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Current uses of check inhibitors in the fight against advanced and/or metastatic lung cancer: will immunotherapy overcome chemotherapy?

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ABSTRACT

Lung cancer is the most common cause of cancer death worldwide. Treatment for lung cancer has become increasingly more complex over the last several years. Immune checkpoint inhibitors have dramatically changed the treatment landscape of advanced nonsmall cell lung cancer (NSCLC). There are currently 3 approved checkpoint inhibitors for patients with NSCLC who progressed after platinum-doublet chemotherapy (Pembrolizumab and /or Nivolumab and /or Atezolizumab). Avelumab and durvalumab are currently under investigation in phase 3 trials. Pembrolizumab has now been approved for first-line use in NSCLC, after a trial showed improved survival compared with chemotherapy in patients who were positive for programmed cell death ligand 1. Giving our patients the best, personalized approach to their individual cancer can improve their quality of life and survival and help us use our

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limited resources most efficiently. In the present review, we provide a new patient-oriented algorithm to guide clinicians' decisions on the best choice of therapy for advanced NSCLC.

Introduction

Nonsmall cell lung cancer (NSCLC) is one of the most common cancers and leading cause of cancer deaths in US and worldwide.[1] A 5-year survival rates of approximately 4.3% for patients with metastatic NSCLC.57% of all new lung cancer cases in the United States are metastatic.[2] The popular belief among oncologists even a few years ago was that immunotherapy would not work in lung cancers. Immunotherapies are providing new hope for treating this disease. Immunotherapy for advanced NSCLC is a hot topic in oncology and is changing the treatment paradigm for patients with advanced NSCLC but how does immunotherapy work in this disease? The immune system is exceedingly complex, and immunity is influenced by tumor, host, and environmental factors that dictate the anticancer response to therapy. In order to defend the tumor from the immune system, tumor cells must put up a barrier that prevents cytotoxic T-cells from killing them. Tumor cells employ a variety of defensive mechanisms; the most significant discovered so far is checkpoint inhibition. Programmed cell death 1 (PD-1) is a transmembrane protein expressed on T cells, B cells, and NK cells. It has 2 ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2. PD-L1 is expressed on the surface of multiple tissue types, including many tumor cells, as well as hematopoietic cells; programmed death-ligand 2 is more restricted to hematopoietic cells.[3] Cancer cells can evade immune attack by expressing PD-L1 (Fig. 1). Immunotherapy provides agents that help the immune system activate against and recognize a cancer. This has been shown to restore T-cell activation leading to amplification of the antitumor response.[4,5] Ipilimumab is a monoclonal antibody that blocks the CTLA-4 receptor. Nivolumab and pembrolizumab are fully humanized IgG4 antibodies against PD-1. Atezolizumab is a fully humanized monoclonal antibody against PDL1.

Incorporating checkpoint inhibitors into the management of NSCLC: an interactive exercise

Immunotherapy in the first-line setting: what have we achieved?

Clinical scenario 1: A 74-year-old never-smoker woman with lung adenocarcinom, diagnosed as stage IVB with metastases to the lymph nodes and bilateral adrenal glands, presents with an excellent performance status. Molecular testing of his tumor revealed negative for epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), and ROS1. PD-L1 level: 70% by 22C3 IHC test. What is the most effective first-line therapy for patients with stage IV NSCL without actionable mutations?

Until recently, combination cytotoxic chemotherapy with a platinum-based doublet has been the standard of care in the first line for patients with advanced, inoperable NSCLC whose tumors do not harbor EGFR mutations or ALK rearrangements. There are 2 phase III randomized studies of PD-1/PD-L1 inhibitors in first-line nonsmall cell lung cancer (Table 1). KEYNOTE-024 enrolled 305 previously untreated advanced NSCLC patients (squamous or nonsquamous) whose tumors expressed high-level (>50%) expression of PD-L1.[6] In this open-label, phase 3 trial, pembrolizumab monotherapy (200 mg intravenous every 3 weeks) was compared with standard platinum-doublet chemotherapy. Patients with an EGFR mutation or ALK rearrangement were excluded from this trial because they were felt to be far more likely to benefit from the targeted therapies against their driver mutations than either chemotherapy or immunotherapy. Pembrolizumab also showed a higher overall response rate (ORR) (45% vs 28%) and median

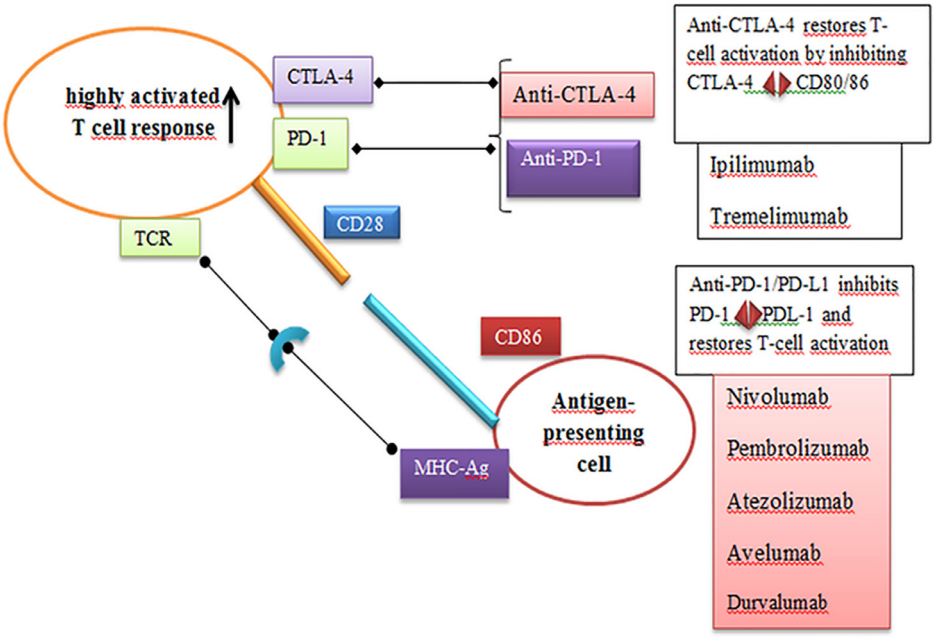

Fig. 1. Strategies to sustain activated tumor-specific T cells include the use of blocking monoclonal antibodies targeting CTLA-4, PD-1, or PD-L1 to neutralize coinhibitory receptors. CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC-TCR, majör histocompatibility complex-T cell receptor; PD-1, programmed death-1 receptor; PD-L1, programmed death-1 ligand; PD-L2, programmed death-2 ligand.

Table 1
Randomized studies of PD-1/PD-L1 inhibitors in first-line NSCLC.

Variable	KEYNOTE 024	CheckMate 026
Phase	III	III
Population	Advanced NSCL	Advanced NSCL
Sample size	305	423
Randomization	Pembrolizumab (200 mg vs platinum-containing chemotherapy	Nivolumab 3 mg/kg vs platinum-containing chemotherapy
Median PFS, mo	10.3 vs 6.0 (HR; 0.5; 95% CI 0.37-0.68, $P < 0.001$)	4.2 vs 5.9 (HR; 1.15; 95% [CI] 0.91-1.45, $P = 0.25$)
Median OS, mo	OS was also statistically significantly improved (HR, 0.60); however, median OS was not reached in either arm by the time of publication.	14.4 vs 13.2 (HR; 1.02; 95% CI, 0.80-1.30).
Effect of PD-L1 expression	PD-L1 tumor proportion score (TPS) $\geq$ 50%	PD-L1 expression $\geq$ 1%

progression free survival (PFS) (10.3 vs 6.0 months, $P < 0.001$). Toxicity was lower with the immunotherapy compared with chemotherapy (grade 3/4 adverse events: 27% vs 53%), and the incidence of all adverse events (AEs) was lower with immunotherapy. Overall survival (OS) was also statistically significantly improved (Hazard ratio [HR], 0.60); however, median OS. A new standard of care for previously untreated patients with tumor PD-L1 staining of at least 50% without EGFR or ALK genomic tumor aberrations should be considered a single-agent pembrolizumab.

In the phase III CheckMate 026 trial, we compared first-line nivolumab with chemotherapy in 541 patients with PD-L1–positive NSCLC who had not received prior systemic therapy.[7] Nivolumab was not associated with significantly longer PFS in the 423 patients with >5% tumor

Table 2
TMB as a biomarker data from checkmate 026 and checkmate 027.

			ORR, % (n)	
Checkmate 026	**Patients with Low/Medium TMB**	PD-L1 Subgroup	Nivolumab	Chemotherapy
		1-49 %	16 (11)	23 (12)
		≥ 50	34 (14)	46 (19)
	Patients with High TMB	PD-L1 Subgroup	Nivolumab	Chemotherapy
		1-49 %	32 (10)	32 (9)
		≥50	75 (12)	25 (8)
	Patients with High TMB		Nivolumab n=47	Chemotherapy n=60
		ORR, %	47	28
		mPFS, mo	9.7	5.8
			Patients with PFS (%)	
Checkmate 027		PD-L1 Subgroup	Nivolumab+ipilimumab	Chemotherapy
	Patients with High TMB	≥1	42	16
		<1	45	8
		Tumor Histologic Type	16	7
		Squamous	46	17
		Nonsquamous		

PD-L1 expression than chemotherapy among patients with previously untreated stage IV NSCLC. OS was similar between groups. CheckMate 026 did not exclusively examine patients with high (≥50%) PD-L1 expression but patients with a higher tumor mutational burden (TMB) seem to benefit more from treatment with immunotherapy than do patients with a lower TMB (Table 2).

CheckMate-227 was conducted in 1739 patients with stage IV or recurrent NSCLC who had not received prior chemotherapy and whose tumors did not harbor ALK or EGFR mutations.[8] In the initial study design, patients were assigned in a 2:1 ratio on the basis of their having high-PD-L1 expression or low PD-L1 expression. Across each of these arms, patients received either a combination of nivolumab and reduced-dose ipilimumab, or nivolumab monotherapy, or histology-based chemotherapy (control arm). Analysis of the coprimary end point in patients with high TMB showed significantly longer PFS with nivolumab plus ipilimumab than with chemotherapy, the median PFS was 7.2 months (95% confidence interval [CI], 5.5-13.2) vs 5.5 months (95% CI, 4.4-5.8) (HR for disease progression or death, 0.58; 97.5% CI, 0.41-0.81; $P < 0.001$) (Table 2). The response rate was 45.3% with nivolumab plus ipilimumab and 26.9% with chemotherapy. Among patients with a low TMB, the median PFS was 3.2 months (95% CI, 2.7-4.3) with nivolumab plus ipilimumab and 5.5 months (95 CI, 4.3-5.6) with chemotherapy. The between-group difference was not significant. Treatment-related select AEs leading to discontinuation were more common with nivolumab plus ipilimumab than with chemotherapy (17.4% vs8.9%). The most common treatment-related select AEs with nivolumab plus ipilimumab was skin reactions (33.9%); the most common grade 3 or 4 treatment-related select AEs was hepatic events (8.0%).

If ≥ 50% PD-L1 expression the National Comprehensive Cancer Network (NCNN) recommends pembrolizumab monotherapy. On the other hand, If < 50% PD-L1 expression NCNN guideline recommends chemotherapy followed by checkpoint inhibitor in ~100% of patients (second line is standard of care for all patients eligible for immunotherapy).

Immunotherapy and chemotherapy combinations

Clinical scenario 2: A 56-year-old white female never-smoker developed increasing right upper quadrant pain while running. She presented to emergency department and was found to have elevated liver function test. Computed Tomography (CT) of the abdomen and pelvis shows innumerable liver metastases, retroperitoneal lymphadenopathy, and a 3-cm mass in right lower lobe. Chest CT confirms right lower lobe mass and mild (1-1.5 cm) mediastinal lymphadenopathy. Ultrasound-guided biopsy of liver metastases shows TTF-1–positive adenocarcinoma, consistent with lung primary. EGFR, ALK, and ROS1 negative; PD-L1 0%. What is achieved by using both chemotherapy and pembrolizumab in this case, or any other PD-1 or PD-L1 inhibitor, together rather than sequencing them one after the other.

Chemotherapy is generally assumed to suppress the immune system. Nevertheless, the possibility remains that cytotoxic chemotherapy could enhance responses to immunotherapy. As it depletes effector and suppressor immune cells, chemotherapy "resets" the immune system, thereby establishing a new immune repertoire.[9] In addition, chemotherapy can mediate a multipronged immunostimulatory effect, thereby reinstating anticancer immunosurveillance. On one hand, antineoplastic agents can increase the antigenicity of malignant cells, improve their immunogenicity, and augment their susceptibility to immune attacks. For example, specific cytotoxic agents might have immunomodulatory effects and, in general, chemotherapy can induce tumor-cell death and the release of tumor antigens,[10] thus facilitating interactions with antigen-presenting cells[11,12] and selective depletion of specific immunosuppressive cell in the tumor microenvironment such as myeloid-derived suppressor cells and regulatory T cells (Tregs)[13-17] and enhaching effector T cells[18,19] increase anticancer immune response.

Cohort G of the KEYNOTE-021 study was an open-label, randomized phase 2 trial of pembrolizumab plus pemetrexed-carboplatin (PC) vs PC alone in patients with previously untreated advanced nonsquamous NSCLC.[20] ORR, the primary end point, for pembrolizumab plus PC and PC were 55% and 29%, respectively. PFS was prolonged with the addition of pembrolizumab to PC (median PFS, 13 vs 6 months; HR 0.53, 95% CI 0.31-0.91). The HR for OS continues to improve for pembrolizumab + PC vs PC. In the last analysis, the HR for OS was 0.59 after a median of 18.7 months follow-up HR for OS was 0.90 in the primary analysis (median 10.6 mo follow-up) and 0.69 at a previous update (median 14.5 months follow-up).[21] Incremental OS benefit, though not statistically significant, continued despite high (~75%) crossover rate to anti–PD-1/PD-L1 therapy in the PC alone arm. The AEs in the phase II study were higher in the combination arm. While the study was well conducted, many clinicians have not incorporated this regimen into practice and anxiously await phase 3 trial results.

KEYNOTE-189 enrolled 616 patients with stage IV NSCLC with no ALK or EGFR mutations who had received no prior therapy for metastatic disease.[22] Patients were randomly assigned in a 2:1 ratio to receive the combination of pembrolizumab plus chemotherapy (n = 410) or chemotherapy alone (n = 206). With a HR of 0.49, patients receiving pembrolizumab plus chemotherapy had a 51% reduced risk for death ($P < 0.00001$) compared with patients receiving chemotherapy. Similarly, patients had a 48% reduced risk for disease progression (HR for PFS, 0.52; $P < 0.00001$). Median OS was not reached for patients receiving the combination of pembrolizumab plus chemotherapy and was 11.3 months for patients receiving chemotherapy alone; correspondingly, median PFS was 8.8 and 4.9 months, respectively. In addition, Gandhi showed that OS and PFS benefits were seen across all subgroups of patients regardless of PD-L1 expression levels; however, OS and PFS benefits were numerically higher for patients with higher PD-L1 levels. ORR was 47.6% for patients receiving pembrolizumab plus chemotherapy and 18.9% for patients receiving chemotherapy alone. Again, ORR benefit was seen across all patient subgroups, regardless of PD-L1 levels. The combination of pembrolizumab plus chemotherapy was associated with more AEs than was chemotherapy alone, such as AEs leading to discontinuation of all treatment (13.8% vs 7.9%). Acute kidney injury occurred more frequently in the pembrolizumab-combination group than in the placebo-combination group (5.2% vs 0.5%).

Immune-related AEs occurred in twice as many patients in the pembrolizumab group as in the chemotherapy group: 22.7% vs 11.9%.

Atezolizumab's T-cell mediated cancer cell killing may be enhanced through bevacizumab's reversal of VEGF-mediated immunosuppression. IMpower150 is a randomized phase 3 study of approximately 1200 patients with nonsquamous histology across 3 treatment arms.[23]

Patients received carboplatin and paclitaxel plus atezolizumab (Arm A) or carboplatin and paclitaxel plus atezolizumab plus bevacizumab (Arm B) vs carboplatin and paclitaxel plus bevacizumab (Arm C) per investigator discretion. Atezolizumab in combination with chemotherapy ± bevacizumab appears to be well tolerated and its safety profile is consistent with known safety risks. PFS benefit was demonstrated with the addition of atezolizumab to bevacizumab + CP (Arm B) vs bevacizumab + CP (Arm C) in all populations tested, including patients with sensitizing EGFR or ALK genetic alterations, low T effector cell levels , PD-L1–negative tumors and liver metastases.

Pembrolizumab in combination with carboplatin and pemetrexed is now US Food and Drug Administration approved for patients regardless of PD-L1 expression.

New perspectives in the second-line treatment of NSCLC patients

Clinical scenario 3: A 55-year-old female, with a 20 pack-year history of smoking, presents to your office for consultation regarding second opinion for metastatic NSCLC, adenocarcinoma histology. Diagnosis of metastatic lung adenocarcinoma from liver lesion biopsy 7 months ago was diagnosed. Molecular testing of his tumor revealed negative for EGFR, ALK, and ROS1.There was an inadequate tissue sample for the PD-L1 test. Completed a course of standard carboplatin and/or pemetrexed chemotherapy followed by maintenance treatment. A recent CT shows disease progression. She has no significant medical problems and the performance status is 1.She wants "the best treatment possible" and desires further treatment. Her oncologist has recommended nivolumab. The patient was rebiopsied. Testing reports PD-L1 < 1%. What is the most effective second-line therapy for patients with stage IV NSCLC?

In 2015 alone, we witnessed FDA approvals for 2 checkpoint inhibitors for use in advanced NSCLC, nivolumab for treatment of squamous[24] disease and pembrolizumab for use in patients with tumors that express PD-L1.[25]

The CheckMate 017 trial was a phase 3 study comparing nivolumab with docetaxel in patients with advanced squamous NSCLC who experienced disease progression during or after initial therapy with platinum-based doublet chemotherapy.[26] A total of 272 patients were randomly assigned to treatment with nivolumab at 3 mg/kg every 2 weeks or docetaxel at 75 mg/m 2 every 3 weeks. The primary end point was median OS. OS was prolonged with nivolumab compared with docetaxel (median OS, 9.2 vs 6.0 months; HR, 0.59; 95% CI, 0.44-0.79; $P < 0.001$) and the 2-year OS rates with nivolumab vs docetaxel were 23% vs 8%. The ORR and median PFS significantly improved for nivolumab compared with docetaxel (ORR, 20% vs 9%; $P = 0.008$; PFS, 3.5 months vs 2.8 months; HR, 0.62; 95% CI, 0.47-0.81; $P < 0.001$). PD-L1 expression was not prognostic or predictive for nivolumab efficacy compared with docetaxel. Rates of grade 3 or 4 treatment-related AEs were considerably lower in the nivolumab arm (7%) compared with the docetaxel arm (55%).

The Checkmate 057 study compared nivolumab with docetaxel in patients with advanced nonsquamous NSCLC who experienced disease progression during or after initial therapy with platinum-based chemotherapy.[27] A total of 582 patients were randomly assigned to treatment with nivolumab (3 mg/kg every 2 weeks) or docetaxel (75 mg/m^2 every 3 weeks). Patients with EGFR-mutant or ALK-translocation NSCLC received prior tyrosine kinase inhibitors. The primary end point was OS. Nivolumab was associated with increased median OS (12.2 vs 9.4 months; HR, 0.72; 95% CI, 0.60-0.88; $P < 0.001$) and 1-year OS (51% vs 39%) compared with docetaxel. The ORR was 19% for nivolumab and 12% for docetaxel ($P = 0.0246$). The median PFS was 2.3 months (95% CI: 2.2-3.3) and 4.2 months (95% CI: 3.4-4.9) in the nivolumab and docetaxel arms, respectively. OS clearly correlated with PD-L1 expression (HR: 1%, HR 0.59 ($P = 0.06$); 5%, HR

0.43 ($P = 0.0004$); and 10%, HR 0.4 ($P = 0.0002$). In patients with PD-L1-negative tumors were survival similar between nivolumab and docetaxel. Grade 3 or 4 treatment-related AEs occurred in 7% and 54% of patients receiving nivolumab and docetaxel, respectively.

The phase II/III KEYNOTE-010 study was evaluating the efficacy of pembrolizumab in patients with previously treated advanced NSCLC.[28] 1034 patients had PD-L1 expression in at least 1% of tumor cell (TCs). Patients were randomly assigned in a 1:1:1 fashion to pembrolizumab, 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel. Both doses of pembrolizumab improved the median OS compared with docetaxel (pembrolizumab, 2 mg/kg, vs docetaxel: HR, 0.71; 95% CI, 0.58-0.88; *P* 5 0.0008; pembrolizumab, 10 mg/kg, vs docetaxel: HR, 0.61; 95% CI, 0.49-0.75; $P < 0.0001$). For the total population, the ORR for pembrolizumab, 2 mg/kg, pembrolizumab, 10 mg/kg, and docetaxel were 18%, 18%, and 9%, respectively. Despite these improvements in OS, no difference was found in PFS among the 3 study arms. On October 2015, FDA approved pembrolizumab for treatment of patients with metastatic NSCLC whose tumor positive for PD-L1 expression.

The POPLAR trial was a phase 2 study comparing atezolizumab with docetaxel in 287 patients with previously treated advanced stage NSCLC.[29] The primary end point was median OS. The median PFS was not markedly different for atezolizumab compared with docetaxel (2.8 vs 3.4 months, respectively; HR, 0.98). However, atezolizumab was associated with a significant improvement in median OS compared with docetaxel (12.6 months vs 9.7 months; HR, 0.73; 95% CI, 0.53-0.99; $P = 0.04$)). PD-L1 expression on tumor cells or tumor-infiltrating immune cells was associated with an OS benefit. Grade 3 or 4 treatment-related AEs were seen in 11% of patients receiving atezolizumab vs 39% in those treated with docetaxel.

The phase 3 OAK study was conducted in 1225 patients with previously treated NSCLC. The patients were randomly allocated to receive either intravenous atezolizumab (1200 mg every 3 weeks) or docetaxel (75 mg/m^{2}every 3 weeks).[30] The median OS was 13.8 months vs 9.6 months on docetaxel (hazard ratio [HR], 0.73; $P = 0.0003$). The subgroup of patients with the highest levels of PD-L1 expression (TC3 group, n = 72) had the most benefit from immunotherapy; OS was 59% greater in patients receiving atezolizumab, (median OS, 20.5 months vs 8.9 months with docetaxel; HR, 0.41; $P < 0.0001$). Fewer patients had treatment-related grade 3 or 4 AEs with atezolizumab vs docetaxel. Azetizolumab offers a new second-line therapeutic strategy for patients with nonsmall cell lung cancer, regardless of the PD-L1 status of the tumor.

What have we learnt from 5 studies?

Level 1 evidence exists to support the use of immunotherapy as second-line treatment of patients with advanced NSCLC (Table 3). In this scenario 3, our overview aims to focus on the second line therapy for metastatic NSCLC. Another important question is how long should checkpoint blockade therapy be continued in responding patients? There are no answers right now: it appears that retreatment of responding patients at the time of disease progression can be effective, but stopping is a topic that should be discussed with the patient.

What is the role of immunotherapy in lung cancer with mutations?

Clinical scenario 4: A 44-year-old never-smoker man was diagnosed with adenocarcinoma of the lung a year ago. Molecular testing of her tumor revealed an exon 19 deletion in *EGFR*. He was started on erlotinib and had a near complete response. Imaging studies over last 6 months show gradual progression at multiple sites and with new lesions detected on last scan. Her tumor was rebiopsied. No EGFR T790M mutation detected. ECOG performance status is excellent (0).

We do not have a lot of clinical data to answer, but we can extrapolate data from some of the reported phase 3 studies in the second-line setting (Table 4). Treatment with tyrosine kinase inhibitors (TKIs erlotinib, gefitinib, afatinib) is indicated for the initial management of patients whose tumors contain an activating mutation in EGFR. Crizotinib for those with the ALK fusion oncogene or ROS1-translocations is the preferred treatment. There are currently no phase III trials comparing immunotherapy vs single-agent chemotherapy among patients with a sensitizing mutation and a choice between them depends on patient and provider preferences, as well as consideration of toxicities. Anti-PD-1/PD-L1 therapy has produced durable responses in NSCLC,

Table 3
Randomized studies of PD-1/PD-L1 inhibitors in second-line NSCLC.

	CheckMate 017[26]	CheckMate 057[27]	KEYNOTE-010[28]	OAK[30]
	Nivolumab vs docetaxel	Nivolumab vs docetaxel	Pembrolizumab (2 mg/kg or 10 mg/kg) vs docetaxel	Atezolizumab vs docetaxel
Phase of study	III	III	II/III	III
PD-L1 selected	No	No	Yes (TPS ≥ 1%)	No
Study size, n	272 (135 vs 137)	582 (292 vs 290)	1033 (344 vs 346 vs 343)	1225 (425 vs 425)
Histology	Squamous	Non-squamous	All-comers	All-comers
Line of therapy, %				
2L	100	88	69	75
3L	0	11	20	25
>3L	0	<1	9	0
Other/unknown	0	0	<1	0
Subsequent therapy (immunotherapy arm vs chemotherapy arm	<1 vs 2	1 vs 2	0.6 vs 1.7 vs 13.1	4.5 vs 17.2
Crossover from chemotherapy arm to study immunotherapy, %	4	6	Not permitted	Not permitted
Median OS, mo	9.2 vs 6.0	12.2 vs 9.5	10.4 vs 12.7 vs 8.5	13.8 vs 9.6
HR vs docetaxel (P value)	0.62 (P = 0004)	0.75 (P < 0.001)	2 mg/kg: 0.71 (P = 0.0008) 10 mg/kg: 0.61 (P < 0.0001)	0.73 (P = 0.0003)

Table 4
What is the role of immunotherapy in lung cancer with mutations?

Study	Weight	Hazard Ratio [95%CI]
EGFR wild type		
Checkmate 057	26.0%	0.66 [0.51,0.86]
KEYNOTE-010	52.0%	0.66 [0.55, 0.80]
POPLAR	11.0%	0.70 [0.47, 1.04]
OAK	NA	0.69 [NA]
Subtotal [95% Cl)]	89.0%	0.66 [0.58,0.76]
EGFR mutated		
Checkmate 057	6.0%	1.18[0.69, 2.00]
KEYNOTE-010	3.8%	0.88[0.45, 1.70]
POPLAR	1.1%	0.99[0.29, 3.40]
OAK	NA	1.24[NA]
Subtotal [95% Cl)]	11.0%	1.05[0.70, 1.55]
Total [95% Cl)]	100.0 %	0.70 [0.61, 0.80]

Favors Anti-PD-1/PD-L1 therapy

Favors Anti-PD-1/PD-L1 therapy

Favors docetaxel

Favors Anti-PD-1/PD-L1 therapy

Favors docetaxel

but responses appear to be less frequent in patients with EGFR mutations.[31] Single center experience on KEYNOTE-001 suggests patients with EGFR mutations that were EGFR TKI naive had improved clinical outcomes compared to those with history of TKI prior to pembrolizumab.[32] In the CheckMate 057 study, exploratory subgroup analysis suggested that patients positive for EGFR mutation may derive less benefit with nivolumab.

What do you do with a patient with an *EGFR* mutation, ≥50% PD-L1 expression, and no other options? We do not have a clear answer, but we would likely say that that it is probably safe to try immunotherapy under very close observation and that if there is any sign of progression, the patient should be switched to something different treatment. We do not have a data set in support of that approach.

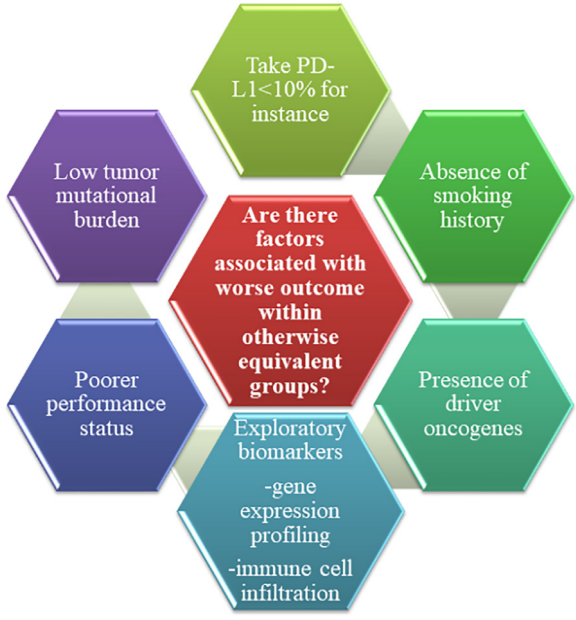

Fig. 2. Complex decisions for immunotherapy.

Predictive biomarkers in PD-1/PD-L1 checkpoint blockade immunotherapy

PD-L1 expression in the tumor is associated with an increased likelihood of response but the predictive validity of this biomarker is still debated. There are several unanswered questions regarding the use of PD-L1 expression in advanced lung cancer (Fig. 2). Different anti-PD-L1 antibodies, different scoring cutoffs, and various scoring algorithms may lead to different results. PD-L1 expression can be heterogeneous even within the same tumor specimen, and therefore there may be false negatives depending on the location of the biopsy. Changing PD-L1 expression over time, after systemic and local therapies. At this point, it is difficult to identify the patient population who may derive the most benefit from this strategy. TMB is a complementary biomarker to PD-L1.[33] However, TMB testing is not standardized. It is associated with PFS, but not OS; and the actual costs are 5-10 times as much as those for immunohistochemistry and require 10 times more tissue. There is a clinical need to predict who will benefit from immunotherapy and to understand mechanisms of therapeutic resistance to improve patient management and outcomes. Immunogram for the cancer-immunity cycle can be used as an integrated biomarker and thus may become a helpful resource toward optimal personalized immunotherapy in the future.

Summary and recommendations

NSCLC remains an important problem worldwide. For patients without an *EGFR* mutation or *ALK* translocation in whom at least 50% of tumor cells stain for PD-L1, NCNN recommend pembrolizumab monotherapy (Fig. 3). On the other hand, if < 50% PD-L1 expression NCNN guideline recommends chemotherapy followed by checkpoint inhibitor in ~100% of patients (second line is standard of care for all patients eligible for immunotherapy). For patients whose tumor contains a driver mutation, use of a specific inhibitor is the preferred initial approach (eg, erlotinib, gefitinib, or afatinib for patients with an activating mutation of EGFR, crizotinib for those with the ALK fusion oncogene or ROS1-translocations). Inhibiting these T-cell checkpoints has been

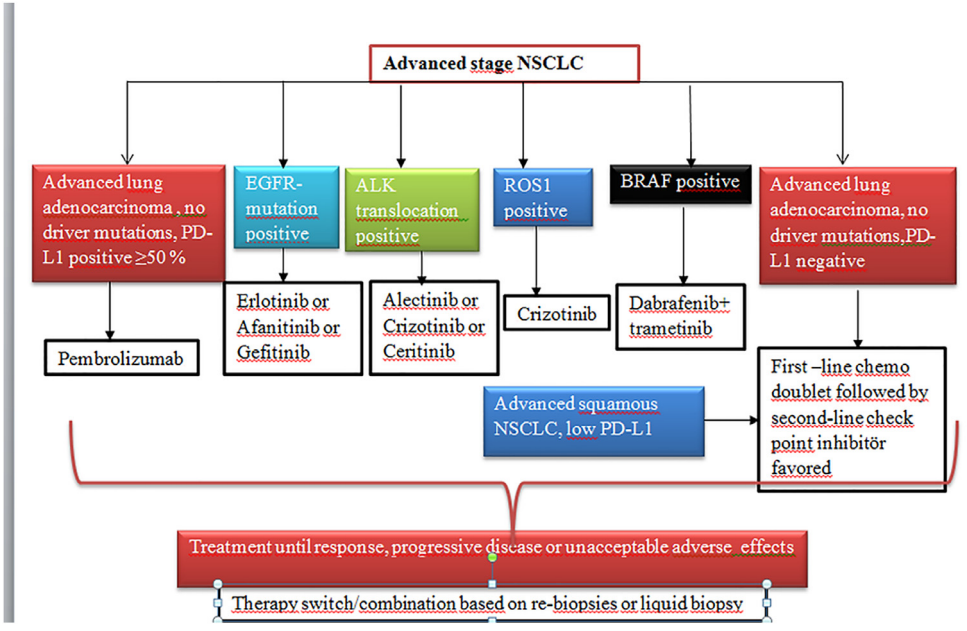

Fig. 3. Personalized therapy in advanced-stage NSCLC: current therapeutic landscape.

revolutionary in the treatment of NSCLC. The opportunities to explore the plethora of potential immunotherapy targets brings forth 2 challenges: (1) the clinical development (based on strong preclinical studies) of optimal pharmacologic targeting and combinatorial approaches (2) the definition of potential biomarkers that can guide the therapeutic choice. Phase III clinical trials evaluating new combination strategies including checkpoint blockade plus chemotherapy and dual checkpoint blockade are enrolling patients.

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