BRIEF REPORT

Pembrolizumab in Combination With Erlotinib or Gefitinib as First-Line Therapy for Advanced NSCLC With Sensitizing *EGFR* Mutation

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ABSTRACT

Introduction: Anti-EGFR agents are standard treatments for patients with *EGFR*-mutant advanced NSCLC. The feasibility of combining erlotinib or gefitinib with the anti–programmed death 1 immunotherapy pembrolizumab was evaluated in the phase 1/2 KEYNOTE-021 study (NCT02039674).

Methods: Adults with previously untreated stage IIIB/IV *EGFR*-mutant NSCLC were treated with pembrolizumab 2 mg/kg intravenously every 3 weeks plus oral erlotinib 150 mg daily in cohort E or oral gefitinib 250 mg daily in cohort F, using a 3 + 3 design with cohort expansion. rTumor response was evaluated per Response Evaluation Criteria in Solid Tumors version 1.1 by blinded independent central review. The primary objective was determination of a recommended phase 2 dose.

Results: Twelve patients enrolled to receive pembrolizumab plus erlotinib and seven to receive pembrolizumab plus gefitinib. No dose-limiting toxicities or grade 5 events occurred. Pembrolizumab plus erlotinib was feasible, with adverse events similar to those expected for monotherapy. However, pembrolizumab plus gefitinib was not feasible due to grade 3/4 liver toxicity in five of seven patients (71.4%), leading to permanent treatment discontinuation in four patients. The most frequently occurring treatment-related adverse events with pembrolizumab plus erlotinib were rash (50.0%), dermatitis acneiform, diarrhea, hypothyroidism, and pruritus (33.3% each). The objective response rate was 41.7%, including response in all four

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patients with programmed death ligand 1 expression 50% or greater.

Conclusions: Although pembrolizumab plus gefitinib was not feasible, the toxicity profile observed with pembrolizumab plus erlotinib suggests combining immunotherapy with anti-EGFR therapy is feasible. Pembrolizumab plus erlotinib did not improve objective response rate compared with previous monotherapy studies; further evaluation would be necessary to evaluate potential effects on other efficacy outcomes.

Keywords: Combination therapy; NSCLC; Pembrolizumab; Erlotinib; Gefitinib

Introduction

Anti-EGFR monotherapy provides improved efficacy and tolerability versus chemotherapy for patients with NSCLC with sensitizing *EGFR* mutations[1]; however, patients inevitably develop resistance. Pembrolizumab, a humanized, immunoglobulin G4 monoclonal antibody against programmed death-1 (PD-1), is an effective first- and second-line treatment option for patients with advanced NSCLC.[1,2] Preclinical studies suggest the PD-1 pathway may contribute to immune escape in *EGFR*-mutant tumors, and clinical studies have shown a positive association between programmed death ligand 1 (PD-L1) expression and response rate and time to progression after treatment with gefitinib or erlotinib.[3,4]

KEYNOTE-021 (ClinicalTrials.gov, NCT02039674) is an open-label, multicohort study in which cohorts E and F, reported here, evaluated pembrolizumab plus erlotinib or gefitinib, respectively, as first-line therapy for patients with advanced *EGFR*-mutant NSCLC.

Materials and Methods

Patients

Enrolled patients were adults with histologically/cytologically confirmed stage IIIB/IV NSCLC (any histology), no previous systemic therapy, confirmed sensitizing *EGFR* mutation, at least one radiographically measurable lesion per Response Evaluation Criteria in Solid Tumors version 1.1, Eastern Cooperative Oncology Group performance status 0/1, life expectancy 3 months or longer, and tumor biopsy sample for PD-L1 evaluation. Exclusion criteria included ongoing systemic corticosteroid use or other immunosuppressive therapy, and untreated brain metastases.

Patients provided written informed consent. The protocol was approved by independent institutional review boards/ethics committees at each site.

Study Design and Treatment

This multicenter, open-label, phase 1/2 study with up to 12 patients planned in cohorts E and F each used a 3 + 3 design followed by cohort expansion (Supplementary Material). Patients received intravenous pembrolizumab 2 mg/kg every 3 weeks plus oral erlotinib 150 mg in cohort E or gefitinib 250 mg daily in cohort F. Dose-limiting toxicity (DLT) included any of the following occurring during the first 3-week treatment cycle, if deemed at least possibly related to study drug: grade 3 (lasting more than 3 days) or grade 4 nonhematologic toxicity; grade 3/4 nonhematologic laboratory abnormality requiring medical intervention, hospitalization, or lasting more than 1 week; grade 4 hematologic toxicity lasting 7 days or more; grade 3/4 febrile neutropenia; thrombocytopenia less than 25,000/mm^3 associated with platelet-requiring or life-threatening bleeding event; greater than 2-week delay in initiating cycle 2 due to treatment-related toxicity; missing more than 10% erlotinib/gefitinib doses because of adverse events (AEs); or grade 5 toxicity. Treatment with erlotinib/gefitinib continued as long as patients derived benefit; pembrolizumab was limited to 2 years.

The primary objective was to determine a recommended dose for evaluation in phase 2 (RP2D).

Assessments

AEs occurring up to 30 days after last dose (up to 90 days for serious AEs) during the study were graded per National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. Radiographic imaging (computed tomography [preferred] or magnetic resonance imaging) was performed at baseline, every 6 weeks for the first 18 weeks, every 9 weeks through the remainder of year 1, and every 12 weeks during year 2. Response was assessed per Response Evaluation Criteria in Solid Tumors version 1.1. Treatment decisions were based on investigator assessment of response. Response evaluation for efficacy analysis was by blinded, independent central review. Responses were required to be confirmed by imaging performed at least 28 days after initial response assessment. Patients with progressive disease who were clinically stable could remain on therapy until confirmation at least 28 days later. At baseline, PD-L1 was assessed in formalin-fixed tumor samples collected at diagnosis of metastatic disease at a central laboratory using the PD-L1 immunohistochemistry 22C3 pharmDx assay (Agilent Technologies, Carpinteria, California).

Statistical Analysis

Analyses included all treated patients. The Kaplan-Meier method was used to assess duration of response

(DOR), progression-free survival (PFS), and overall survival (OS) (see Supplementary Material for definitions).

Results

Baseline Characteristics

Twelve patients enrolled to receive pembrolizumab plus erlotinib (between April 28, 2014 and November 2, 2015) and seven to receive pembrolizumab plus gefitinib (between July 21, 2014, and December 8, 2015) (Table 1). Most patients had stage IV disease and were mostly white in the pembrolizumab-plus-erlotinib cohort, and Asian in the pembrolizumab-plus-gefitinib cohort (Table 2).

Toxicity

No DLTs or grade 5 AEs occurred in either cohort. Pembrolizumab plus erlotinib was deemed feasible, with cohort expansion proceeding to 12 patients. The RP2D was pembrolizumab 2 mg/kg every 3 weeks plus erlotinib 150 mg daily. However, pembrolizumab plus gefitinib was deemed not feasible due to liver toxicity occurring outside the defined period for DLT; recruitment in this cohort ceased after seven patients enrolled, and no RP2D was established.

Key safety results are listed in Table 3. The most frequent treatment-related AEs with pembrolizumab plus erlotinib were skin reactions and diarrhea. Grade 3 or greater skin toxicity occurred in two patients. The most common immune-mediated AEs and infusion reactions reported (irrespective of attribution to treatment by the investigator) were hypothyroidism (33.3%) and severe skin reactions (16.7%). Three patients had treatment-related alanine aminotransferase (ALT; grade 1, n = 1; grade 2, n = 2) and aspartate aminotransferase (AST; grade 1, n = 2; grade 2, n = 1) elevations that resolved in two patients; in the third patient, the events resolved, reoccurred, and were continuing at the last assessment. One patient experienced neuralgic amyotrophy in conjunction with liver function test (LFT) elevation (both grade 3) during treatment cycle 1, which resolved approximately 5 months and within 3 weeks, respectively, following treatment discontinuation. Another patient experienced rash and autoimmune hepatitis, underwent additional serum chemistry laboratory assessments, and received prednisone; no biopsies were performed.

The most frequent treatment-related AEs with pembrolizumab plus gefitinib were ALT/AST elevations and diarrhea. Five patients (71.4%) had treatment-related

Table 1. Patient Disposition

	Pembrolizumab + Erlotinib (n = 12)	Pembrolizumab + Gefitinib (n = 7)
Discontinued, n (%)	7 (58.3)	7 (100.0)
Due to adverse events	3 (25.0)	5 (71.4)
Due to progressive disease/clinical progression	3 (25.0)	1 (14.3)
Due to physician decision	1 (8.3)	0
Due to patient request	0	1 (14.3)
Median follow-up, mo	18.6	13.0
Range	4.8-23.0	0.2-27.2
Median pembrolizumab infusions	18.0	3.0
Range	2-28	1-5

Data cutoff: November 7, 2016.

Table 2. Baseline Demographic and Disease Characteristics

	Pembrolizumab + Erlotinib (n = 12)	Pembrolizumab + Gefitinib (n = 7)
Men, n (%)	6 (50.0)	3 (42.9)
Age, median (range), y	59.5 (49-74)	68.0 (38-71)
Race, n (%)		
Asian	3 (25.0)	7 (100.0)
White	9 (75.0)	0
Asian region, n (%)		
East Asian	2 (16.7)	7 (100.0)
Non-East Asian	10 (83.3)	0
Smoking status, n (%)		
Never smoker	6 (50.0)	4 (57.1)
Ex-smoker	5 (41.7)	3 (42.9)
Current smoker	1 (8.3)	0
ECOG PS, n (%)		
0	5 (41.7)	7 (100.0)
1	7 (58.3)	0
Histology, n (%)		
Adenocarcinoma	9 (75.0)	6 (85.7)
NSCLC not otherwise specified	3 (25.0)	1 (14.3)
Metastatic stage, n (%)		
M0	2 (16.7)	0
M1A	8 (66.7)	5 (71.4)
M1B	2 (16.7)	2 (28.6)
Cancer stage, n (%)		
IIIB	1 (8.3)	0
IV	11 (91.7)	7 (100.0)
Presence of brain metastasis, n (%)	2 (16.7)	1 (14.3)
Tumor size,[a] median (range), mm	n = 10 46.5 (15-106)	n = 7 70.0 (18-165)
PD-L1 TPS, n (%)		
<1%	2 (16.7)	6 (85.7)
1%-49%	6 (50.0)	0
≥50%	4 (33.3)	1 (14.3)
Received prior systemic adjuvant/ neoadjuvant therapy, n (%)	1 (8.3)	0

[a]Sum of the longest diameters of target lesions.
ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1; TPS, tumor proportion score.

Table 3. Summary of Adverse Events

	Pembrolizumab + Erlotinib (n = 12)		Pembrolizumab + Gefitinib (n = 7)	
Treatment-related AEs, n (%)				
Any grade	12 (100.0)		6 (85.7)	
Grade 3	4 (33.3)		3 (42.9)	
Grade 4	0		2 (28.6)	
Grade 5	0		0	
Led to discontinuation	3 (25.0)		5 (71.4)	
Led to death	0		0	
	Any Grade	Grade 3	Any Grade	Grade 3/4
Treatment-related AEs occurring in ≥15% of patients in either arm, n (%)				
Rash	6 (50.0)	1 (8.3)	2 (28.6)	0
Dermatitis acneiform	4 (33.3)	0	0	0
Diarrhea	4 (33.3)	0	4 (57.1)	0
Pruritus	4 (33.3)	0	2 (28.6)	0
Hypothyroidism	4 (33.3)	0	0	0
Alanine aminotransferase increased	3 (25.0)	0	5 (71.4)	5 (71.4)
Arthralgia	3 (25.0)	0	0	0
Aspartate aminotransferase increased	3 (25.0)	0	5 (71.4)	4 (57.1)
Pyrexia	3 (25.0)	0	0	0
Rash maculopapular	3 (25.0)	1 (8.3)	0	0
Decreased appetite	2 (16.7)	0	1 (14.3)	0
Dizziness	2 (16.7)	0	0	0
Dry eye	2 (16.7)	0	0	0
Dry skin	2 (16.7)	0	0	0
Fatigue	3 (25.0)	0	0	0
Ingrowing nail	2 (16.7)	0	0	0
Nausea	2 (16.7)	0	0	0
Skin bacterial infection	2 (16.7)	0	0	0
	Any Grade	Grade 3	Any Grade	Grade 3/4
Immune-mediated AEs and infusion reactions occurring in >0% of patients, n (%)				
Any event	6 (50.0)	2 (16.7)	1 (14.3)	0
Hypothyroidism	4 (33.3)	0	0	0
Severe skin reactions	2 (16.7)	2 (16.7)	0	0
Uveitis	1 (8.3)	0	0	0
Colitis	1 (8.3)	0	0	0
Hepatitis	1 (8.3)	1 (8.3)	0	0
Pneumonitis	0	0	1 (14.3)	0

Data cutoff: November 7, 2016.
AE, adverse event.

ALT (grade 3, n = 3; grade 4, n = 2) and AST increases (grade 2, n = 1; grade 3, n = 3; grade 4, n = 1), leading to permanent study treatment discontinuation in four patients, as described in greater detail in Table 4. These ALT/AST increases resolved, although safety follow-up in one patient showed grade 1 jaundice still recovering at their last on-study assessment (there were no other reports of jaundice). No grade 3 or greater skin toxicity was reported with pembrolizumab plus gefitinib. Only one immune-mediated AE and infusion reaction (irrespective of attribution to treatment) was reported (grade 1 pneumonitis).

Efficacy

Confirmed objective response rates (ORRs) were 41.7% and 14.3% with pembrolizumab plus erlotinib and pembrolizumab plus gefitinib, respectively (all partial responses) (Table 5, Fig. 1). All patients with PD-L1 tumor proportion score (TPS) greater than or equal to 50% who received pembrolizumab plus erlotinib responded and had DORs of 18.3, 7.7 (ongoing), 14.7 (ongoing), and 7.8 (ongoing) months. Median PFS was 19.5 (95% confidence interval [CI]: 3.0–19.5) months and 1.4 (95% CI: 0.2–13.0) months with pembrolizumab plus erlotinib and pembrolizumab plus gefitinib,

Table 4. Description of Key Liver-Related Adverse Events and Management in Patients Who Received Pembrolizumab Plus Gefitinib

Patient No.	Type of AE	Severity of AE	Onset of AE	Duration of AE	Treatment With Corticosteroids	Effect on Study Treatment	Outcome of AE
1	ALT increase	Grade 4	Day 29	36 days	Days 39-63	Treatment interrupted	Resolved
	AST increase	Grade 3	Day 29	19 days			Resolved
2	ALT increase	Grade 3	Day 35	16 days	Days 42-70	Treatment discontinued	Resolved
	AST increase	Grade 3	Day 35	22 days			Resolved
3	ALT increase	Grade 3	Day 63	58 days	Days 85-120	Treatment discontinued	Resolved
	AST increase	Grade 3	Day 63	43 days			Resolved
4	ALT increase	Grade 4	Day 36	56 days	Days 36-61, 76-98	Treatment discontinued	Resolved
	AST increase	Grade 4	Day 36	63 days			Resolved
	Jaundice	Grade 1	Day 65	–			Recovering at the time of last follow-up
5	ALT increase	Grade 3	Day 43	29 days	Days 53-101	Treatment discontinued	Resolved
	AST increase	Grade 2	Day 43	14 days			Resolved

All patients received additional serum chemistry and hematology labs, 3 had urinalysis, and 3 had abdominal ultrasounds. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; No., number.

respectively. Median OS was not reached (NR) and 13.0 (95% CI: 0.2–NR) months, respectively (Table 5).

Discussion

Pembrolizumab 2 mg/kg every 3 weeks plus erlotinib 150 mg daily was found to be feasible for phase 2 evaluation. AEs were generally similar to those expected for these therapies alone, including skin reactions and grade 1/2 LFT elevations.[5,6] Because of the small sample size, it is uncertain whether the observed toxicities were additive, versus potential interactions between treatments that may have worsened toxicity, as reported for the anti−PD-L1 monoclonal antibody durvalumab plus the EGFR tyrosine kinase inhibitor (TKI) osimertinib.[7]

Pembrolizumab plus gefitinib was not deemed feasible for phase 2 evaluation due to liver toxicity, in line with previous clinical studies and a recent meta-analysis.[5,8] Liver toxicity has also been reported in studies with other anti−PD-(L)1 agents as monotherapy and in combination with EGFR TKIs.[7,9,10]

The ORR observed with pembrolizumab plus erlotinib was similar to that reported in previous first-line

Table 5. Efficacy Outcomes

	Pembrolizumab + Erlotinib (n = 12)	Pembrolizumab + Gefitinib (n = 7)
Objective response[a]	5 (41.7)	1 (14.3)
Complete response	0	0
Partial response	5 (41.7)	1 (14.3)
Stable disease	5 (41.7)	0
Progressive disease	1 (8.3)	2 (28.6)
Not evaluable	1 (8.3)	4 (57.1)
Time to response, median (range), mo	2.7 (1.3-4.0)	1.4 (1.4-1.4)
Duration of response, median (range), mo	18.3 (7.7+-18.3)	NR (1.4+-1.4+)
Objective response rate by PD-L1 status, n/N (%)		
TPS ≥50%	4/4 (100)	0/1 (0)
TPS 1%-49%	1/6 (16.7)	–
TPS <1%	0/2 (0)	1/6 (16.7)
Progression-free survival		
Number of events	4 (33.3)	4 (57.1)
Median progression-free survival, mo (95% CI)	19.5 (3.0-19.5)	1.4 (0.2-13.0)
6-month progression-free survival rate, % (95% CI)	81.8 (44.7-95.1)	47.6 (7.5-80.8)
Overall survival		
Number of events	2 (16.7)	3 (42.9)
Median overall survival, mo (95% CI)	NR (19.5-NR)	13.0 (0.2-NR)
6-month overall survival rate, % (95% CI)	91.7 (53.9-98.8)	85.7 (33.4-97.9)

Data are n (%), unless otherwise noted.
Data cutoff: November 7, 2016.
[a]Confirmed responses per blinded independent central review.
CI, confidence interval; NR, not reached; PD-L1, programmed death ligand 1; TPS, tumor proportion score; +, ongoing response.

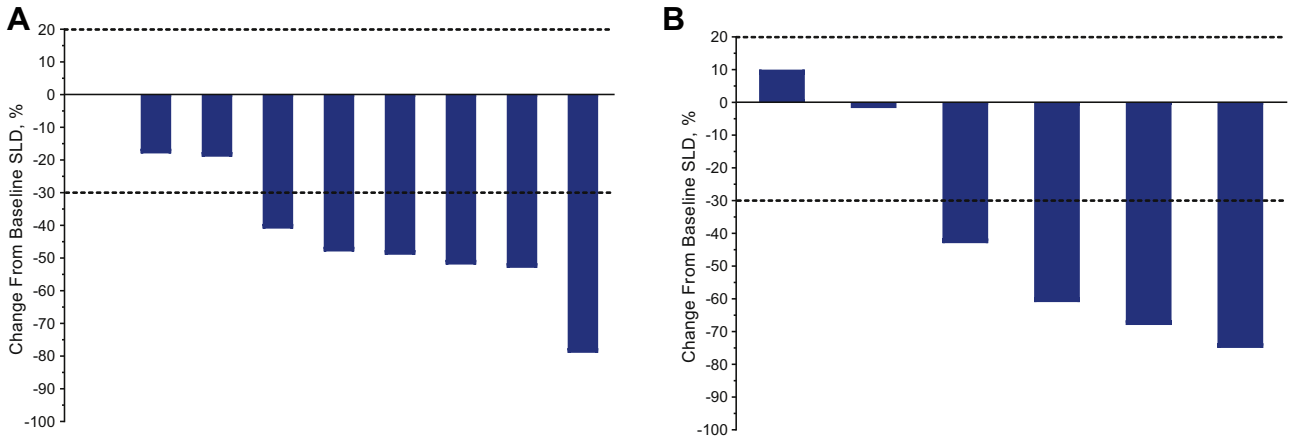

Figure 1. Waterfall plots of maximum tumor change from baseline in (*A*) cohort E treated with pembrolizumab plus erlotinib and (*B*) cohort F treated with pembrolizumab plus gefitinib, patients with measureable disease at baseline. One patient in cohort F did not have any post-screening lesion measurement; therefore, they are not included in this figure. Response could only be confirmed in one patient in cohort F, showing PR (change from baseline SLD, −75%); the other five patients either did not have confirmatory scans and were not evaluable for response, or the subsequent scan revealed disease progression. PR, partial response; SLD, sum of the longest diameters of target lesions.

monotherapy studies.[6,11,12] Although the ORR in patients with PD-L1 TPS greater than or equal to 50% (4 of 4; 100%) is noteworthy, as was the durability of response in this group, there were too few patients to draw meaningful conclusions regarding possible additive or synergistic antitumor effects compared with monotherapy. It is possible that an enhanced antitumor effect with pembrolizumab plus erlotinib might be more apparent in evaluations of DOR and/or PFS, which is again limited by small cohort size. Further evaluation would be necessary to conclusively associate PD-L1 status with clinical benefit with this combination.

The phase 1 CheckMate 012 study evaluated nivolumab plus erlotinib in patients with *EGFR*-mutated advanced NSCLC.[13] One patient was TKI-naive; 20 had received prior erlotinib. The most frequent treatment-related AE (less than 100 days after last dose) was rash (48%), and the rate of grade 3 treatment-related AEs was 24% (no grade 4/5 treatment-related AEs occurred). As in our study, the combination was associated with liver toxicity: treatment-related ALT (one grade 3) and AST (two grade 3) elevations occurred in three patients each. In TKI-treated patients, ORR was 15% (3 of 20; 1 complete response) with DOR ranging from 13.8 to 38.2 months; the TKI-naive patient experienced complete response with a DOR of 61.8 (ongoing) months. Median PFS was 5.1 (95% CI: 2.3–12.1) months and OS was 18.7 (95% CI: 7.3–not available) months (TKI-treated patients). Together with cohort E of KEYNOTE-021, these data support the feasibility of combining erlotinib with PD-1 inhibitors and suggest that such combinations may be associated with durable responses.

A recent meta-analysis suggested that, in the second-line setting, OS benefit from anti−PD-(L)1 therapy may occur in patients with wild-type *EGFR* but not with *EGFR* mutation.[7] Additionally, recent studies have provided support for newly developed EGFR inhibitors in certain subsets of patients.[14,15] Overall, in the context of incrementally efficacious targeted therapy for *EGFR*-mutant NSCLC, other mechanisms of immune escape may need to be investigated.

In conclusion, combining pembrolizumab 2 mg/kg every 3 weeks and erlotinib 150 mg daily is feasible. High-grade hepatic toxicity observed with pembrolizumab plus gefitinib prohibited further evaluation of this combination. Given the small sample size, further exploration would be needed to make conclusions about the clinical efficacy of pembrolizumab plus erlotinib.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of*

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References

1. National Comprehensive Cancer Network (NCCN). *NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Non-small cell lung cancer. Version 5*. 2018. https://www.nccn.org. Accessed July 2, 2018.
2. Lopes G, Wu Y-L, Kudaba I, et al. Pembrolizumab versus platinum-based chemotherapy as first-line therapy for advanced/metastatic NSCLC with a PD-L1 tumor proportion score $\geq$ 1%: open-label, phase 3 KEYNOTE-042 study. *J Clin Oncol*. 2018;36:abstr LBA4.
3. Akbay EA, Koyama S, Carretero J, et al. Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. *Cancer Discov*. 2013;3:1355–1363.
4. D'Incecco A, Andreozzi M, Ludovini V, et al. PD-1 and PD-L1 expression in molecularly selected non-small-cell lung cancer patients. *Br J Cancer*. 2015;112:95–102.
5. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med*. 2009;361:947–957.
6. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13:239–246.
7. Tsakonas G, Ekman S. Oncogene-addicted non-small cell lung cancer and immunotherapy. *J Thorac Dis*. 2018;10:S1547–S1555.
8. Yang Z, Hackshaw A, Feng Q, et al. Comparison of gefitinib, erlotinib and afatinib in non-small cell lung cancer: a meta-analysis. *Int J Cancer*. 2017;140:2805–2819.
9. De Velasco G, Je Y, Bosse D, et al. Comprehensive meta-analysis of key immune-related adverse events from CTLA-4 and PD-1/PD-L1 inhibitors in cancer patients. *Cancer Immunol Res*. 2017;5:312–318.
10. Mennitto A, Grassi P, Ratta R, Verzoni E, Prisciandaro M, Procopio G. Nivolumab in the treatment of advanced renal cell carcinoma: clinical trial evidence and experience. *Ther Adv Urol*. 2016;8:319–326.
11. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375:1823–1833.
12. Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med*. 2015;372:2018–2028.
13. Gettinger S, Hellmann MD, Chow LQM, et al. Nivolumab plus erlotinib in patients with EGFR-mutant advanced NSCLC. *J Thorac Oncol*. 2018;13:1363–1372.
14. Mok TS, Wu YL, Ahn MJ, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. *N Engl J Med*. 2017;376:629–640.
15. Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med*. 2018;378:113–125.