, nivolumab was compared with docetaxel in the second-line setting in NSCLC patients with squamous histology (1). Patients were 1:1 randomized to receive either nivolumab 3 mg/kg every 2 weeks or docetaxel 75 mg/m^2 every 3 weeks until disease progression or unacceptable toxicity. Nivolumab showed a significant OS benefit (9.2 months vs. 6.0 months; hazard ratio [HR], 0.59; 95% confidence interval [CI], 0.44–0.79; p<0.001), and the objective response rate (ORR) was 20% in the nivolumab arm, as compared to 9% in the docetaxel arm. The expression of PD-L1 stratified at 1%, 5%, or 10% was not found to be predictive of benefit. Treatment-related adverse events (AEs) occurred less frequently in nivolumab arm (58% any grade and 7% grade 3 or 4 AEs vs. 86% any-grade and 55% grade 3 or 4 AEs) compared with docetaxel arm.

CheckMate057 trial, which assessed efficacy of nivolumab compared to docetaxel in the second-line setting in NSCLC patients with nonsquamous histology also showed survival

benefit for nivolumab (1). The same dose and schedule of nivolumab and docetaxel were used as in CheckMate017 trial, and the median OS was superior in the nivolumab arm (12.2 months vs. 9.4 months; HR, 0.73; 95% CI, 0.59–0.89; p<0.002). The ORR was 19% for nivolumab and 12% for docetaxel, and efficacy was greater with nivolumab at pre-specified PD-L1 expressions of 1%, 5% or 10%. Treatment-related AEs occurred less frequently in nivolumab arm (69% any-grade and 10% grade 3 or 4 AEs vs. 88% any-grade and 54% grade 3 or 4 AEs).

The 3-year OS data were recently presented, showing ongoing progression free survival (PFS) and OS benefits for nivolumab for both the squamous and nonsquamous histologies (15). The 3-year OS rates for CheckMate017 and CheckMate057 were 16% and 18% respectively, and among patients who showed response to nivolumab, 26% and 23% showed ongoing responses, respectively.

KEYNOTE010 trial was an open-label, phase II/III trial which randomized NSCLC patients 1:1:1 to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m^2 every 3 weeks (2). Both squamous and nonsquamous histologies were included in this trial, and patients were required to have tumors expressing PD-L1. The OS was superior for both doses of pembrolizumab compared to docetaxel (10.4 months for pembrolizumab 2 mg/kg, 12.7 months for pembrolizumab 10 mg/kg, and 8.5 months for docetaxel). Patients who expressed PD-L1 expression of ≥50% showed greater benefit with pembrolizumab, and the median PFS was also statistically improved in these group of patients. Safety was improved for patients in the pembrolizumab arm, grade 3 or greater toxicities occurring at 13% in pembrolizumab 2 mg/kg arm, 16% in pembrolizumab 10 mg/kg arm, and 35% in docetaxel arm.

OAK trial evaluated the efficacy and safety of atezolizumab compared with docetaxel in NSCLC patients of both squamous and nonsquamous cell histologies (3). PD-L1 expression was not required for eligibility and patients were randomized to receive either atezolizumab 1,200 mg or docetaxel 75 mg/m^2 every 3 weeks. The median OS was prolonged in the atezolizumab arm compared to docetaxel arm (13.8 months vs. 9.6 months; HR, 0.73; 95% CI, 0.62–0.87; p=0.0003), and benefit was consistent regardless of PD-L1 expression. The greatest OS benefit was observed in patients having highest PD-L1 expression (20.5 months vs. 8.9 months; HR, 0.41; 95% CI, 0.27–0.64; p<0.0001). Intriguingly, patients with brain metastases seemed to benefit from atezolizumab treatment in a subgroup analysis, which was not observed in other studies with PD-1 inhibitors (1,16). Atezolizumab had a better safety profile, showing fewer treatment-related AEs compared to docetaxel (15% vs. 43%).

Overall, the above trials showed consistent improvement in OS and ORR with PD-L1 or PD-L1 inhibitor monotherapy compared with standard chemotherapy, with less toxicity. However, the trials showed heterogeneous cut-offs and diagnostic methods for PD-L1 testing, and whether PD-L1 expression should be required in selecting patients for second-line immunotherapy remains unclear. Several immunohistochemistry assays are available for evaluating PD-L1 expression levels (17). The 22C3 pharmDx assay (Agilent) was used in the pivotal pembrolizumab studies and it is approved as a companion diagnostic assay to categorize PD-L1 expression on tumor cells according to the tumor proportion score. In addition, 28-8 PharmDx (Agilent) was recognized as a complementary diagnostic assay of nivolumab based on evidence that patients with positive PD-L1 expression in tumor cells have a higher clinical benefit of nivolumab. The Ventana platform was used to develop the SP142 Abs in conjunction with atezolizumab, but recent study sponsored by the National Comprehensive Cancer Network and the Blueprint Project showed that SP142 had lower sensitivity because pathologists do not concordantly read PD-L1 expression on immune cells (18).

PD-1/PD-L1 inhibitor monotherapy in previously untreated NSCLC

The KEYNOTE-024 and -042 studies compared the efficacy of pembrolizumab monotherapy to standard platinum-based chemotherapy in previously untreated NSCLC patients. The phase III KEYNOTE-024 trial enrolled the patients with squamous and nonsquamous NSCLC with PD-L1 expression on at least 50% of the tumor cells (8). The results showed that pembrolizumab had superior PFS compared to chemotherapy (10.3 months vs. 6.0 months; HR, 0.50; 95% CI, 0.37–0.68; p<0.001). The frequency of treatment-related AEs of any grade and grade ≥3 were significantly lower in the pembrolizumab arm than in the chemotherapy arm (73.4% vs. 90% and 26.6% vs. 53.3%, respectively). According to KEYNOTE-024 trial, pembrolizumab monotherapy is now regarded as a standard of care therapy for NSCLC patients (squamous or nonsquamous histology) with PD-L1 expression of at least 50%.

The KEYNOTE-042 trial assessed the efficacy of pembrolizumab monotherapy in patients with PD-L1 expression on at least 1% of tumor cells (19). NSCLC patients with squamous or nonsquamous histologies were randomized 1:1 to receive either pembrolizumab 200 mg or platinum-based chemotherapy, without crossover to pembrolizumab. Pembrolizumab monotherapy significantly improved OS in all pre-specified PD-L1 expression subgroups (TPS≥1%, ≥20%, ≥50%). The magnitude of OS benefit was greatest in the patients with TPS≥50% (20 months vs. 12.2 months; HR, 0.69; 95% CI, 0.56–0.85; p=0.0003), but the OS benefit was not seen patients with TPS ≥1%–49%. These results suggest that patients with PD-L1 TPS≥50% were driving the OS benefit, which is consistent with the results from KEYNOTE-024 trial.

On the contrary, CheckMate026 trial, a phase III study of nivolumab versus platinum-based chemotherapy in patients with treatment-naïve advanced NSCLC with a PD-L1 TPS of ≥1%, did not show any clinical benefit (20). In the primary efficacy analysis of patients with a PD-L1 TPS of ≥5%, nivolumab did not show significant improvement in either PFS or OS. Additional exploratory subgroup analyses also did not show any significant difference in PFS or OS in patients with a PD-L1 TPS≥50%. Of note, an exploratory analysis was conducted to see the role of TMB, and patients with high TMB (as defined as ≥243 missense mutations) showed higher response rate (47% vs. 28%) and prolonged PFS (9.7 months vs. 5.8 months; HR, 0.62; 95% CI, 0.38–1.00). However, no significant difference was observed in OS regardless of TMB.

MYSTIC trial compared both durvalumab monotherapy and durvalumab in combination with tremelimumab with the platinum-doublet chemotherapy in the first-line setting in patients 25% or greater PD-L1 expression (21). This trial, however, did not meet its primary endpoint of improved PFS compared with the chemotherapy in either the durvalumab monotherapy or durvalumab plus tremelimumab. Therefore, pembrolizumab remains the only FDA-approved single-agent, immune checkpoint inhibitor (ICI) in the first-line setting in advanced NSCLC patients.

PD-1/PD-L1 inhibitor in combination with chemotherapy

The addition of PD-1/PD-L1 inhibitor to standard chemotherapy in treatment-naïve NSCLC patients was investigated, regardless of PD-L1 expression. The rationales behind combining immunotherapy to chemotherapy are that cytotoxic chemotherapeutic agents may 1) induce immunological activity (22); 2) cytotoxic agents may increase presentation of tumor Ags (23); 3) reduce regulatory T cells (24) and myeloid derived suppressor cells (25); 4) induce PD-L1 expression on tumor cells (23).

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KEYNOTE-189 was a phase III, placebo-controlled double-blinded trial which assessed first-line platinum-based chemotherapy with or without pembrolizumab in *EGFR/ALK*-wild type, nonsquamous NSCLC patients (26). The ORR was 47.6% in the pembrolizumab-chemotherapy arm *vs.* 18.9% in the placebo-chemotherapy arm (p<0.001). The median OS was not reached at the time of analysis for the pembrolizumab-chemotherapy arm vs. 11.3 months for placebo-chemotherapy arm (HR, 0.49; 95% CI, 0.38–0.64; p<0.001), and the OS advantage was achieved in all PD-L1 subgroups. The median PFS was 8.8 months *vs.* 4.9 months (HR, 0.52; 95% CI, 0.43–0.64; p<0.001), but no PFS benefit was evident adding pembrolizumab in patients with PD-L1 TPS<1%. In terms of safety, neither an increase in AEs nor an increase in immune-mediated AEs were reported in pembrolizumab-chemotherapy arm. On the basis of KEYNOTE-189 results, pembrolizumab in combination with pemetrexed and carboplatin as first-line treatment in metastatic nonsquamous NSCLC became a new standard, regardless of PD-L1 expression (27).

Impower150 evaluated the role of atezolizumab combined with chemotherapy for the first-line treatment of metastatic nonsquamous NSCLC. Patients were randomized to 3 groups: atezolizumab, bevacizumab, carboplatin, and paclitaxel (ABCP); ACP; and BCP. While the data comparing ABCP and BCP are available, both the median PFS and OS were improved in the atezolizumab-containing arm (PFS, 8.3 months vs. 6.8 months; OS, 19.2 months vs. 14.7 months) compared with the patients treated with BCP (28). Of note, patients with *EGFR* and *ALK* alterations were included in this trial, and they also had benefit from atezolizumab-containing arm (HR, 0.59; 95% CI, 0.37–0.94). A higher incidence of grade ≥3 AEs was observed in the atezolizumab-containing arm (55.7% vs. 47.7%), mainly anorexia, nausea, diarrhea, neutropenia, thrombocytopenia and febrile neutropenia. A total of 77.% of the immune-related AEs in ABCP group were grade 1 or 2 and manageable, and none were grade 5.

IMpower132 also assessed the role of atezolizumab in first-line chemotherapy combinations for advanced nonsquamous NSCLC. There was an improvement in PFS in the atezolizumab-containing arm (7.6 months vs. 5.2 months) and benefit was seen in both PD-L1 positive and negative group (29).

KEYNOTE-407 and IMpower131 trial investigated the efficacy of PD-1/PD-L1 inhibitor in metastatic squamous NSCLC in combination with chemotherapy. In KEYNOTE-407 trial, patients were randomized to receive 4 cycles of carboplatin and a taxane with or without pembrolizumab (30). As expected, patients in the pembrolizumab-containing group showed a significantly improved OS compared with those in the chemotherapy group (15.9 months vs. 11.3 months; HR, 0.64; 95% CI, 0.49–0.85; p<0.001). Benefit was seen in all PD-L1 TPS groups, and pembrolizumab did not significantly increase treatment-related toxicity.

IMpower131 trial examined atezolizumab with chemotherapy consisting of carboplatin with either paclitaxel (ACP) or nab-paclitaxel (ACnP) against carboplatin plus nab-paclitaxel (CnP) control (31). While the results were positive in terms of its primary endpoint of median PFS for ACnP versus CnP (6.3 months vs. 5.6 months; HR, 0.715; 95% CI, 0.603–0.848; p=0.0001), the median OS were not different between 2 groups.

Immunotherapy combinations

In CheckMate227, treatment-naïve patients with advanced NSCLC were randomized to nivolumab plus ipilimumab, nivolumab, and histology-based chemotherapy arms (14). According to PD-L1 expression, patients were divided into PD-L1≥1% and <1%, and further

randomized 1:1:1 to nivolumab plus ipilimumab, platinum-based chemotherapy, or nivolumab monotherapy (PD-L1≥1% group) or nivolumab plus platinum-based chemotherapy (PD-L1<1% group). The study protocol was later modified to include a co-primary endpoint of PFS in patients with high TMB, as defined by ≥10 mutations per megabase. This was due to the previous finding that high TMB was associated with enhanced response rate and PFS, independent of tumor PD-L1 expression (11). Among patients with high TMB, nivolumab plus ipilimumab arm showed a significantly prolonged PFS than chemotherapy arm (7.2 months vs. 5.5 months; HR, 0.58; 95% CI, 0.41–0.81; p<0.001). However, in patients with lower TMB, median PFS was shorter in patients in nivolumab plus ipilimumab arm compared with those in chemotherapy arm (3.2 months vs. 5.5 months; HR, 1.07, 95% CI, 0.56–1.10). However, the median OS was not significantly different among high TMB (32). Incidence of grade 3 or higher AEs were similar (31.2% in nivolumab plus ipilimumab vs. 36.1% in chemotherapy arm).

In CheckMate568, the association of efficacy with PD-L1 expression and TMB was assessed in patients who received first-line nivolumab plus ipilimumab (33). Higher response rates and improved PFS were observed in patients with TMB of 10 or more mut/Mb versus TMB of fewer than 10 mut/Mb, irrespective of PD-L1 expression. This analysis supported TMB of 10 or more mut/Mb as a clinically meaningful cutoff for response and PFS in patients receiving first-line nivolumab plus ipilimumab.

Currently, novel targets and combinations are underway to enhance antitumor immune response. **Supplementary Table 1** shows a selected list of novel immunotherapy trials in clinical development in solid tumors and lymphomas. Novel combination strategies can be classified according to mechanism of action: 1) Co-inhibitory blockade; 2) Costimulation; 3) Bispecific T cell engager Ab constructs; and 4) Priming. First of all, agents that block co-inhibitory receptors apart from CTLA-4 and PD-1/PD-L1 include V-domain immunoglobulin suppressor of T cell activation, lymphocyte-activation gene-3 (LAG-3), T cell immunoglobulin- and mucin-domain-containing module 3 (TIM-3), T cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibitory motif domain, and B7-H3. Since a considerable proportion of patients remain unresponsive to immunotherapeutics targeting the inhibitory receptors CTLA-4, PD-1 or PD-L1, targeting novel inhibitory pathways in combination with current immunotherapies may improve clinical outcomes. Therefore, clinical trials involving novel checkpoint targets such as V-domain immunoglobulin suppressor of T cell activation /PD-1H (NCT02671955), B7-H3 (NCT01391143, NCT02475213, NCT00844064), LAG-3 (NCT01968109, NCT02460224, NCT00732082, NCT00349934) are ongoing, often in combination with PD-1 inhibitors. A first-in-human study of human LAG-3 monoclonal Ab (REGN3767) in combination with PD-1 inhibitor (cemiplimab) was recently reported, and early efficacy signals were detected with acceptable safety profiles (34). Secondly, costimulatory agents are OX40, GITR, ICOS, 4-1BB, and CD40. Besides, costimulatory molecules such as OX40, GITR, ICOS, 4-1BB (CD137), CD40 can augment immunological responses against malignant cells. Bispecific Abs, vaccines, oncolytic viruses and cytokines are also passive and active immunotherapies. Bispecific T cell engager Ab constructs are a type of fusion protein that is designed by linking the targeting regions of 2 Abs. One arm of the molecule binds to the surface of cytotoxic T cells, and the other arm binds to a specific protein found primarily on tumor cells (35). Moreover, bispecific Abs to TIM-3 have also been developed. RO7121661 (bispecific Ab to TIM-3 and PD-1) and LY3415244 (bispecific Ab to TIM-3 and PD-L1) are currently under clinical investigation. Oncolytic viruses selectively kill cancer cells and stimulate the immune system (e.g., T-Vec), while dendritic cell vaccines (e.g., sipuleucel-T) involve the extraction of

dendritic cells from the patient, exposure to cancer cells or Ags, and reintroduction of now active immune cells to the patient (36). STimulator of INterferon Genes agonist, a phase 1b study of MIW815 in combination with PD-1 inhibitor (PDR001), was recently reported in patients with advanced solid tumors. The preliminary response was higher in patients with moderate to high baseline PD-L1 expression (ORR 25.0%) as compared to patients with low PD-L1 expression (ORR 4.5%), and increase in $CD8^+$ T cells in tumor after drug injection was suggested as a pharmacodynamics marker, reflecting therapeutic benefit (37). Further understanding of the basic biology of these novel targets is imperative to the development of effective cancer immunotherapy.

PD-1/PD-L1 inhibitor in EGFR and ALK altered patients

The role of PD-1/PD-L1 inhibitor in oncogene-addicted NSCLC is still unclear, and currently TKIs are the standard treatment options in patients with *EGFR*- or *ALK*-altered tumors. Targeted therapy in combination with PD-1/PD-L1 inhibitors have been tried, trials have been prematurely stopped due to toxicity issues. A phase 1b TATTON trial testing osimertinib (EGFR TKI) plus nivolumab was closed early due to high incidence of interstitial lung disease (38%) (38). In addition, the CAURAL phase III trial evaluating the combination of osimertinib and durvalumab in EGFR T790M positive patients was also prematurely stopped due to safety concerns. However, in *ALK*-rearranged NSCLC patients, combination of alectinib (ALK TKI) and atezolizumab showed acceptable toxicity, but ORR was not improved compared to alectinib alone (39). Due to high incidence of high-grade toxicities with combination of TKI and immunotherapy, further development should be cautiously considered.

A single agent pembrolizumab was investigated in a phase II trial of patients with *EGFR*-mutant, PD-L1-positive (≥1%) advanced NSCLC. All patients were treatment-naïve, but after enrolling 11 out of 25 patients, the trial was terminated early due to lack of efficacy (40). To date, ICIs are not considered effective in oncogene-addicted patients. Other interventional strategies are underway to evaluate the combination of ICIs plus chemotherapy in the resistant setting (NCT02864251, NCT03256136, NCT03515837), as well as combination with anti-CD73 therapies (NCT03454451) based on preclinical rationale (41).

PATIENT SELECTION AND BIOMARKERS

Figure 1 shows the first-line treatment algorithm. So far, PD-L1 expression by immunohistochemistry is the only approved biomarker to select patients for immunotherapy. As mentioned earlier, there are different methods of cutoffs and interpretation because companies use different PD-L1 assays (Dako 28-8, Dako 22C3, Ventana SP142, Ventana SP263 for nivolumab, pembrolizumab, atezolizumab and durvalumab, respectively). Moreover, even PD-L1 negative patients may respond to anti-PD-1/PD-L1 inhibitor, while some PD-L1 highly positive patients do not show response. Therefore, PD-L1 expression is still an incomplete marker.

According to results of CheckMate227 trial, TMB was considered as a potential and new biomarker, independently from PD-L1 expression. Recently, blood TMB was also evaluated in pretreated NSCLC patients who were enrolled in OAK and POPLAR studies (42), in treatment-naïve NSCLC patients in a phase II, B-F1RST trial receiving atezolizumab (43), and in patients in MYSTIC trial (21). These studies suggested that TMB was feasible in the majority of patients, and the rate of high TMB (≥10 mut/megabase) was between 23% and 30%. In addition, blood TMB and tissue TMB correlated significantly in the pooled analysis,

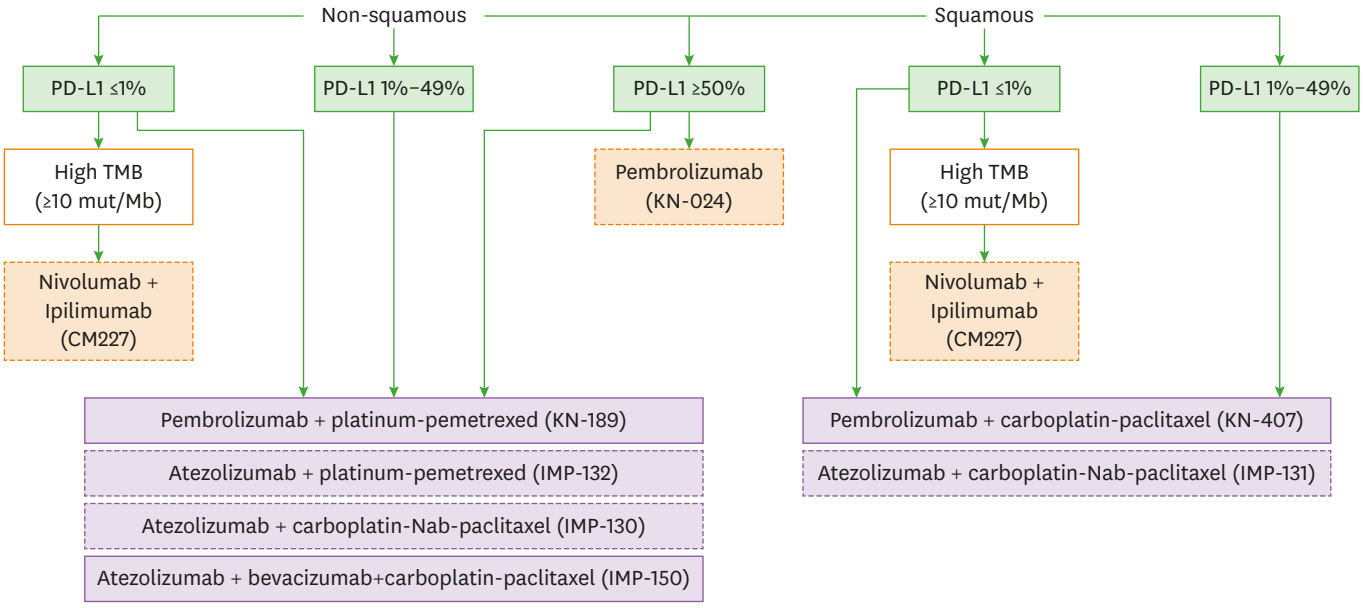

Figure 1. First-line treatment algorithm. Dashed boxes indicate treatments which did not receive approval from regulatory agencies yet.
TMB, tumor mutational burden.

suggesting that TMB may be more easily tested on blood rather than on tumor tissues. However, like PD-L1, TMB results may vary according to different platforms of sequencing, and testing costs are high for routine clinical practice. Although TMB can be complementary to PD-L1 immunohistochemistry, future prospective randomized studies are required to assess the clinical value of TMB as a predictive biomarker for anti-PD-1/PD-L1 inhibitors.

TOXICITY PROFILES

Immune-related adverse events (irAEs) are ICI-mediated inflammatory side effects (44). The pathophysiology underlying irAEs is largely unknown but is believed to be related to the disruption of immunologic homeostasis (45). Recent studies suggest that the occurrence of irAEs predicts the treatment efficacy of ICIs in NSCLC (46,47), but at the same time, is more likely to be associated with treatment discontinuation. Adverse events from ICIs can affect one or several different systemic organ systems. Toxicities can occur as various symptoms and signs: skin (rash, pruritus), gastrointestinal (colitis), liver (transaminitis), pancreas (pancreatitis), endocrine (thyroiditis, adrenal insufficiency, hypophysitis, type 1 diabetes mellitus), lung (pneumonitis), kidney (proteinuria), eye (uveitis, episcleritis), nervous system (myasthenia gravis, peripheral neuropathy, encephalitis, transverse myelitis), cardiovascular (myocarditis), and musculoskeletal (arthritis). The incidence of grade 3 or higher toxicities is 7% to 13% in NSCLC patients treated with PD-1 axis inhibitors (48). As ICIs increase the activity of the immune system, T cells can attack healthy cells in the body, causing inflammatory conditions that mimic a range of autoimmune conditions, some of which can be serious (49). These immune-related AEs can occur at any time during treatment or even after treatment is discontinued. The severity of AEs can range from asymptomatic to severe or life-threatening and they may cumulate over the course of therapy. Combination treatment may increase the severity of adverse events, so more caution is required. Regular monitoring including laboratory tests and physical exams needs to be conducted to detect any potential

immune-related AEs, because most AEs can be managed effectively if detected and treated early (50).

TREATMENT DURATION

While current dosing and duration guidelines are based primarily on initial clinical trials conducted for approval of the ICIs, the optimal duration of treatment still needs to be explored. Similar to chemotherapeutic agents, the duration of treatment of all 5 currently approved PD-1/PD-L1 inhibitors are until disease progression or unacceptable toxicity. However, since immunotherapy work with a completely different mechanism compared to chemotherapy, using the same therapy duration may not be optimal. For example, it remains undecided whether we can discontinue the therapy in patients with complete response. In a retrospective study, they suggest stopping treatment is a viable option in patients with complete response as the durability of response is maintained in about 80%–90% of patients (51). Treatment holidays and possibly stopping immune based therapy early is a concept that needs further research using novel trial designs.

HYPERPROGRESSION

There is an emerging evidence that PD-1/PD-L1 inhibitors can lead to hyperprogressive disease (HPD), similar to a flare-up of tumor growth leading to dismal outcome. A recent meta-analysis to identify baseline patient factors associated with risks of developing HPD was reported. Although there was no standard definition of HPD, the incidence of HPD ranged from 1% to 30% (52). In this report, they identified serum LDH above the upper normal limit, more than 2 metastatic sites, liver metastases, Royal Marsden Hospital prognostic score of 2 or above as positively associated with HPD, and positive PD-L1 expression status that was inversely correlated with HPD. In another analysis, genomic alterations in genes such as *EGFR*, *MDM2/4* and *DNMT3A* were associated with HPD (53). In a recent exploratory biomarker analysis of patients with HPD, a lack of pre-existing antitumor immunity correlated with HPD, represented by a lower frequency of effector/memory subsets and a higher frequency of exhausted T cells populations in patients with HPD (54). Molecular mechanisms of hyperprogression are yet to be elucidated.

CONCLUSIONS

Although ICIs have been adopted for a limited amount of time so far, they ushered in a new era in the management of advanced NSCLC. Clinicians are now faced with numerous options of treatment such as PD-1 inhibitor monotherapy or PD-1/PD-L1 inhibitor plus chemotherapy, and a growing number of patients are achieving durable responses. Better predictive biomarkers are required to optimize the benefit of immunotherapy, and further studies are needed to determine the mechanism of resistance to ICIs and how to overcome it. In summary, ICIs have changed the treatment landscape in advanced NSCLC and ongoing translational and clinical studies are highly awaited to further improve outcomes for these patients. Expanding clinical benefit to the majority of patients and preventing drug resistance requires a better understanding of the mechanisms that lead to an effective anti-tumor

response. The development of new combination strategies will shed the light to the next advances of cancer immunotherapy.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1

Selected trials of novel immunotherapy combination

Click here to view

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