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Efficacy and safety of programmed cell-death-protein-1 and its ligand inhibitors in pretreated patients with epidermal growth-factor receptor-mutated or anaplastic lymphoma kinase-translocated lung adenocarcinoma

Olivier Bylicki, MD^a, Florian Guisier, MD^b, Isabelle Monnet, MD^c, H el ene Doubre, MD^d, Radj Gervais, MD^e, Henri Janicot, MD^f, Maurice Perol, MD^g, Pierre Fournel, MD^h, R egine Lamy, MDⁱ, Jean-Bernard Auliac, MD^j, Christos Chouaid, MD, PhD^{c,*}

Abstract

Immune-checkpoint inhibitor (ICI) efficacy in patients with non-small cell lung cancer (NSCLC) harboring molecular alterations remains poorly elucidated. This study was undertaken to determine ICI efficacy against epidermal growth-factor receptor (*EGFR*)/anaplastic lymphoma kinase (*ALK*)/c-ros oncogene 1 (*ROS1*)-mutated NSCLC patients in the real-world setting.

In this retrospective, multicenter study on adults with ICI-treated *EGFR*-mutated or *ALK*- or *ROS1*-translocated NSCLCs, we analyzed clinical characteristics and outcomes: ICI-treatment duration, and progression-free survival (PFS), objective response rate, duration of response, and overall survival (OS) from immunotherapy initiation.

Fifty-one NSCLC patients (mean age, 58.0 years) were included from 20 French centers: 61% were never-smokers and 59% were women. Among them, 82% had *EGFR*-activating mutations, 16% *ALK* translocations, or 2% *ROS1* translocations. Before ICI therapy, patients had received a median of 3 treatment lines (including tyrosine-kinase inhibitor). The median PFS was 2.1 (95% confidence interval [CI], 1.5–3.2) months for the entire cohort, 2.2 (95% CI, 1.4–3.2) for *EGFR*-mutated patients, and 2.4 (95% CI, 2.1–not reached) months for *ALK*-translocated patients. The median OS was 14.7 (95% CI, 12.1–19.2) months for the entire population and 13.9 (95% CI, 8.8–20.0) and 19.2 (95% CI, 13.1–not reached) months for *EGFR*-mutated and *ALK*-translocated patients, respectively. Seven (13.7%) patients were treated with ICI for >9 months. Toxicities were reported in 22% (11/51), including 8% (4/51) grade ≥ 3 .

In this real-world setting, analysis of ICI PFS against *EGFR*-mutated or *ALK*-translocated NSCLC patients appeared close to that observed in pretreated unselected NSCLC patients. The more promising OS probably linked to post-ICI treatments. Large prospective studies on these patient subsets are needed.

Abbreviations: ALK = anaplastic lymphoma kinase, ECOG PS = the Eastern Cooperative Oncology Group performance status, EGFR = epidermal growth-factor receptor, GFPC = French Lung Cancer Group, HR = hazard ratio, ICI = immune-checkpoint inhibitor, NSCLC = non-small-cell lung cancer, OS = overall survival, PFS = progression-free survival, ROS-1 = c-ros oncogene 1, TKIs = tyrosine-kinase inhibitors.

Keywords: anaplastic lymphoma kinase translocation, epidermal growth-factor receptor-activating mutations, immune-checkpoint inhibitors, non-small-cell lung cancer, programmed cell-death-protein-1 and its ligand inhibitors, c-ros oncogene 1 translocation

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Key Points

- Our results do not support decreased ICI efficacy in patients with *EGFR*-mutated or *ALK*-translocated NSCLC.
- In the real-world setting, ICI impact on *EGFR*-mutated or *ALK*-translocated unselected NSCLC was close to that previously observed but it should be used preferably after the failure of other therapeutics (tyrosine-kinase inhibitors and chemotherapy).
- Large prospective studies are needed to better define the place of ICI in the armamentarium for patients with *EGFR*-mutated or *ALK*-translocated NSCLC.

1. Introduction

The understanding of the molecular characteristics of tumor cells in non-small cell lung cancer (NSCLC) has changed considerably within the last decade.^[1] As a consequence, the management of patients with locally advanced or metastatic NSCLCs has been improved with innovative therapies, such as immune-checkpoint inhibitors (ICIs) and, for patients with oncogenic drivers, targeted tyrosine-kinase inhibitors (TKIs).^[2]

Therapies targeting epidermal growth-factor–receptor (*EGFR*)-activating mutations were shown to be beneficial for patients harboring them. Notably, the authors of several phase III trials comparing *EGFR*-TKIs (gefitinib, erlotinib, afatinib) reported longer progression-free survival (PFS) and higher objective response rates (ORRs) compared with chemotherapy.^[3–11] However, despite these innovative therapies, patients finally progressed after a median of 9 to 12 months.^[12,13] Patients who acquire the *T790M* resistance mutation are eligible to receive a third-generation *EGFR*-TKI (e.g., osimertinib).^[14] For patients with *ALK* or *ROS* translocations, PFS increased under first-line crizotinib, compared with platinum-based doublet chemotherapy.^[15] Other TKIs that target translocated *ALK* have been developed to counter acquired resistance to crizotinib.^[16–18]

Humanized monoclonal antibodies have been designed to block the interaction between programmed cell-death-protein-1 (PD-1) and its ligand (PD-L1) that is a negative regulator of T-cell anti-tumor defense.^[19] Both anti-PD-1 (nivolumab, pembrolizumab) and anti-PD-L1 (atezolizumab) ICIs have demonstrated their benefit in comparison with chemotherapy.^[20–25] Only low percentages of patients with *EGFR* mutations or *ALK* translocations were included in those trials. A meta-analysis showed no evidence of an advantage of second-line PD-1/PD-L1 inhibitors over docetaxel for patients with *EGFR*-mutated advanced NSCLCs.^[26] However, the small sizes of these subgroups and a posteriori analyses prevented drawing firm conclusions. Overall, about 200 patients with *EGFR* mutations and 20 with *ALK* translocations included in those randomized trials were treated with second/third-line PD-1/PD-L1 inhibitors.^[27]

The purpose of this retrospective study in the real-world setting is to gain better understanding of *EGFR*-mutated or *ALK*- or *ROS*-translocated advanced NSCLCs treated with ICI after progression on targeted treatment.

2. Materials and methods

2.1. Study design and patients

The IMAD study (GFPC 03–2016) was a retrospective, multicenter study conducted in French Lung Cancer Group (GFPC) centers. Its primary objective was to assess ICI efficacy (ORR, duration of response [DOR], PFS, and overall survival [OS]) after progression on targeted therapy for NSCLCs harboring *EGFR* mutations or *ALK/ROS1* translocations. The secondary objective was the assessment of safety.

Adult NSCLC patients were enrolled in the study when they met the following criteria: lung adenocarcinoma with *EGFR*-activating mutations, *ALK* translocations, or *ROS1* translocations; prior targeted treatment for *EGFR* mutation or *ALK* translocation; ICI as second-or-more treatment line. Patients included in a clinical immunotherapy trial were excluded.

2.2. Data collection

Patient demographics and clinical characteristics at NSCLC diagnosis were obtained from patient files and included: age; sex; smoker status; ethnicity; cancer stage; number and sites of metastases; presence of *EGFR*-activating mutations, *ALK* translocations and *ROS1* translocations; treatment lines (chemotherapy or TKIs) before ICI; the Eastern Cooperative Oncology Group performance status (ECOG PS) at immunotherapy onset; clinical response to ICI therapy; adverse event (AE) type and grade on ICI; and post-immunotherapy treatment.

2.3. Statistical analyses

OPFS was defined as the time from ICI initiation to progression on ICI. Progression was defined as Response Evaluation Criteria In Solid Tumors version 1.1 criteria (RECIST 1.1)^[28] radiological or clinical progression (deteriorated clinical status preventing systemic treatment) or death. Assessments were done in each participating center without centralized imaging review.

OS was calculated from ICI starting to death, the ORR to ICI as the best observed according to RECIST1.1 (radiological assessment were done every 6 weeks). AEs were reported according to Common Terminology Criteria for Adverse Events (CTCAEs) version 4.

The Kaplan–Meier method was used to estimate PFS and OS for the entire cohort and according to the molecular genotypes.

All statistical analyses were computed with the RStudio statistical software (Version 1.1.383, RStudio, Boston, MA).

2.4. Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki. Participating centers were responsible for obtaining patient consent and institutional approval. All contributors were trained in good clinical practices. The study was purely an academic collaboration and was not funded by industry.

3. Results

3.1. Patient characteristics

Fifty-one patients were included in 20 medical centers (Table 1). The mean (\pm standard deviation) age at diagnosis was 58.0 ± 8.8

Table 1
Characteristics of the 51 patients.

Characteristic	Value
Age at diagnosis, yrs	
Mean \pm SD	58.0 \pm 8.8
Median (range)	63 (36–83)
Female gender, n (%)	30 (59)
Ethnicity, n (%)	
Caucasian	47 (92)
Asian	3 (6)
Other	1 (2)
Smoking, n (%)	
Current smoker	4 (8)
Former smoker	14 (27)
Never-smoker	31 (61)
Unknown	2 (4)
No. of metastatic sites at diagnosis, median (range)	3.6 (1–7)
≥ 1 bone metastases	44 (86%)
$1 \geq 1$ liver metastasis	42 (76%)
$1 \geq 1$ cerebral metastasis	40 (78%)
Molecular genotype, n (%)	
<i>EGFR</i> -activating mutation	42 (82)
<i>L858R</i> (exon 21)	14 (27)
Deletion of exon 19	20 (39)
G719X (exon 18)	3 (6)
Other	5 (10)
<i>EGFR</i> ^{T790M} -resistance mutation	8
<i>ALK</i> translocation	8 (16)
<i>ROS1</i> translocation	1 (2)
ECOG PS at immunotherapy onset, n (%)	
0	6 (11.5)
1	37 (73)
2	6 (11.5)
3	2 (4)

ALK = anaplastic lymphoma kinase, ECOG PS = the Eastern Cooperative Oncology Group performance status, EGFR = epidermal growth-factor receptor, ROS1 = c-ros oncogene-1.

years, 30/51 (59%) patients were women and 31/51 (61%) were never-smokers. They had a median of 3.6 (range, 1–7) metastatic sites at diagnosis. At that time, 42/51 (82%) patients had an *EGFR* mutation, 8/51 (16%) harbored an *ALK* translocation, and 1/51 (2%) carried a *ROS1* translocation. The most frequent *EGFR* mutations at diagnosis were deletion in exon 19 and point mutation in exon 21 (*L858R*), which accounted for 81% (34/42) of all *EGFR* mutations.

Before starting ICI therapy, patients had received a median of 3 (range, 1–9) treatment lines, including TKI for all patients: first-line treatment for 45% (23/51) and second-line treatment for 49% (25/51) (Table 2); 8/42 (19%) *EGFR* patients carried the T790M resistance mutation and received osimertinib as second- or third-line therapy before ICI introduction.

3.2. ICI therapy and clinical outcomes

At immunotherapy initiation, ECOG PS was < 2 for 84% (43/51) of the patients (Table 1). Immunotherapy treatments were mainly PD-1 inhibitors: nivolumab for 92% (47/51) of patients and pembrolizumab for 5% (2/51). Seven (13.7%) patients were treated for > 9 months with ICI. Post-immunotherapy, 23/51 (45%) patients received chemotherapy and 15/51 (29%) received a TKI (Table 2).

Partial responses (RECIST criteria) were observed in 10 (20%) patients, stable disease in 9 (18%), and progressive disease in 32

Table 2
Characteristics of the 51 patients' prior treatments and immunotherapy.

Prior treatment	Value
Previous lines of therapy	
Number, median (range)	3 (1–9)
Prior TKI, n (%)	51 (100)
First line, n (%)	
Chemotherapy	28 (55)
TKI	23 (45)
Second line, n (%)	
Chemotherapy	26 (51)
TKI	25 (49)
Immunotherapy, n (%)	
PD-1 inhibitors	
Nivolumab	47 (92)
Pembrolizumab	2 (5)
PD-L1 inhibitors	
Durvalumab	1 (2.5)
Atezolizumab	1 (2.5)
Treatment post-immunotherapy, n (%)	
Chemotherapy	23 (45)
TKI	15 (29)
Supportive care	8 (16)
Radiotherapy (only)	1 (2)
NA	4

NA = not available, PD-1 = programmed cell-death-protein-1 (PD-1), PD-L1 = PD-1 ligand (PD-L1), TKI = tyrosine kinase inhibitor.

(63%). Among the 10 responders, 8 had an *EGFR* mutation and 2 had an *ALK* translocation. Patient characteristics according to type of response are reported in Table 3. The DORs of the *EGFR*-mutated and *ALK*-translocated patients with partial responses were 11.9 (95% confidence interval [CI], 5.6–not reached) months and 9 months (95% CI, 10.9–NR), respectively.

Median follow-up lasted 22 months. Median PFS for the cohort was 2.1 (95% CI, 1.5–3.2) months, with no significant difference ($P = 0.5$) according to the oncogenic mutations: 2.2 (95% CI, 1.4–3.2) months for *EGFR*-mutated patients, 2.4 (95% CI, 2.1–not reached) months for *ALK*-translocated patients and

Table 3
Characteristics of the population according to treatment response.

Characteristic	All (N = 51)	Partial response (n = 10)	Stable disease (n = 9)	Progressive disease (n = 32)
se				
Sex				
Female	30	5	6	18
Male	21	5	3	13
Smoking				
Current smoker	4	0	1	3
Former smoker	14	4	3	7
Never-smoker	31	6	5	20
Oncogenic alteration				
<i>EGFR</i> mutation	42	8	7	27
<i>ALK</i> translocation	8	2	2	4
<i>ROS1</i> translocation	1	0	0	1

ALK = anaplastic lymphoma kinase, EGFR = epidermal growth-factor receptor, ROS1 = c-ros oncogene-1.

Table 4
Progression-free survival and overall survival from immunotherapy initiation according to type of molecular alteration.

Survival alteration	N	Median survival, mo	95% CI
Progression-free survival			
All mutations	51	2.1	1.5–3.2
<i>EGFR</i> mutation	42	2.2	1.4–3.2
Exon 19 deletion	20	1.6	1.4–3.1
<i>L858R</i>	14	2.5	1.5–11.9
<i>G719X</i>	3	12	0.4–not reached
<i>L747P</i>	1	6	NA
Double	4	2.3	0.8–not reached
<i>ALK</i> translocation	8	2.4	2.1–not reached
<i>ROS1</i> translocation	1	1.4	NA
Overall survival			
All mutations	51	14.7	12.1–19.2
<i>EGFR</i> mutation	42	13.9	8.8–20.0
<i>ALK</i> translocation	8	19.2	13.1–not reached
<i>ROS1</i> translocation	1	2.8	NA

ALK=anaplastic lymphoma kinase, CI=confidence interval, EGFR=epidermal growth-factor receptor, NA=not applicable, ROS1=c-ros oncogene-1.

1.4 months for the *ROS1* patient (Table 4 and Fig. 1). For this cohort, the 12-month PFS rate was 9% (95% CI, 0.03–0.23) and 12-month OS was 63% (95% CI, 0.51–0.78).

Median OS for the cohort lasted 14.7 (95% CI, 12.1–19.2) months: 13.9 (95% CI, 8.8–20.0) months for *EGFR*-mutated patients, 19.2 (95% CI, 13.1–not reached) months for *ALK*-translocated patients, and 2.8 months for the *ROS1*-translocated patient (Table 4 and Fig. 2).

3.3. Safety

Eleven (22%) patients experienced AEs, including 4 (8%) grade 3 to 5 (Table 5). Grade 3 to 5 immune-mediated AEs occurred in 2 patients (hyperthyroidism or hypothyroidism).

4. Discussion

This retrospective study included patients with NSCLCs harboring *EGFR*-activating mutations, or *ALK*- or *ROS1*-translocations treated with ICI, after having progressed on targeted treatment and chemotherapy. Their characteristics at enrollment were as expected for a cohort of NSCLC patients including: a high percentage with *EGFR* mutations, 59% women and 61% were never-smokers.^[29]

Median cohort PFS lasted 2.1 (95% CI, 1.5–3.2) months, with no significant difference according to tumor genotyping. Median OS lasted 14.7 (95% CI, 12.1–19.2) months, with a trend for longer OS for patients with *ALK* mutations (19.2 months).

Only low percentages of patients with *EGFR* mutation (7%–15%) or *ALK* translocation (<1%–4%) had been included in phase III trials on ICI for NSCLC.^[30–32] Subgroup analyses of survival data concerned patients with *EGFR* mutations, but not *ALK* translocation because of their small numbers. In the Checkmate-057 study,^[20] the OS hazard ratio (HR) for nivolumab versus docetaxel for the subgroup of patients with *EGFR* mutations was 1.18 (95% CI, 0.69–2.00), indicating no benefit of the ICI treatment over chemotherapy. In the Keynote-010 study^[22] on NSCLC patients who progressed on platinum therapy, no significant OS benefit was found for ICI treatment in

the subgroup of patients with *EGFR* mutations. The OAK study on NSCLC patients with second-line treatment or patients with *EGFR* mutations found that atezolizumab did not prolong OS.^[24] Therefore, the median OS observed in our cohort (14.7 months) of heavily pretreated patients was close to that observed for other pretreated and unselected NSCLC patients enrolled in phase III trials.

A meta-analysis of 3 randomized studies with nivolumab, pembrolizumab, or atezolizumab as second-line therapy for advanced NSCLC confirmed that ICI significantly prolonged OS compared with docetaxel for *EGFR* wild-type patients (n=1362; HR, 0.66 [95% CI, 0.58–0.76]; $P < .0001$), but not *EGFR*-mutated patients (n=186; HR, 1.05; 95% CI, 0.70–1.55; $P < .81$; treatment–mutation interaction, $P = .03$).^[26] Nevertheless, these results must be interpreted prudently because these analyses were computed a posteriori on subgroups with very small samples and without prior stratification on *EGFR*-mutation presence or absence. Moreover, the *EGFR* status was not determined for 19% of patients. In order to properly evaluate PD-1/PD-L1-inhibitor efficacy in *EGFR*-mutated and *ALK*-translocated NSCLC patients, prospective trials specifically enrolling patients with these profiles are needed. The recent ATLANTIC phase II study compared the clinical efficacy of durvalumab as third-line or more for *EGFR*-/*ALK*- or *EGFR*+/*ALK*+ NSCLC patients according to PD-L1 expression on tumor cells.^[31] Patients with *EGFR*-/*ALK*- NSCLCs had a higher ORR than those with *EGFR*+/*ALK*+ NSCLCs. Nevertheless, their findings suggest that *EGFR*+/*ALK*+ NSCLC patients could also benefit from ICI, especially *EGFR*+ patients with $\geq 25\%$ PD-L1-expressing tumor cells.

Few data obtained in real-life settings from patients with *EGFR* mutations or *ALK* translocations and treated with ICI are available. Gainor et al^[34] retrospectively studied 58 NSCLC patients treated with ICI (monotherapy or in combination with *EGFR*-TKI or chemotherapy): 22 patients with *EGFR* mutations, 6 with *ALK* translocations, and 30 without molecular alterations. Only 1 (3.6%) mutation/translocation-group patient responded, compared with 22.3% of those without molecular alterations. PFS lasted 2.1 (95% CI, 1.8–2.1) months for patients with *EGFR* mutation or *ALK* translocation and 2.6 (95% CI, 1.9–6.4) months ($P = .018$) for those with wild-type *EGFR* and without *ALK* translocation. Although we observed higher response rates herein, PFS (2.1 months) for our cohort was comparable to theirs. Immunotherapy efficacy is very uncertain, particularly as first-line therapy for patients with *EGFR* mutations. In a phase II trial, *EGFR*+ patients with TKI-naïve PD-L1+ (>1%) expression received first-line pembrolizumab; none responded.^[35] The study was stopped due to lack of efficacy.

Another real-life study, a retrospective, multicenter analysis,^[36] included 110 *EGFR*-mutated and 18 *ALK*-translocated advanced NSCLC patients treated with ICI. Their median PFS of 2.0 months for *EGFR*-mutated patients and 2.1 months for *ALK*-translocated patients, with median OS at 8.8 and 17 months, respectively, agree with our results.

The relationship between PD-L1 expression and PD-1/PD-L1-inhibitor efficacy against *EGFR*-mutated NSCLCs is controversial. Early retrospective studies reported increased PD-L1 expression in *EGFR*-mutated NSCLCs.^[30–32] Notably, Azuma et al^[30] reported PD-L1 overexpression in patients with surgically resected NSCLCs harboring *EGFR*-mutations. Those observations seemed to suggest that these patients should

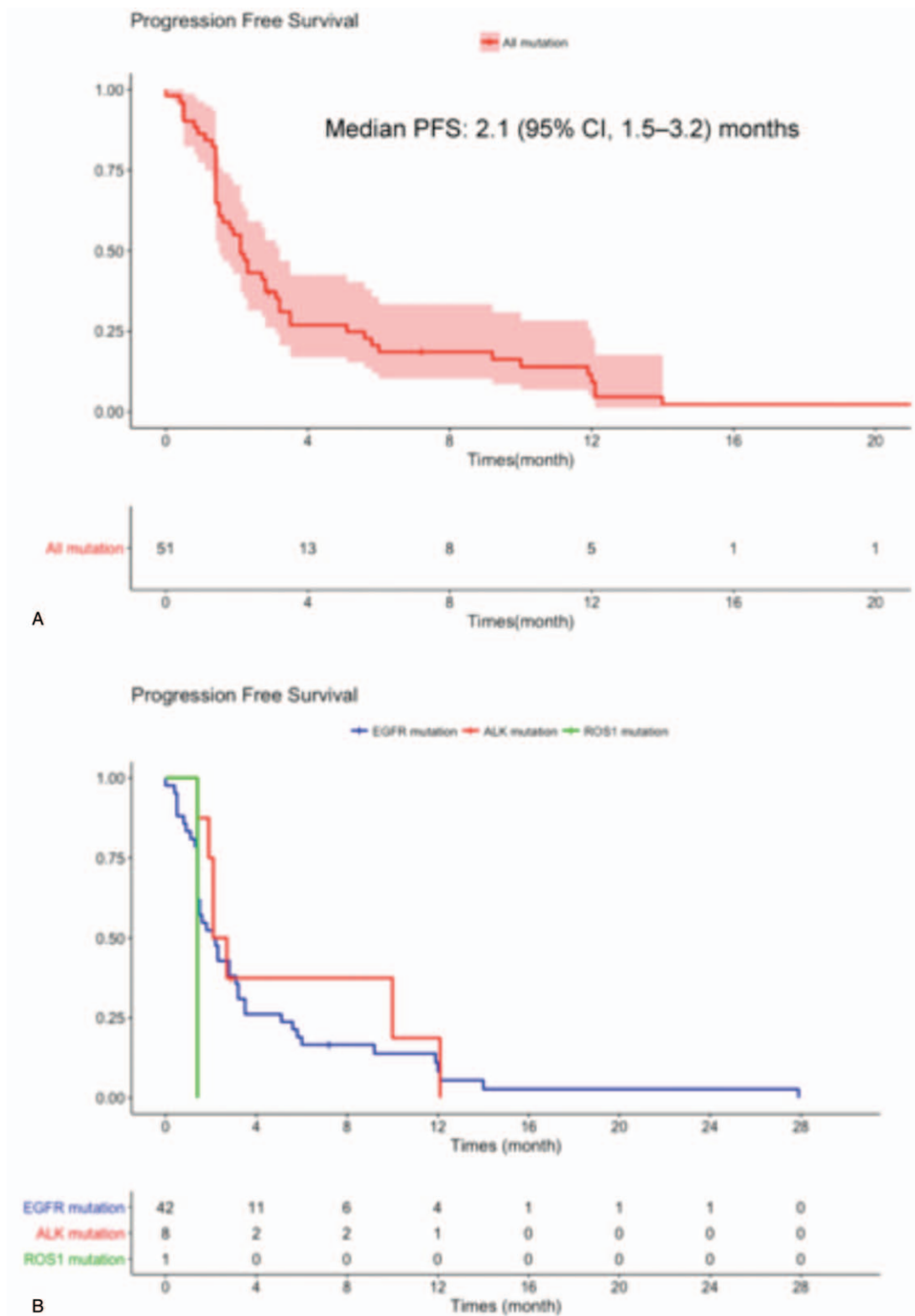


Figure 1. Progression-free survival (PFS) from immunotherapy initiation for the entire cohort (A) and according to the type of molecular alteration (B).

be more sensitive to ICIs. However, based on their recent meta-analysis of 18 studies (3969 patients), Soo's et al^[37] reported that NSCLCs with *EGFR* mutations were less frequently PD-L1-positive, in comparison to wild-type *EGFR* NSCLCs

(HR, 0.59 [95% CI, 0.39–0.92] $P < .021$). That meta-analysis highlighted the marked heterogeneity among the studies in the absence of standardized methods to determine PD-L1 expression.

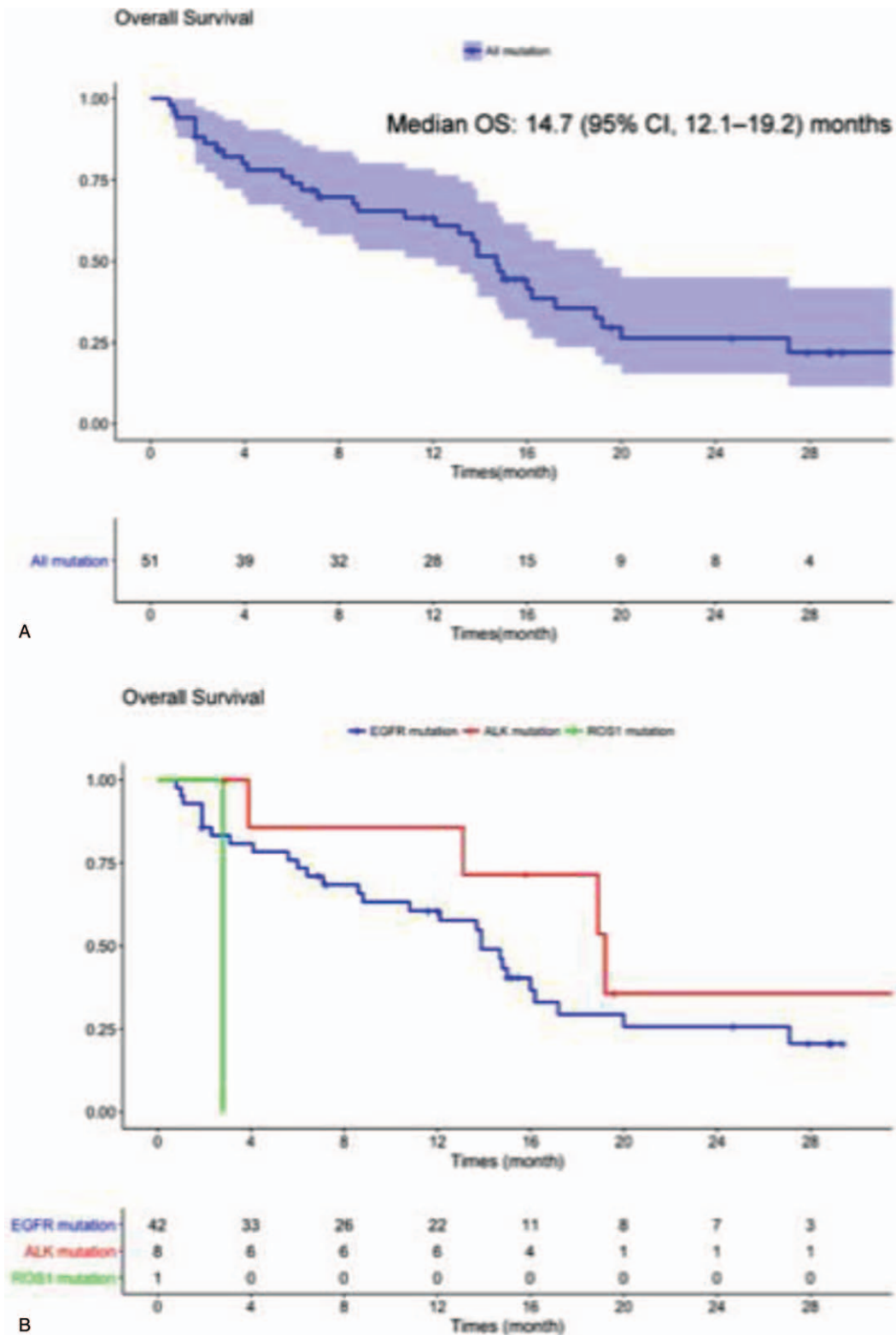


Figure 2. Overall survival (OS) from immunotherapy initiation for the entire cohort (A) and according to the type of molecular alteration (B).

Several mechanisms potentially explaining the poor response of pretreated *EGFR*-mutant NSCLCs to PD-1/PD-L1 inhibitors have been proposed. Among them, a lack of T-cell infiltration into the tumor microenvironment could explain lower responses to PD-1/PD-L1–pathway blockade.^[38] Ongoing clinical trials

have been designed to combine ICI and TKI as a strategy for optimizing their efficacies in patients with *EGFR*-mutated or *ALK*-translocated NSCLCs.^[27] The phase III randomized IMpower-150 trial compared patients with stage-IV non-squamous NSCLCs, ECOG PS=0/1, with 3 arms: carbopla-

Adverse event	Any grade (N=51)	Grade 3–5 (N=51)
Any	11 (22)	4 (8)
Treatment-related		
Fatigue	2 (4)	1 (2)
Anorexia	2 (4)	0
Chest pain	1 (2)	1 (2)
Immune-mediated		
Hyperthyroidism	3 (6)	1 (2)
Hypothyroidism	1 (2)	1 (2)
Colitis	1 (2)	0
Skin reaction	1 (2)	0

Results are expressed as n (%).

tin-paclitaxel-bevacizumab, atezolizumab-platinum-based chemotherapy + bevacizumab (quadritherapy) or without.^[39] Patients received 4 to 6 treatment cycles and maintenance therapy with bevacizumab, atezolizumab + bevacizumab, or atezolizumab, depending on the arm, until progression. Quadritherapy, compared with carboplatin-paclitaxel-bevacizumab, respectively, obtained a significant PFS benefit (8.3 vs 6.8 months), and an OS gain (19.8 vs 14.9 months).^[38] That benefit was observed regardless of the tumor cell or inflammatory cell (IC) PD-L1-expression level, even when those cells were PD-L1-negative and was even better for patients with liver metastases. An important element was the notable quadritherapy efficacy for patients with *EGFR* mutations or *ALK* translocations with disease progression after targeted therapy. Median OS was not reached (NR vs 17.5 months; HR 0.54 [95% CI 0.29–1.03]).^[39]

When efficacy was observed in this real-life study on oncogenically mutated NSCLCs, PFS and OS were always close to those obtained by patients without such genetic anomalies.^[40,41] Thus, for 303 non-selected patients with advanced NSCLCs progressing after a platinum-doublet chemotherapy, median PFS and OS on nivolumab were 2.6 (95% CI 2.1–3.5) and 11.3 (95% CI: 8.5–13.8) months, respectively, similar to the 2.4 and 14.7 months reported herein. In another recent analysis on 530 patients evaluated for *KRAS* mutations, 206 (39%) were positive while 324 (61%) carried wild-type *KRAS*. *KRAS* status did not influence nivolumab efficacy in terms of ORR (20% vs 17%, $P=.39$) and disease control rate (47% vs 41%, $P=.23$). For the *KRAS*-positive/mutated and *KRAS*-negative/wild-type groups, respectively, median PFS lasted 4 and 3 months, and median OS 11.2 and 10 months. As in our study, observed PFS is disappointing especially considering 20% RR.^[40]

Grade 3–5 AEs occurred in 8% of the cohort patients. Immune-mediated AEs were expected and the most frequent was hyperthyroidism for 3 patients, including 1 patient with grade 3 to 5. These results obtained in a real-life setting confirm the good ICI safety profile reported in phase III trials.

Our findings do not support decreased efficacy of PD-1/PD-L1 inhibitors in pretreated patients with an *EGRF* mutation or *ALK* translocation. Some limitations must nevertheless be taken into consideration. It has the limitation inherent in retrospective studies; the analyses rely on data recorded in patient files and, therefore, must be interpreted with caution. PFS, OS, and ORR were not compared for patients harboring *EGFR* mutations or *ALK/ROS* translocations and those without. If ICI PFS appeared close to that observed in pretreated unselected NSCLC patients in randomized-controlled trials the more promising OS probably

linked to post ICI treatments. Clinical outcomes according to PD-1 expression were not reported because this evaluation was rarely done routinely at the onset of the management of these patients. PD-L1 expression of could not be obtained for the majority of patients because it simply was not part of the diagnostic work-up of patients in 2014 to 2015 and, by the time it became standard practice, most of the tumor material had most often already been exhausted. Finally, in light of the retrospective design of the study, AEs were probably underestimated, especially grade 1/2. Nonetheless, one of the study's strengths is the enrollment of a real-life cohort composed of 51 heavily pretreated patients with molecular alterations given ICI inhibitors, a rare patient profile in randomized-clinical trials.

5. Conclusion

In this real-world setting analysis, ICI PFS in *EGFR*-mutated, *ALK*- or *ROS1*-translocated NSCLC patients appeared close to that observed in pretreated unselected NSCLC patients in randomized-controlled trials or observational studies. The more promising OS probably linked to post ICI treatments. Large prospective studies on these patient subsets are needed to better discern the place of ICIs in their treatment.

Author contributions

Conceptualization: Olivier Bylicki, Florian Guisier, Maurice Perol, Christos Chouaid.

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References

- Thomas A, Liu SV, Subramaniam DS, et al. Refining the treatment of NSCLC according to histological and molecular subtypes. *Nat Rev Clin Oncol* 2015;12:511–26.
- Novello S, Barlesi F, Califano R, et al. Metastatic non-small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2016;27(suppl):v1–27.
- Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–57.
- Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010;11:121–8.

- [5] Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380–8.
- [6] Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011;12:735–42.
- [7] Han JY, Park K, Kim SW, et al. First-SIGNAL: first-line single-agent irstress versus gemcitabine and cisplatin trial in never-smokers with adenocarcinoma of the lung. *J Clin Oncol* 2012;30:1122–8.
- [8] 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 (EUR-TAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239–46.
- [9] Wu YL, Zhou C, Hu CP, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. *Lancet Oncol* 2014;15:213–22.
- [10] Inoue A, Kobayashi K, Maemondo M, et al. Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin-paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002). *Ann Oncol* 2013;24:54–9.
- [11] Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013;31:3327–34.
- [12] Gao G, Ren S, Li A, et al. Epidermal growth factor receptor-tyrosine kinase inhibitor therapy is effective as first-line treatment of advanced non-small-cell lung cancer with mutated EGFR: a meta-analysis from six phase III randomized controlled trials. *Int J Cancer* 2012;131:E822–9.
- [13] Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2005;352:786–92.
- [14] Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med* 2011;3:75ra26.
- [15] Solomon BJ, Mok T, Kim DW, et al. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med* 2014;371:2167–77.
- [16] Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. *Lancet Oncol* 2016;17:234–42.
- [17] Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med* 2014;370:1189–97.
- [18] Larkins E, Blumenthal GM, Chen H, et al. FDA approval: alectinib for the treatment of metastatic, ALK-positive non-small cell lung cancer following crizotinib. *Clin Cancer Res* 2016;22:5171–6.
- [19] Sunshine J, Taube JM. PD-1/PD-L1 inhibitors. *Curr Opin Pharmacol* 2015;23:32–8.
- [20] Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med* 2015;373:1627–39.
- [21] Brahmer J, Reckamp KL, Baas P, et al. Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. *N Engl J Med* 2015;373:123–35.
- [22] Herbst RS, Baas P, Kim DW, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016;387:1540–50.
- [23] Garon EB, Rizvi NA, Hui R, et al. Pembrolizumab for the treatment of non-small-cell lung cancer. *N Engl J Med* 2015;372:2018–28.
- [24] Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet* 2016;387:1837–46.
- [25] Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017;389:255–65.
- [26] Lee CK, Man J, Lord S, et al. Checkpoint inhibitors in metastatic EGFR-mutated non-small cell lung cancer—a meta-analysis. *J Thorac Oncol* 2017;12:403–7.
- [27] Bylicki O, Paleiron N, Margery J, et al. Targeting the PD-1/PD-L1 immune checkpoint in EGFR-mutated or ALK-translocated non-small-cell lung cancer. *Target Oncol* 2017;12:563–9.
- [28] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228–47.
- [29] Mazza V, Cappuzzo F. Treating EGFR mutation resistance in non-small cell lung cancer – role of osimertinib. *Appl Clin Genet* 2017;10:49–56.
- [30] Azuma K, Ota K, Kawahara A, et al. Association of PD-L1 overexpression with activating EGFR mutations in surgically resected nonsmall-cell lung cancer. *Ann Oncol* 2014;25:1935–40.
- [31] 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.
- [32] Tang Y, Fang W, Zhang Y, et al. The association between PD-L1 and EGFR status and the prognostic value of PD-L1 in advanced non-small cell lung cancer patients treated with EGFR-TKIs. *Oncotarget* 2015;6:14209–19.
- [33] Garassino MC, Cho BC, Kim JH, et al. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. *Lancet Oncol* 2018;19:521–36.
- [34] Gainor JF, Shaw AT, Sequist LV, et al. EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer (NSCLC): a retrospective analysis. *Clin Cancer Res* 2016;22:4585–93.
- [35] Lisberg A, Cummings A, Goldman JW, et al. A phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor naïve patients with advanced NSCLC. *J Thorac Oncol* 2018;13:1138–45.
- [36] Mazieres J, Drilon A, Mhanna L, et al. Efficacy of immune-checkpoint inhibitors (ICI) in non-small cell lung cancer (NSCLC) patients harboring activating molecular alterations (ImmunoTarget). *J Clin Oncol* 2018;36:9010.
- [37] Soo RA, Lim SM, Syn NL, et al. Immune checkpoint inhibitors in epidermal growth factor receptor mutant non-small cell lung cancer: current controversies and future directions. *Lung Cancer* 2018;115:12–20.
- [38] Dong ZY, Zhang JT, Liu SY, et al. EGFR mutation correlates with uninflamed phenotype and weak immunogenicity, causing impaired response to PD-1 blockade in non-small cell lung cancer. *Oncoimmunology* 2017;6:e1356145.
- [39] Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med* 2018;378:2288–301.
- [40] Passiglia F, Cappuzzo F, Alabiso O, et al. Efficacy of nivolumab in pre-treated non-small-cell lung cancer patients harbouring KRAS mutations. *Br J Cancer* 2019;120:57–62.
- [41] Costantini A, Corny J, Fallet V, et al. Efficacy of next treatment received after nivolumab progression in patients with advanced nonsmall cell lung cancer. *ERJ Open Res* 2018;4: pii: 00120-2017.