

# Immune checkpoint inhibitors in oncogene-addicted non-small cell lung cancer: a systematic review and meta-analysis

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**Background:** Treatment of oncogene-addicted non-small cell lung cancer (NSCLC) has been changed by the advent of tyrosine kinase inhibitors (TKIs). Albeit great benefits are achieved with target therapies, resistance invariably occurs and recourse to alternative treatments is unavoidable. Immune checkpoint inhibitors (ICIs) role and the best setting of immunotherapy administration in oncogene-driven NSCLC are matter of debate.

**Methods:** We performed a systematic literature review through PubMed, in order to gather all the available information regarding ICI activity and efficacy in oncogene-addicted NSCLC, from both prospective trials and retrospective series. A meta-analysis of objective response rate in different molecular subgroups was provided. Combinatorial strategies including ICIs and related toxicities were also recorded.

**Results:** Eighty-seven studies were included in the qualitative analysis. *EGFR* mutation may be a biomarker of poor response to single-agent ICIs (7% of *EGFR*-mutant NSCLC patients achieved disease response in prospective trials), while encouraging results have been shown with combination strategies. *KRAS*-mutated disease (response rate, RR, 22%) has different clinical and pathological characteristics, and the co-existence of additional mutations (e.g., *STK11* or *TP53*) influence tumor microenvironment and response to immunotherapy. Other molecular alterations have been marginally considered prospectively, and data from clinical practice are variegated, given poor effectiveness of ICIs in *ALK*-rearranged disease (RR 9.5%, pooling the data of retrospective studies) or some encouraging results in *BRAF*- (RR 25%, retrospective data) or *MET*-driven one (with estimations conditioned by the presence of both exon 14 skipping mutations and gene amplification in reported series).

**Conclusions:** In oncogene-addicted NSCLC (with the exception of *KRAS*-mutated), ICIs are usually administered at the failure of other treatment options, but administering single-agent immunotherapy in later disease phases may limit its efficacy. With the progressive administration of TKIs and ICIs in early-stage disease, molecular characterization will become fundamental in this setting.

**Keywords:** Lung adenocarcinoma, advanced disease, PD-1/PD-L1, adverse events, combination therapies, molecular subgroups.

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## Introduction

The treatment of non-small cell lung cancer (NSCLC) has widely changed in the last decade. In particular, in non-squamous NSCLC, treatment has shifted towards an oncogene-driven approach that has generated significant benefit for patients, globally leading to better survival outcomes, coupled with a good toxicity profile and improved quality of life (1).

The most common driver in NSCLC is represented by mutant *KRAS*, observed in about 25–30% of patients (2,3). Differently from others targetable alterations, *KRAS* mutations are usually detected in current/former smokers and, albeit specific inhibitors have been recently proven promising (4), no drugs are approved for clinical use yet. Mutations in the *EGFR* kinase domain occur in 11–16% of patients in Western countries, and this rate is higher in the Asian population (5,6). 4–7% of patients harbor *ALK* gene rearrangements and less than 2% of patients contain alterations of *ROS1*, *BRAF*, *MET*, *RET*, *HER2*, *NTRK*, although relatively rare (7,8). The development and availability of selective agents (TKIs, tyrosine kinase inhibitors) that target these specific alterations has revolutionized the outcomes of patients suffering from oncogene-addicted NSCLC. Despite the major survival improvements generated by the availability of novel-generation inhibitors and new treatment strategies (9), resistance to targeted agents invariably occurs, and this opens many questions about the subsequent therapies in this subgroup of patients.

Alongside chemotherapy, still a valid therapeutic option at the development of resistance to TKIs, immunotherapy represents a pillar in the current management of NSCLC, albeit its role in oncogene-addicted cases (other than *KRAS*-mutant ones) remains debated, as initial evidence is quite discouraging (10). One of the main issues regarding immune checkpoint inhibitors (ICIs) is indeed the identification of patients that are more likely to benefit, and to identify the precise factors predictive of response. On the other hand, one of the major challenges in the continuous care of oncogene-addicted NSCLC is to wisely use all the therapeutic strategies available. In this population, the best setting of immunotherapy administration and the identification of patients suitable for driving benefit from ICIs are not yet defined.

In the present review, we systematically gather all the available evidence concerning activity and efficacy of ICI administration, as single agents or as combinatorial

strategies, in oncogene-addicted NSCLC patients. We moreover performed a meta-analysis of objective responses reported with ICIs in differential molecular subgroups of NSCLC. A significant amount of evidence has already been published dealing with immunotherapy role in oncogene-addicted NSCLC. Nevertheless, the goal of the present work is to present all the data, driven both from prospective studies and retrospective series, approaching independently every single molecular entity (e.g., *EGFR* and *KRAS* mutations, *ALK* rearrangements and other “rare” NSCLC activating alterations). We aim indeed to provide treating physicians with a complete view of the clinical data on this topic. We present the following article in accordance with the PRISMA reporting checklist (available at <http://dx.doi.org/10.21037/tlcr-20-941>).

## Methods

### *Search strategy and selection criteria*

The review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The search was conducted in accordance with the principles outlined in the Cochrane Handbook for Systematic Reviews of Interventions. The database searched was MEDLINE (data cutoff of March 1<sup>st</sup>, 2020). The search items were “(lung neoplasms OR lung cancer, OR carcinoma[MeSH Terms]) AND (checkpoint inhibitors OR check-point inhibitors OR PD-1 OR PD-L1 OR nivolumab OR pembrolizumab OR atezolizumab OR durvalumab OR avelumab) AND (EGFR OR ALK OR ROS1 OR BRAF OR MET OR KRAS OR MET OR oncogene addicted)”; “(nivolumab OR pembrolizumab OR atezolizumab OR immune checkpoint inhibitor) AND non-small cell lung cancer”; “(lung neoplasms OR lung cancer, OR carcinoma [MeSH Terms]) AND (checkpoint inhibitors OR check-point inhibitors OR PD-1 OR PD-L1 OR nivolumab OR pembrolizumab OR atezolizumab OR durvalumab OR avelumab)” (only clinical trials were selected in the search of this latter item.).

We aimed to collect all evidence concerning activity and efficacy of ICI in oncogene-addicted NSCLC populations. Assuming that these patients do not harbor a differential risk of ICI-dependent adverse events compared to patients lacking a molecular driver, we did not address toxicities issues regarding ICI monotherapy or combinations with treatments (e.g., chemotherapies) that have been evaluated in larger populations, regardless of mutational status. On

the contrary, as combinatorial strategies involving targeted agents and ICI represent a prerogative of oncogene-addicted cases, data regarding adverse events of these treatments were collected.

Inclusion criteria for studies to be included in the qualitative and quantitative synthesis were represented by the presence of at least one measure of activity [i.e., response and disease control rates, progression-free survival (PFS) and/or efficacy [overall survival (OS)]. Exclusion criteria were: articles not written in English, reviews, commentaries, opinions, case reports, studies gathering the outcomes of different oncogene-addicted patients (e.g., *EGFR*-mutated and *ALK*-rearranged ones versus wild-type ones), not relevant articles. Case reports usually describe the positive outcomes of ICI administration in peculiar situations, suggesting an intrinsic publication bias, potentially leading to overestimate the real benefit in the specific oncogene-driven population. In the same way, case series were considered only if consecutive patients were included, meaning that no selection bias had been performed. As we are dealing with different oncogene-addicted entities, only studies reporting the outcomes of single oncogene-addicted populations were considered. Studies reporting outcomes of oncogene-addicted NSCLC populations, but lacking patients' number, were excluded, as well as translational-biomarker studies including patients enrolled in clinical trials, whose outcomes had been reported in these latter. Concerning different publications presenting data from the same clinical trial, the reports including the outcomes of oncogene-addicted patients and the ones with the longest follow-up were prioritized. We encountered studies that only reported the statistical differences (e.g., hazard ratios, HR, p values) between two oncogene-addicted entities (e.g., *EGFR*-mutated versus wild-type population), lacking a numerical value describing the outcomes measures (e.g., median progression-free survival, PFS, or overall survival, OS). When we faced these studies, only prospective clinical trials were included. Only the studies, prospective and retrospective, that clearly reported the objective responses and the number of treated patients were included in the meta-analysis.

#### **Data extraction and risk of bias assessment**

Two reviewers (Giorgia Guaitoli and Francesco Facchinetti) independently screened titles and abstracts of all identified references. Full-text documents of reports of potential interest were independently assessed by the two reviewers

to determine whether they met the predefined inclusion criteria. Any disagreements were solved by consensus or arbitration by a third person (Marcello Tiseo). A data extraction form was developed specifically for the purpose of this assessment to collect information on patient characteristics, type of treatments, and outcome measures.

#### **Data synthesis and analysis**

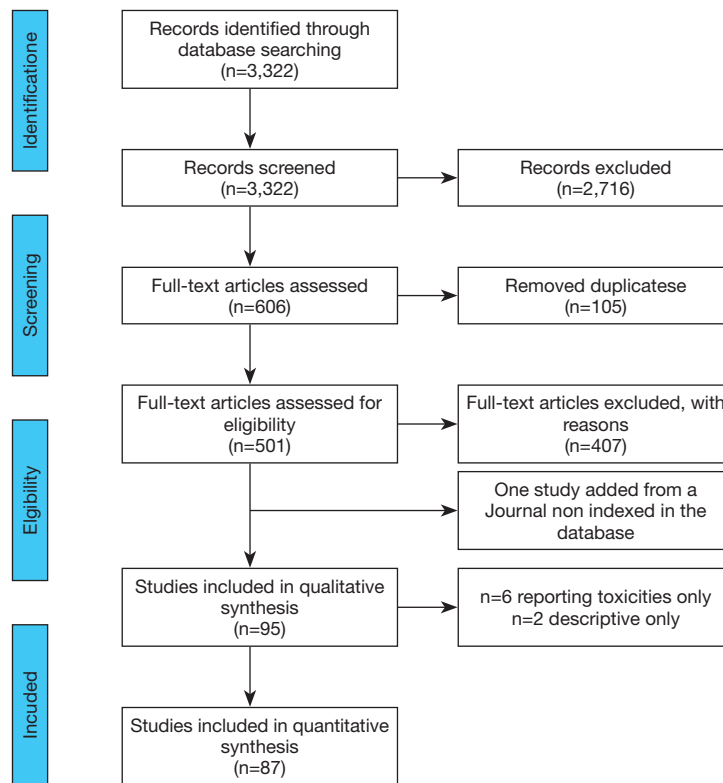
Descriptive statistics were used to summarize characteristics data of patients and tumors. The main results were summed in a table and a quantitative synthesis was planned for all the reported cases.

A narrative synthesis was provided instead of statistical analysis with regard to efficacy outcomes (PFS, OS). Meta-analysis on objective response rate was performed with MedCalc Statistical Software version 19.4.1 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2020). Meta-analysis was performed separately (I) for prospective trials and (II) for retrospective studies. The software uses a Freeman-Tukey transformation (arcsine square root transformation) to calculate the weighted summary proportion under the fixed and random effects model. Heterogeneity is measured by Cochran's Q, calculated as the weighted sum of squared differences between individual study proportion and the pooled proportion across studies. Q is distributed as a chi-square statistic with k (number of studies) minus 1 degrees of freedom. When the number of included studies is small, Q has low power to test heterogeneity, whilst Q has too much power if the number of studies is large. The I<sup>2</sup> statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance. I<sup>2</sup> = 100% × (Q - df)/Q. Unlike Q it does not inherently depend upon the number of studies considered.

## **Results**

### **Results of the systematic search**

Our search strategies in MEDLINE identified a total of 3,322 titles (*Figure 1*). 2,716 of them were excluded as not pertinent to our review. Of the 606 remaining studies, 105 were considered duplicates. 501 full-texts were then evaluated. Among them, 407 study were excluded (n=367 not containing data of interest; n=28 case reports; n=12 not written in English). 94 study were therefore included in the final analysis and we add one title (11), whose Journal



**Figure 1** PRISMA flow diagram depicting the systematic review process leading to the identification of studies included in the systematic review.

is not MEDLINE indexed, as Authors were aware of its relevance for the topic. Six studies only reported toxicities issues due to combination of targeted with immunotherapy agents and two studies were considered only as descriptive (i.e., no specific data of a peculiar subset of oncogene-addicted patients was reported). 87 studies were therefore included in the qualitative analysis: 34 contain prospective data from clinical trials, whereas 53 report the outcomes of oncogene-addicted NSCLC patients as retrospective series/registries. With regard to prospective clinical studies, the ICI evaluated (as mono-therapy or within combinatorial strategies) has always been reported. Concerning retrospective data, the large majority of studies reported outcomes from single-agent anti-PD-1/PD-L1 treatments (especially nivolumab), while a minority of patients had been exposed to combinations involving anti-CTLA-4 agents.

### *EGFR-driven NSCLC and ICIs*

Non-smokers patients globally derive inferior benefit from

ICIs (12,13), and patients with oncogene aberrations (with the exception of *KRAS*) have a negligible tobacco exposure; they may indeed have less somatic mutations (recapitulated by tumor mutation burden, TMB) and lower tumor immunogenicity (14-16). Of note, EGFR-driven diseases have a low co-localization of PD-L1 tumor cells and CD8+ TILs (tumor infiltrating lymphocytes), especially if compared with *KRAS*-mutant NSCLC (17-21). A positive effect of TKIs administration on these parameters, measured compared biopsies obtained at baseline at resistance, proposed by Isomoto and colleagues (22), had not been registered in a previous work by Gainor and collaborators (17). Then the hypothesis that the lack of an inflammatory microenvironment and the lower concurrent expression of PD-L1 and TILs may support immune-resistance in these tumors (17). Nevertheless, in functional *in vitro* studies, mutant EGFR has been showed to up-regulate PD-L1 through intracellular signaling, thus suggesting the co-existence of the two targets may provide a potential molecular background for ICI activity (23,24).

**Table 1** Data about EGFR-positive patients in phase 2 or 3 clinical trials comparing immune checkpoint inhibitors with chemotherapy

Clinical Trial	Borghaei, <i>N Engl J Med</i> 2015 (27)	Herbst, <i>Lancet</i> 2016 (31)	Fehrenbacher, <i>Lancet</i> 2016 (30)	Rittmeyer, <i>Lancet</i> 2016 (28)
Phase	3	2–3	2	3
Immunotherapy	Nivolumab	Pembrolizumab 2 mg/kg Pembrolizumab 10 mg/kg	Atezolizumab	Atezolizumab
Comparator	Docetaxel	Docetaxel	Docetaxel	Docetaxel
Line of Treatment	2 <sup>nd</sup> line	≥2 <sup>nd</sup> line	2 <sup>nd</sup> /3 <sup>rd</sup> line	2 <sup>nd</sup> /3 <sup>rd</sup> line
Number of pts, EGFR+/overall	82/582	86/1,033	19/287	85/850
EGFR+ in immunotherapy arm	44	28 (2 mg/kg); 32 (10 mg/kg)	11	42
PFS in EGFR+, HR (95% CI)	1.46 (0.90–2.37)	1.79 (0.94–3.42)	NA	NA
PFS in EGFR WT, HR (95% CI)	0.83 (0.65–1.06)	0.83 (0.71–0.98)	NA	NA
OS in EGFR+, HR (95% CI)	1.18 (0.69–2.00)	0.88 (0.45–1.70)	0.99 (0.29–3.40)	1.24 (0.71–2.15)
OS in EGFR WT, HR (95% CI)	0.66 (0.51–0.86)	0.66 (0.55–0.80)	NA	0.69 (0.57–0.83)

Pts, patients; EGFR+, EGFR positive; WT, wild-type; OS, overall survival; PFS, progression free survival; HR, hazard ratio; CI, confidence interval; NA, not available.

### Data from clinical trials with single-agent anti-PD-1/PD-L1

*EGFR*-mutated NSCLC is the oncogene-addicted subgroup most represented in clinical trials with immunotherapy, that appears to be poorly effective in this population. Indeed, even if some responses are reported, and some of them are protracted (25,26), a long-term benefit in PFS and OS is generally lacking, especially if compared with the wild-type (WT) population.

In particular, results of phase 2 and 3 trials of second line immunotherapy compared with docetaxel, suggest that ICIs do not add any advantage over chemotherapy in this subgroup of patients (27–31). In the OAK trial, second line atezolizumab improved OS in all predefined subgroups, with the exception of *EGFR*-mutated patients [HR 1.24; 95% confidence interval (95% CI): 0.71–2.18 versus 0.69; 95% CI: 0.57–0.83 in the *EGFR* WT) and this was confirmed also in the Japanese population (28,32). Consistently, still with the limitation of subgroup analyses, also nivolumab and pembrolizumab failed in outperforming docetaxel in this setting (27,31) (Table 1).

Nevertheless, in all phase 3 studies, *EGFR*-mutated patients were a low percentage of the overall population (between 6% and 14%), precluding the identification of a subgroup of patients more likely to benefit from immunotherapy (e.g., according to PD-L1 status or type of mutation).

In phase 1 or 2 trials (Table 2) (33–41), conflicting ORRs are reported, including the absence of response (37–39) or some prolonged responses, as in CA209-003 (26). This study enrolled 13 *EGFR*-mutated patients and two of them were still alive at 5-years follow-up: one harboring an exon 20 insertion (pretreated with erlotinib), and one harboring an exon 18 missense mutation (TKI-naïve) (26).

Albeit responses occur regardless of mutational status, ORRs are usually lower in mutant patients than in those WT status (34,40). When pooling activity data in the meta-analysis indeed, ORR was 7.2% (95% CI: 3.7–11.6) and 21.3% (95% CI: 17.9–24.9) in the *EGFR*-mutant (n=187) and in the *EGFR*-WT (n=1264) populations, respectively (Figure 2, Tables S1, S2). Heterogeneity among studies was low ( $I^2=10.2%$ ) for *EGFR*-mutant and moderate ( $I^2=47.7%$ ) for *EGFR*-WT. The absence of previous or current smoking attitude, that usually characterize *EGFR*-positive patients, may play a role in the poor responses reported.

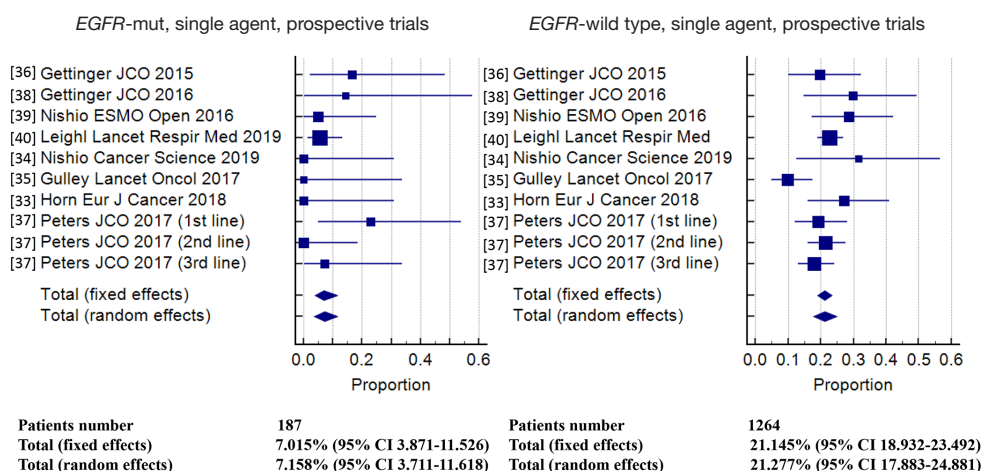
The chance of obtaining an objective response was significantly lower in *EGFR*-mutant patients compared to *EGFR*-WT [odds ratio (OR) 0.33, 95% confidence interval 0.19–0.59,  $P=0.002$ ], without significant heterogeneity among studies.

Even in setting different from advanced disease, immunotherapy does not seem to improve outcomes, again with the limitation of subgroups. In the PACIFIC trial in stage III NSCLC, durvalumab after chemo-radiotherapy,

**Table 2** Data about EGFR-positive patients in phase 1 or 2 single-arm clinical trials with immune checkpoint inhibitors monotherapy

Reference	Gettinger, <i>J Clin Oncol</i> 2015 (26,33)	Gettinger, <i>J Clin Oncol</i> 2016 (34)	Nishio, <i>ESMO Open</i> 2016 (35)	Leighi, <i>Lancet Respir Med</i> 2019 (36)	Nishio, <i>Cancer Science</i> 2019 (37)	Gulley, <i>Lancet Oncol</i> 2017 (38)	Horn, <i>Eur J Cancer</i> 2018 (31)	Peters, <i>J Clin Oncol</i> 2017 (38)
Phase	1	1	2	1	1b	1b	1	2
Immunotherapy	Nivolumab	Nivolumab	Nivolumab	Pembrolizumab	Pembrolizumab	Avelumab	Atezolizumab	Atezolizumab
Line of Treatment	≥2 <sup>nd</sup> line	1 <sup>st</sup> line	≥2 <sup>nd</sup> line	≥1 <sup>st</sup> line	2 <sup>nd</sup> line	2 <sup>nd</sup> line	≥1 <sup>st</sup> line	≥1 <sup>st</sup> line
Number of pts EGFR+/overall	12/129	8/52	20/76	3/101 naïve 74/449 pretreated	10/38	9/184	10/89	45/543
ORR EGFR+	16.7% (2/12)	14% (1/7)	5% (1/20)	5.4% (4/74) <sup>a</sup>	0% (0/10)	0% (0/9)	0% (0/10)	23% (3/13) <sup>c</sup>
ORR in EGFR WT	19.6% (11/56)	30% (9/30)	28.6% (16/56)	23% (102/449) <sup>b</sup>	29.6%	10% (10/101)	27% (15/55)	19% (20/104) <sup>c</sup>
mPFS EGFR+ months (95% CI)	NA	1.8 (range 0.2–7.6+)	2.7 (1.2–2.9)	NA	2	5.4 (1.9–24.0)	NA	5.5 (2.6–8.3) <sup>c</sup>
mPFS EGFR WT months (95% CI)	NA	6.6 (range <0.1–28.0+)	2.8 (1.4–5.6)	NA	5	11.7 (6.3–14.3)	NA	5.5 (3.0–6.9) <sup>c</sup>
mOS in EGFR+ months (95% CI)	NA	NA	14.2 (5.7–15.4)	6.0 (4.4–8.8)	10 (3–NR)	3.0 (1.1–NE)	8 (range 1–24)	20.1 (NE–NE) <sup>c</sup>
mOS in EGFR WT months (95% CI)	NA	NA	19.5 (15.0–NA)	12.0 (9.2–14.3)	20 (8–27)	8.6 (7.6–NE)	18 (range 1–62)	NE (15.5–NE) <sup>c</sup>

<sup>a</sup>mutated pretreated. <sup>b</sup>pretreated overall. <sup>c</sup>first-line treatment; <sup>d</sup>second-line treatment; <sup>e</sup>third-line treatment. EGFR+, EGFR positive; ORR, objective response rate; WT, wild-type; CI, confidence interval; mPFS, median progression-free survival; mOS, median overall survival; NA, not available; NE, not estimable.



**Figure 2** Meta-analysis of objective responses according to *EGFR* status in prospective trials of single-agent immune checkpoint inhibitors.

significantly improved PFS and OS in the global population and in a wide range of subgroups, while the benefit for *EGFR*-positive patients (n=45) is at least uncertain (HR for PFS 0.76; 95% CI: 0.35–1.64) (42,43).

### Real-life experiences with single-agent anti-PD-1/PD-L1

Moving to real-life data, the evidence of ICIs effectiveness in the *EGFR*-mutated population mainly derives from retrospective cohorts of pretreated patients (Table 3 and Table 4).

In studies comparing the outcomes of *EGFR*-mutated NSCLC with the WT counterpart (Table 3), the activity of ICIs and their impact on survival estimations appear almost invariably disappointing in the first group of patients. Similarly to what observed for the prospective trials, pooling the results of retrospective experiences, ORR in *EGFR*-mutant (n=1,069) and *EGFR*-WT (n=2,212) subgroups were 11.1% (95% CI: 9.3–13.0) and 25.7% (95% CI: 20.6–31.1), respectively (Tables S3, S4). There was no evidence of heterogeneity ( $I^2 = 0\%$ ) among proportions in *EGFR*-mutant, and evidence of significant heterogeneity ( $I^2 = 75.5\%$ ) among proportions in *EGFR*-WT.

In the subgroup analysis of nivolumab expanded access program reported by Garassino and colleagues, 90% of the patients had previously received *EGFR*-TKIs and all but one had been exposed to at least a chemotherapy regimen (44). Of interest, the benefits driven from nivolumab were differential according to smoking status. Out of the 51 never-smokers, *EGFR*-mutated patients, disease response and stability were recorded in one and 10 cases, respectively, with

a median PFS of 2 months and a median OS of 5.6 months. On the other hand, among the 34 *EGFR*-positive cases, either current or former smokers, responses and stabilities were observed in seven and nine cases respectively, with a median PFS and OS of 4 and 14.1 months, respectively (44). Given the questionable role of median estimation of survival in evaluating immunotherapy effectiveness (17,82), 6-months PFS, 12-months PFS and 12-months OS resulted 9.8% and 36.4%, 4.9% and 30.3%, 37.8% and 55.6% in the two respective groups. Irrespective of smoking status, Mazières and colleagues reported a 6-month and a 12-month PFS rates of 18% and 6% for *EGFR*-positive patients exposed to ICIs (68). In a previous report, Yoshida and collaborators suggested that smoking exposure, duration of previous *EGFR*-TKI therapy and type of *EGFR* mutation had an impact on nivolumab PFS (63). Similar impact of the type of *EGFR* mutation on ICIs outcomes has been reported in two additional large series, as in both cases *EGFR*<sup>L858R</sup> patients experienced better outcomes compared to *EGFR*<sup>del19</sup> ones (68,69). Facing a lack of definite conclusion on the role of PD-L1 expression for the prediction of ICIs benefit in *EGFR*-driven diseases (68,69), nivolumab activity has been suggested to be correlated with CD8+ TILs density (64). Dealing with long-term survivorship provided by ICI (83), no patients among the 42 oncogene-addicted ones (39 *EGFR*-positive, three *ALK*-rearranged), experienced a survival longer than three years in the study provided by Hu-Lieskovan and colleagues (84).

### Combinatorial strategies

To achieve better response or delay/overcome resistance,

**Table 3** Comparison between EGFR mutated and wild-type patients receiving immune checkpoint inhibitors in single cohorts

Reference	EGFR status	CR+PR [%]	SD [%]	PD [%]	P value	mPFS (mo)	Stats PFS	mOS (mo)	Stats OS
Garassino, <i>J Thorac Oncol</i> 2018 (44)	MUT 102	9 [9]	22 [22]	65 [64]	0.007	3.0	0.004	8.3	P=0.46
	WT 1,293	253 [20]	339 [26]	661 [51]		3.0		11	
Morita, <i>Lung Cancer</i> 2020 (45)	MUT 116	10 [9]	38 [33]	68 [58]	NA	1.5	P<0.0001 Multiv +	12.1	P=0.46
	WT 641	145 [22]	235 [37]	261 [41]		2.3		14.6	
Yamaguchi, <i>Thorac Cancer</i> 2019 (46)	MUT 14	1 [7]	3 [21]	10 [72]	NA	NA	NA	NA	NA
	WT 104	33 [32]	30 [29]	40 [39]					
Ishii, <i>Thorac Cancer</i> 2020 (47)	MUT 25	7 [28]	5 [20]	13 [52]	NA	NA	NA	NA	NA
	WT 66	13 [20]	17 [26]	36 [54]					
Lin, <i>J Cancer</i> 2018 (48)	MUT 25	3 [13]	5 [18]	17 [69]	NA	1.3	P=0.02	10.5	P=0.867
	WT 36	16 [45]	13 [37]	7 [18]		2.8		NR	
Omori, <i>Mol Clin Oncol</i> 2019 (49)	MUT 13	0 [0]	NA	NA	0.09	NA	NA	NA	NA
	WT 44	13 [29]							
Ahn, <i>J Cancer Res Clin Oncol</i> 2019 (50)	MUT 23 <sup>a</sup>	3 [13]	5 [22]	15 [65]	NA	1.6	P<0.01	4.4	P<0.01 Multiv+
	WT 131	NA	NA	NA		3.8		13.5	
Fujimoto, <i>Lung Cancer</i> 2018 (51)	MUT 94	6 [7]	16 [17]	72 [76]	NA	~2	P<0.001	NA	NA
	WT 371	NA	NA	NA		~2.8			
Kobayashi, <i>Int J Clin Oncol</i> 2017 (52)	MUT 16	1 [6]	NA	NA	0.638	NA	NA	NA	NA
	WT 28	4 [14]							
Gainor, <i>Clin Cancer Res</i> 2016 (17)	MUT 22	1 [4]	NA	NA	0.053 <sup>c</sup>	2.07 <sup>c</sup>	P=0.018 <sup>c</sup>	NA	NA
	WT 30	7 [23]				2.58			
Cho, <i>J Cancer Res Clin Oncol</i> 2019 (53)	MUT 38	6 [16]	NA	NA	0.046 Multiv +	1.9	P=0.04, Multiv +	NA	NA
	WT 140	46 [33]				3.0			
Juergens, <i>Curr Oncol</i> 2018 (54)	MUT 25	NA	NA	NA	NA	1.87 <sup>b</sup>	P=0.009	3.38	P=0.002
	WT 229					3.45 <sup>b</sup>		13.37	
Hsu, <i>Plos One</i> 2018 (55)	MUT 7	NA	NA	NA	NA	11.53	P=0.949	11.53	P=0.969
	WT 17					4.9		13.0	
Areses Manrique, <i>Transl Lung Cancer Res</i> 2018 (56)	MUT 6 <sup>a</sup>	NA	NA	NA	NA	NA	NA	4.8	P=0.12
	WT 182							12.8	
Kim, <i>Cancer Chemother Pharm</i> 2017 (57)	MUT 4	NA	NA	NA	NA	1.3	P<0.001	24.5	P<0.001
	WT 28					5.6		2.8	

<sup>a</sup>including 1 ALK+ pt. <sup>b</sup>time-to-treatment discontinuation. <sup>c</sup>if considering also the six non-responding ALK+ patients in the group of EGFR-mutated. MUT, mutated; WT, wild-type; CR, complete responses; PR, partial responses; SD, stable diseases; PD, progressive diseases; NA, not available; Multiv +, positive association at the multivariate analysis; mPFS, median progression-free survival; mo, months; Stats, statistics; mOS, median overall survival.



**Table 4** Studies reporting the outcomes of *EGFR*-mutated patients receiving immune checkpoint inhibitors

Reference	Patients EGFR+	CR+PR [%]	SD [%]	PD [%]	mPFS (mo)	mOS (mo)
Bylicki <i>Med Baltimore</i> 2020 (58)	42	8 [19]	7 [16]	27 [64]	2.2	13.9
Sakamoto <i>Mol Clin Oncol</i> 2019 (59)	24 <sup>a</sup>	4 [17]	4 [17]	15 [63]	2.00	NA
Sato <i>Plos One</i> 2019 (60)	9	1 [11]	0 [0]	7 [78]	1.00	NR <sup>c</sup>
Ng <i>Cancer</i> 2019 (61)	12	0 [0]	2 [17]	10 [83]	1.43	NA
Kobayashi <i>Clin Lung Cancer</i> 2018 (62)	16	0 [0]	5 [31]	11 [69]	NA	NA
Yoshida <i>Ann Oncol</i> 2018 (63)	24	2 [8]	4 [17]	18 [75]	NA	NA
Haratani <i>Ann Oncol</i> 2017 (64)	25	5 [20]	4 [16]	16 [64]	1.5	NA
Yamada <i>Cancer Med</i> 2019 (65)	27	6 [22]	5 [19]	13 [48]	57.5 d	76.5 d
Song <i>Sci Rep</i> 2019 (66)	3	1 [33]	2 [67]	0 [0]	NA	NA
Fang <i>Clin Cancer Res</i> 2019 (67)	7	0 [0]	1 [14]	6 [86]	NA	NA
Mazières <i>Ann Oncol</i> 2019 (8)	115	14 [12]	24 [21]	77 [67]	2.1	10
Hastings <i>Ann Oncol</i> 2019 (69)	171	17 [10]	34 [20]	113 [66]	1.8	9.4
Guibert <i>Lung Cancer</i> 2019 (70)	5	0 [0]	0 [0]	5 [100]	NA	NA
de Vries <i>Ann Oncol</i> 2019 (71)	5	2 [40]		3 [60]	NA	NA
Oya <i>Oncotarget</i> 2017 (72)	22	2 [9]	NA	NA	1.9	8.4
Schouten <i>Lung Cancer</i> 2018 (73)	9	0 [0]	NA	NA	NA	NA
Bagley <i>Lung Cancer</i> 2017 (74)	12	1 [8]	NA	NA	NA	NA
Rizvi <i>J Clin Oncol</i> 2018 (75)	17	1 R or SD >6 mo [7]		NA	NA	NA
Costantini <i>Lung Cancer</i> 2019 (76)	10	9 no early PD [90]		1 early PD [10]	NA	NA
Kitadai <i>J Cancer Res Clin Oncol</i> 2019 (77)	26 <sup>b</sup>	NA	NA	NA	1.00	2.71
Takeda <i>Oncotarget</i> 2018 (78)	5 ex20	1 [20]	1 [20]	3 [60]	NA	NA
Taniguchi <i>Ann Oncol</i> 2018 (79)	3 G719X <sup>d</sup>	1 [33]	2 [66]	0 [0]	NA	NA
	1 del ins ex 19 + T790M <sup>d</sup>	0 [0]	[0]	1		
Landi <i>J Immunother Cancer</i> 2019 (80)	47 Bone mets+	1 [2] P=0.03	NA	NA	2.0 P=0.14	5.4 P=0.04
	55 Bone mets -	8 [14]	NA	NA	3.0	12.8
Gainor <i>Ann Oncol</i> 2020 (81) PD-L1 ≥50%	13 never-light smokers	3 [23]	NA	NA	NA	NA
	4 heavy smokers	0 [0]				

<sup>a</sup>including one rearranged each for *ALK*, *ROS1*, *RET*. <sup>b</sup>including one KRAS+ and one ROS1+. <sup>c</sup>only one patient had received EGFR-TKI before nivolumab. <sup>d</sup>all cases with PD-L1 TPS >50%. EGFR+, EGFR-mutated; CR, complete responses; PR, partial responses; SD, stable diseases; PD, progressive diseases; NA, not available; mPFS, median progression-free survival; mo, months; mOS, median overall survival; d, Days; mets, metastases.

combination strategies with different ICIs, or with ICIs and chemotherapy or target therapies have been designed (85-90) (Table 5).

To date, Impower 150 is the only phase 3 trial with

consistent results regarding *EGFR*-mutated patients, showing an improvement in both PFS and OS with the combination of atezolizumab + bevacizumab + carboplatin + paclitaxel (85,92). Survival benefit was obtained despite

**Table 5** Phase 1–3 clinical trials about combination strategies including *EGFR*- and/or *KRAS*-mutated patients

Reference	Rizvi, <i>J Clin Oncol</i> 2016 (86)	Hellmann, <i>Ann Oncol</i> 2019 (91)	Gettinger, <i>J Thorac Oncol</i> 2018 (88)	Gubens, <i>Lung Cancer</i> 2019 (90)	Hellmann, <i>Lancet Oncol</i> 2017 (87)	Reck, <i>Lancet Respir Med</i> 2019 (85)
Phase	1	1b	1	1-2	1	3
Treatment schedule	Nivolumab + Platinum doublet	Atezolizumab + Cobimetinib	Nivolumab + Erlotinib	Pembrolizumab + Ipilimumab	Nivolumab + Ipilimumab	ABCP vs. ACP vs. BCP
Number of patients	56	28 <sup>a</sup>	21	51	77	1202
EGFR						
Number	6	NA	21	11	8	124
ORR in EGFR+	17% (1/6)		15% (3/20)	10% (1/10)	50% (4/8)	70.6% (24/34) ABCP, 35.6% (16/45) ACP, 41.9% (18/43) BCP
ORR in EGFR WT	47% (14/30)		NA	NA	NA	NA
mPFS in EGFR+ (months)	4.8 (range 0.9–6.8)		5.1 (2.3–12.1)	NA	NA	10.2 ABCP, 6.9 BCP, 0.61 (0.36–1.03) <sup>b</sup>
mPFS in EGFR WT (months)	7.5 (range <0.1–28.9+)		NA	NA	NA	NA
mOS in EGFR+ (months)	20.5 (range 9.4–35.0+)		18.7 (7.3–NA)	NA	NA	NE ABCP, 18.7 BCP, 0.61(0.29–1.28) <sup>c</sup>
mOS in EGFR WT (months)	24.5 (range 6.2–35.1)		NA	NA	NA	NA
KRAS						
Number	10	12	NA	NA	NA	NA
ORR in KRAS+	30% (3/10)	8% (1/12)				
ORR in KRAS WT	46% (6/13)	33% (4/12)				
mPFS in KRAS+ (months)	4.9 (range <0.1–21.8)	NA				
mPFS in KRAS WT (months)	7.1 (range 0.9–10.1)	NA				
mOS in KRAS+ (months)	20.9 (range 6.2–29.7+)	NA				
mOS in KRAS WT (months)	27.2 (range 12.0–35.0+)	NA				

<sup>a</sup>28 NSCLC pts of 152 pts overall. <sup>b</sup>With *EGFR* sensitising mutation: 10.3 vs. 6.1 mo, HR 0.41 (95% CI: 0.23–0.75). <sup>c</sup>With *EGFR* sensitising mutation: NE vs. 17.5 mo, HR 0.31 (95% CI: 0.11–0.83). ORR, objective response rate; mPFS, median progression-free survival; mOS, median overall survival; HR, hazard ratio; CI, confidence interval; ABCP, atezolizumab + bevacizumab + paclitaxel + carboplatin; ACP, atezolizumab + paclitaxel + carboplatin; BCP, bevacizumab + paclitaxel + carboplatin; NA, not available.

a lower PD-L1 positivity rate in the mutated population compared with the WT one, suggesting that chemotherapy and bevacizumab may enhance immunotherapy activity, favoring neoantigen release or T-cell tumor infiltration (85). In particular, benefits were obtained with the addition

of both immunotherapy and anti-angiogenic agent to platinum-based chemotherapy: this combination significantly improved ORR, PFS and OS when compared with bevacizumab + chemotherapy (while a formal comparison with immunotherapy + chemotherapy was not

reported). In the EGFR-positive subgroup (n=124), the addition of atezolizumab prolonged mPFS: 10.2 months (95% CI: 7.9–15.2) *vs.* 6.9 (95% CI: 5.7–8.5); HR 0.61 (95% CI: 0.14–1.07). Additionally, overall survival was not estimable (95% CI: 17.0–NE) *vs.* 18.7 months (13.4–NE); HR 0.61 (95% CI: 0.29–1.28). Moreover, when selecting for common, sensitizing mutations (exon 19 deletion and L858R mutation, n=61), OS HR 0.31 (95% CI: 0.11–0.83) was reported (Table 5) (85).

In the phase 1 trial of pembrolizumab + ramucirumab, one EGFR-positive patient, previously treated with erlotinib, experienced stable disease as best response, and discontinued treatment after nine cycles (93). With the combination of nivolumab plus chemotherapy responses were obtained regardless of *EGFR* or *KRAS* status, with 1-year OS rates similar between oncogene-addicted and WT subgroups, still with shorter mOS and mPFS in the mutated subgroups (86).

The phase 1 trial Checkmate-012 was specifically designed for an *EGFR*-mutant population and enrolled chemotherapy-naïve patients to receive a combination of nivolumab plus erlotinib. Of the 21 patients included, 20 were already pretreated with erlotinib, in all cases discontinued due to disease progression. Responses were achieved in three cases (ORR 15%) including one complete response (CR) (88). mOS and mPFS were 18.1 and 5.1 months respectively, numerically longer in smoker patients than in non-smoker patients. ORR was higher in PD-L1  $\geq 1\%$ . The single TKI-naïve patient enrolled, achieved a CR (the patient harbor L858R + S768I mutation, with PD-L1 65%) (88).

In a post-hoc analysis of the phase 1 trial combining nivolumab plus ALT-803 (IL-15 superagonist), two patients with PD-L1 expression included between 1% and 50% experienced stable disease, and one of them was an *EGFR*-mutated patient harboring exon 20 mutation, treated with the combination for 17 months (94). In CA209-003, a patient harboring exon 20 mutation achieved durable benefit with immunotherapy, and indeed this may be relevant considering that this type of mutation correlates with resistance to clinically available TKIs and poor prognosis (95,96).

### Toxicity issues in TKI-ICI combinations and sequential treatments

#### *Evidence from clinical trials*

In almost all immunotherapy trials that allowed *EGFR*-mutated patients inclusion, their enrollment was permitted

at the failure of a previous line with TKI. If this strategy did not show particular efficacy, it did not raise relevant toxicities issues, while the reverse strategy (immunotherapy followed by target therapy) or the combination of ICIs + TKI appear to be dangerous in some experiences (89,97). The phase 2 trial of first line pembrolizumab in *EGFR*-mutated patients ceased prematurely for futility: indeed, of 10 patients no-one achieved a response (89). What is even more interesting, is that in seven patients treated with second line erlotinib, 86% experienced a treatment-related adverse event.

A rate of interstitial lung disease (ILD) higher than expected has been reported in TATTON trial (97). Despite 43% ORR, all patients treated with durvalumab plus osimertinib discontinued treatment. The most common adverse events (AEs) were rash, vomiting and diarrhea, but the 22% rate of ILD was high enough to cause the early recruitment termination in the phase 3 CAURAL trial (98).

According to phase 1 trials preliminary results, combinations of immunotherapy plus a first generation TKI seem more tolerable (88,99,100).

#### *Evidence from clinical practice*

The toxicity alerts emerging from the sequential administration of ICIs and *EGFR*-TKIs have also been reported in clinical practice. If treatment with *EGFR*-TKIs followed by ICIs seems to be safe (101,102), the inverse sequence can be accompanied by a remarkable proportion of AEs, suggesting a putative role of ICIs in “priming” the toxicity exerted by *EGFR*-TKIs. Severe immune-related AEs (mainly ILD) occurred in six out of 41 patients receiving osimertinib after ICIs and were more common among patients initiating osimertinib within three months since ICIs last dose (101). Any-grade ILD was reported in 18 out of 70 patients (26%) of patients receiving the sequence of nivolumab and *EGFR*-TKIs (103) and a similar proportion was reported in an additional smaller series of 26 patients (102). Grade 3–4 liver toxicity occurred in four out of seven patients receiving the sequential treatment with nivolumab and osimertinib (104). Takenaka and colleagues reported the case of a patient experiencing colitis while receiving nivolumab; after its resolution, colitis was re-exacerbated by osimertinib administration (105). Globally, compared to first- and second-generation *EGFR*-TKIs, osimertinib appears to retain the higher risk of inducing immune-related AEs (irAEs) when administered after ICIs (101,102).

According to the current guidelines nevertheless (106,107), the administration of ICIs before *EGFR*-TKI

should be exceptional (e.g., in the case of an *EGFR* mutation status unknown at the beginning of ICI, subsequently turning out positive), given the opposite levels of activity and efficacy in favor of targeted agents. The standard of care is incorporating chemotherapy + bevacizumab + atezolizumab in the treatment of *EGFR*-mutated patients after all the targeted treatment options. No alerts concerning irAEs emerged in Impower150 trial with regard to patients having previously received *EGFR*-TKIs (85), and the lack of relevant AEs in the case of the sequence encompassing *EGFR*-TKI followed by ICIs is reassuring in this sense. On the other hand, attention should be addressed to locally-advanced NSCLC patients treated with chemo-radiotherapy followed by durvalumab (43) regardless of mutational status, who then progress on or after anti-PD-L1 therapy completion and undergo *EGFR*-TKI treatment due to the detection of *EGFR* mutation.

### ***KRAS*-driven NSCLC and ICIs**

Especially when compared with other oncogene-driven tumors, the immune context characterizing *KRAS*-mutant diseases appear more prone to ICIs activity. Higher PD-L1 expression (both by tumor and immune cells), increased TILs density and TMB, that usually characterize *KRAS*-mutated patients, are likely a consequence of their smoking habits, differently from other molecular alterations (14,17,21,108-110).

### **Perspective evidences, real-life experiences and combinatorial strategies**

Albeit responses are reported, results in *KRAS*-mutated patients are not uniform and it remains difficult to draw strong conclusions.

In the Checkmate 057 trial, nivolumab performed even better in *KRAS*-positive patients than in *KRAS* WT population (HR for OS 0.52, 95% CI: 0.29–0.95) (27), while with atezolizumab OS was similar between *KRAS*-mutated and *KRAS* WT or unknown patients (28,111). In the phase 2 BIRCH trial with atezolizumab, 28% of patients (n=137) were *KRAS*-mutated and objective responses have been reported regardless of *KRAS* status, with higher rates and a trend for prolonged mOS and mPFS in second-line treatment (cohort 2) (40). On the contrary, phase 1 experiences with avelumab and atezolizumab report numerically lower ORR in mutated patients than in wild-type, with shorter mOS (38,39), while first-line nivolumab performed better in *KRAS*-mutated patients in terms of

ORRs and mPFS (34) (Table 6). In the meta-analysis of prospective trials, 21.9% (95% CI: 14.0–30.9) and 17.4% (95% CI: 11.3–24.5) of *KRAS*-mutant (n=198) and *KRAS*-WT (n=452) patients experienced disease response, respectively (Figure 3, Tables S5, S6), with moderate but non statistically heterogeneity among studies ( $I^2 = 50.7%$ ) in *KRAS*-mutant and statistically significant heterogeneity among studies ( $I^2 = 64.8%$ ) in *KRAS*-WT.

When compared within a random-effects model, the chance of obtaining an objective response was not significantly different between *KRAS*-mutant patients and *KRAS*-WT patients (OR 1.54, 95% CI: 0.81–2.92,  $P=0.19$ ), without significant heterogeneity among studies.

The activity and efficacy of the combination of platinum-pemetrexed chemotherapy with pembrolizumab, the new standard of care for the first-line treatment in non-squamous NSCLC lacking *EGFR* and *ALK* abnormalities (especially in the case of PD-L1 TPS <50%), have been validated regardless of *KRAS* status (110).

Albeit rarely showed as significantly conditioning better activity and effectiveness of ICIs compared to *KRAS*-WT cases in real-life studies, the presence of *KRAS* mutations can globally be interpreted as a potential marker of benefit to immunotherapy in lung cancer patients (Table 7). With the intrinsic limitation due to the retrospective nature of the majority of the studies, disease control was observed in approximately 50% of patients. In the meta-analysis, 26.7% (95% CI: 20.5–33.4) out of 811 *KRAS*-mutated and 22.4% (95% CI: 13.3–33.0) out of 529 *KRAS*-WT NSCLC experienced disease response (Tables S7, S8), with statistically significant heterogeneity in both series ( $I^2 = 70.8%$  and 80.4%, respectively).

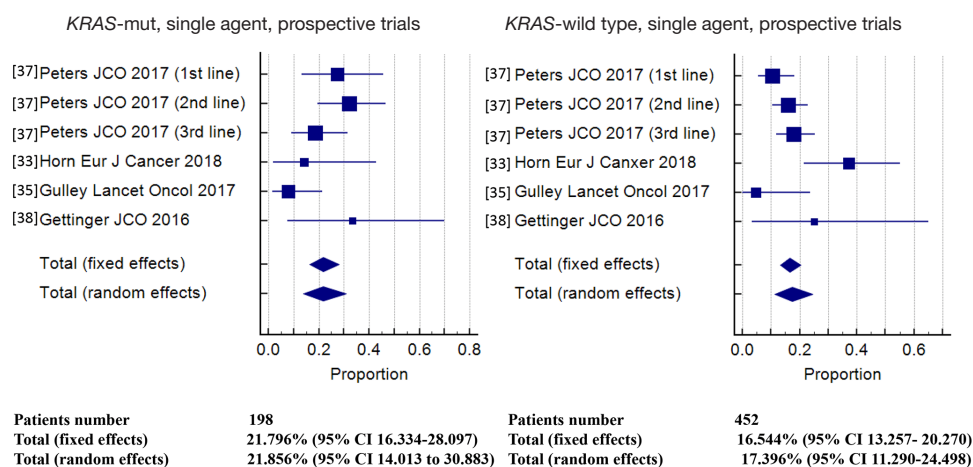
In the study provided by Mazières and collaborators, out of 271 *KRAS*-mutated patients receiving ICIs, 38% and 26% were reported as progression-free at six and 12 months, respectively (68). In the series including the largest number of *KRAS*-mutated NSCLC, median OS was always longer than one year from ICIs initiation (68,112,114), a relevant result in this population of pretreated patients.

Combination strategies, that may be appealing in this setting, are in the preliminary phase of development. The phase 1 trial about the combination of nivolumab plus chemotherapy included 10 *KRAS*-mutated patients that, despite shorter mPFS and mOS, showed 1-year OS rates similar to WT ones (90% vs. 100%). For the combination of pembrolizumab plus epacadostat (IDO1 inhibitor), five responses were reported, including two *KRAS*-mutated

**Table 6** Data about KRAS-positive patients in phase 1-3 clinical trials about immune checkpoint inhibitors monotherapy

Clinical Trial	Borghaei, <i>N Engl J Med</i> 2015 (27)	Rittmeyer, <i>Lancet</i> 2016 (28)	Peters, <i>J Clin Oncol</i> 2017 (40)	Horn, <i>Eur J Cancer</i> 2018 (39)	Gulley, <i>Lancet Oncol</i> 2017 (38)	Gettinger, <i>J Clin Oncol</i> 2016 (34)
Phase	3	3	2	1	1b	1
Immunotherapy	Nivolumab	Atezolizumab	Atezolizumab	Atezolizumab	Avelumab	Nivolumab
Comparator	Docetaxel	Docetaxel	NA	NA	NA	NA
Line of treatment	2 <sup>nd</sup> line	2 <sup>nd</sup> /3 <sup>rd</sup> line	≥ 1st line	≥ 1st line	2 <sup>nd</sup> line	1 <sup>st</sup> line
Number of Patients KRAS+/overall	62/582	59/850	137/488	14/89	21/184	9/52
KRAS+ in immunotherapy Arm	28	42	137	14	21	9
ORR in KRAS+	NA	NA	32% (16/50) <sup>b</sup>	19% (10/54) <sup>c</sup>	8% (3/38)	33% (3/9)
ORR in KRAS WT	NA	NA	16 (24/150) <sup>b</sup>	18% (24/134) <sup>c</sup>	5% (1/21)	25% (2/8)
PFS in KRAS+ (95% CI), median	HR 0.82 (0.47-1.43)	NA	8.3 mo (1.6-12.7) <sup>a</sup>	2.6 mo (1.4-2.8) <sup>c</sup>	6.1 mo (5.4, 12.1)	11.8 mo (range <0.1-28.0+)
PFS in KRAS WT (95% CI), median	HR 1.52 (1.03-2.25)	NA	4.8 mo (2.8-6.9) <sup>a</sup>	2.8 mo (1.9-3.0) <sup>c</sup>	11.5 mo (6.0, 18.0)	2.3 mo (range 1.2-11.6+)
OS in KRAS+ (95% CI), median	HR 0.52 (0.29-0.95)	HR 0.71 (0.38-1.35)	NE (NE-NE) <sup>a</sup>	12.1 mo (6.9-NE) <sup>c</sup>	8.1 mo (3.7-10.7)	NA
OS in KRAS WT (95% CI), median	HR 0.98 (0.66-1.48)	HR 0.83 (0.58-1.18)	20.1 mo (14.1-20.1) <sup>a</sup>	13.8 mo (10.6-NE) <sup>c</sup>	NE (5.6-NE)	NA

<sup>a</sup>first-line; <sup>b</sup>second-line; <sup>c</sup>third-line. KRAS+, KRAS-positive; WT, wild-type; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; mo, months; NA, not available; NE, not estimable.



**Figure 3** Meta-analysis of objective responses according to *KRAS* status in prospective trials of single-agent immune checkpoint inhibitors.

patients (118) and with atezolizumab plus cobimetinib responses were observed regardless of *KRAS* status (91).

No particular toxicities issues have been risen about immunotherapy in *KRAS*-mutated patients.

### Co-existing molecular alterations affecting ICIs activity and efficacy in *KRAS*-mutated disease

Within the *KRAS*-mutant population of NSCLC patients, several entities with a putative prognostic/predictive role in immunotherapy have been recognized. Co-mutant *KRAS/STK11* (up to 30% of *KRAS*-positive cases) adenocarcinomas are associated with a “cold” immune micro-environment (119). Indeed, while *KRAS* mutations are accompanied by relatively high levels of PD-L1 expression and TILs density (see above), *STK11* mutational inactivation is characterized by low PD-L1 expression, TILs reduction, accumulation of neutrophils boosting T-cell exhaustion, and a pro-tumoral cytokine milieu (119-121). These characteristics are likely to mechanistically affect the poor outcomes of *KRAS/STK11*-mutated NSCLC patients receiving single agent immunotherapy, with a relevant proportion of primary resistance (RR 0–7.4%; median PFS and OS 1.8 and 6.8 months, respectively) (122). On the other hand, the opposite immune features of *KRAS/TP53*-mutant tumors (accounting for an 30–40% of *KRAS*-positive NSCLC) ostensibly lead to significant benefit observed in patients harboring the two mutational events (RR 35.7–57.1%; median PFS and OS 3 and 16 months, respectively) (119,122). The co-occurrence of *KRAS* and *STK11* mutations has been moreover proposed as a mutational

marker of hyper-progressive disease (HPD) in NSCLC patients receiving ICIs, as all the three patients suffering from *KRAS/STK11*-positive lung cancer in the series from Kim and colleagues experienced HPD (123).

In another retrospective series with a lower patients’ number, the impact of *STK11* and *TP53* status did not emerge as impacting on ICIs activity and effectiveness in *KRAS*-mutant NSCLC, while *KEAP1* or *NFE2L2* mutations negatively affected the prognosis of *KRAS*-positive NSCLC patients undergoing immunotherapy (117).

Of interest, among *KRAS*-mutated lung cancers only 4% harbor both *STK11* and *TP53* mutations, making the occurrence of triple mutation less frequent than expected by chance (122,124).

### *ALK*-driven NSCLC and ICIs

#### Perspective evidences, real-life experiences, combinatorial strategies and toxicity issues

Few *ALK*-positive patients have been enrolled in clinical trials with ICIs, and their outcome is usually not reported. Among *ALK*-rearranged patients treated with pembrolizumab or avelumab in second or subsequent lines, none achieved a response (27,37,38).

Collecting data about retrospective series, 71 *ALK*-rearranged NSCLC have been exposed to ICIs (Table 8). Although no hints on efficacy outcomes can be driven, only 9.6% (95% CI: 4.1–17.1) of the patients experienced disease response (Table S9), without significant heterogeneity among studies ( $I^2=0\%$ ). As reported by Mazières and colleagues, PFS-rate at six and 12 months was 12% and

**Table 7** Clinical evidence of immune checkpoint activity and effectiveness in KRAS-mutant non-small cell lung cancer patients

Reference	Patients KRAS status	CR+PR [%]	SD [%]	PD [%]	mPFS (mo)	Stats PFS	mOS (mo)	Stats OS
Passiglia, <i>Br J Cancer</i> 2019 (112)	MUT 206	41 [20] <sup>a</sup>	55 [27] <sup>a</sup>	110 [53]	4	P=0.56	11.2	P=0.86
	WT 324	55 [17] <sup>a</sup>	79 [24] <sup>a</sup>	190 [59]	3		10.0	
Lin, <i>J Cancer</i> 2018 (48)	MUT 10	3 [30]	3 [43]	1 [14]	3.8	P=0.457	5.9	P=0.614
	WT 28	4 [14]	4 [25]	8 [50]	1.3		10.5	
Garde-Noguera, <i>Clin Transl Oncol</i> 2018 (113)	MUT 19	3 [15] <sup>a</sup>	NA	NA	1.5	P=0.345	2.6	P=0.299
	WT 32	9 [26] <sup>a</sup>	NA	NA	2.4		5.4	
Jeanson, <i>J Thorac Oncol</i> 2019 (114)	MUT 162	30 [19] <sup>a</sup>	48 [30] <sup>a</sup>	84 [52]	3.09 <sup>b</sup>	P=0.584	14.29 <sup>b</sup>	P=0.682
	WT 120	17 [14] <sup>a</sup>	42 [35] <sup>a</sup>	61 [51]	2.66 <sup>b</sup>		11.14 <sup>b</sup>	
Torralvo, <i>Cancer Genomics Proteomics</i> 2019 (115)	MUT 21	13 [62]	4 [19]	4 [19]	13.6	NA	18.5	NA
	WT 17	8 [49]	2 [10]	7 [41]	8.4		16.8	
Gianoncelli, <i>Anticancer Res</i> 2020 (116)	MUT 43	8 [19] <sup>a</sup>	14 [34] <sup>a</sup>	19 [46]	4.6	P=0.58	13.0	P=0.38
	WT 117	32 [36] <sup>a</sup>	17 [19] <sup>a</sup>	39 [44]	3.3		8.1	
de Vries <i>Ann Oncol</i> 2019 (71)	KRAS+ 54	26 [48]		28 [52]	NA	NA	NA	NA
Costantini <i>Lung Cancer</i> 2019 (76)	KRAS+ 50	42 no early PD [84]		8 early PD [16]	NA	NA	NA	NA
Ng <i>Cancer</i> 2019 (61)	KRAS+ 56	9 [16]	23 [41]	24 [43]	4.57	NA	NA	NA
Oya <i>Oncotarget</i> 2017 (72)	KRAS+ 14	4 [28]	NA	NA	1.9	NA	6.6	NA
Schouten <i>Lung Cancer</i> 2018 (73)	KRAS+ 84	19 [23]	NA	NA	NA	NA	NA	NA
Rizvi <i>J Clin Oncol</i> 2018 (74)	KRAS+ 83	30 [36] R or SD >6 mo		NA	NA	NA	NA	NA
Mazières <i>Ann Oncol</i> 2019 (68)	KRAS+ 246	64 [26]	57 [23]	125 [51]	3.2	NA	13.5	NA
Guibert <i>Lung Cancer</i> 2019 (70)	KRAS+ 10	NA	NA	NA	7.5	NA	NA	NA
Arbour, <i>Clin Cancer Res</i> 2018 (117)	KRAS+ only 60	NA	NA	NA	NA	NA	NR	–
	KRAS+/KEAP1+ or NFE2L2+ 26						6	P=0.006 (Multiv +)
	KRAS+/STK11+ 26						11	0.3
Gainor <i>Ann Oncol</i> 2020, PD-L1 ≥50% (81)	17 never-light smokers	4 [23]	NA	NA	NA	NA	NA	NA
	95 heavy smokers	40 [42]						

<sup>a</sup>not statistically significant. <sup>b</sup>mean values. MUT, mutated; WT, wild-type; +, positive/mutant; CR, complete responses; PR, partial responses; SD, stable diseases; PD, progressive diseases; NA, not available; Multiv +, positive association at the multivariate analysis; mPFS, median progression-free survival; mo, months; Stats, statistics; mOS, median overall survival.

**Table 8** Clinical evidence of immune checkpoint activity and effectiveness in *ALK*-rearranged non-small cell lung cancer patients

Reference	Patients ALK+	CR+PR [%]	SD [%]	PD [%]	mPFS (mo)	mOS (mo)
Mazières, <i>Ann Oncol</i> 2019 (68)	19	0 [0]	6 [32]	13 [68]	2.5	17.0
Heo, <i>Thorac Cancer</i> 2019 (125)	14	2 [14]	2 [14]	9 [64]	2.2	5.7
Fujimoto, <i>Lung Cancer</i> 2018 (51)	11	2 [18]	1 [8]	8 [74]	NA	NA
Bylicki, <i>Med Baltimore</i> 2020 (58)	8	2 [25]	2 [25]	4 [50]	2.4	19.2
Costantini, <i>Lung Cancer</i> 2019 (76)	2	1 no early PD [50]		1 early PD [50]	NA	NA
Ng, <i>Cancer</i> 2019 (61)	4	0 [0]	1 [25]	3 [75]	1.17	NA
Kobayashi, <i>Clin Lung Cancer</i> 2018 (62)	3	0 [0]	3 [100]	0 [0]	NA	NA
Bagley, <i>Lung Cancer</i> 2017 (74)	3	0 [0]	NA	NA	NA	NA
Gainor, <i>Clin Cancer Res</i> 2016 <sup>a</sup> (17)	6	0 [0]	NA	NA	NA	NA
Guibert, <i>Lung Cancer</i> 2019 (70)	1	0 [0]	0 [0]	1 [100]	NA	NA

<sup>a</sup>see table 3 for additional information. CR, complete responses; PR, partial responses; SD, stable diseases; PD, progressive diseases; NA, not available; mPFS, median progression-free survival; mo, months; mOS, median overall survival.

6%, respectively (n=23 ALK-positive patients) (68). As preclinical models suggest PD-L1 expression induction by *EML4-ALK* fusion gene (126), the combination of immunotherapy with ALK inhibitors has been largely evaluated. Most evidence are from early phase studies, and efficacy considerations are only partial. Given the extremely positive results in managing ALK-positive disease since the introduction of second- and third-generation TKIs (127,128), the expected readout in this setting of combination is not the achievement of positive ORR, but the obtaining of prolonged responses and the potential reversal of resistance to single-agent TKIs.

Two phase 1–2 trials about combination of crizotinib with an anti-PD-1 agent have been early interrupted and the combination was not recommended. In the Checkmate 370 trial about combination of nivolumab and crizotinib as first-line treatment, severe hepatotoxicity was reported in 38% (5/13 these evidences and despite 38% rate of partial response, further evaluations of the combination were therefore not endorsed (129). The trial about combination with pembrolizumab terminated early due to difficult accrual after the advent of second-generation inhibitors, so the maximum tolerated dose was not determined. Of note, of nine enrolled patients, four dose limiting toxicities were reported, with three cases of grade  $\geq 3$  transaminase increase (130).

In the phase 1b dose escalation trial, ceritinib in combination with nivolumab showed promising activity at both dosages (450 and 300 mg), especially in treatment

naïve patients and in PD-L1 positive ones, still with many toxicities, including unusual high rate of rash. Despite its activity, toxicity issues suggest to evaluate different schedules of drug administration, and parameters to select patients more likely to respond to combination would be recommended (131).

The combination of the current standard of care in the first-line setting of *ALK*-rearranged NSCLC, alectinib with atezolizumab seems more manageable in treatment-naïve patients (132). Of note, in this phase 1b trial by Kim *et al.*, alectinib was administered alone for 7 days, and atezolizumab was introduced after this safety evaluation. Despite 6 patients out of 21 discontinued one of two treatments, no severe adverse events were observed and no dose limiting toxicities were reported, ORR was 81% and mPFS was 21.7 months (95% CI: 10.3–21.7) (132).

The Javelin lung 101 trial enrolled pretreated ALK-positive and ALK-negative patients based on preclinical assumptions about synergistic activity of ALK inhibitors and immunotherapy in NSCLC (133). Avelumab was administered in combination with crizotinib in ALK-negative patients, or with lorlatinib in *ALK*-rearranged ones (134). The third-generation inhibitor provide an acceptable safety profile and its activity will be further evaluated.

Even if hepatic toxicity is commonly associated with ALK inhibitors (135), immunotherapy seems to increase toxicity rates, but mechanisms behind this amplification are not fully elucidated. The majority of studies are dealing



**Table 9** Clinical evidence of immune checkpoint activity and effectiveness in *BRAF*-mutant non-small cell lung cancer patients

Reference	Patients <i>BRAF</i> status	CR+PR [%]	SD [%]	PD [%]	mPFS (mo)	mOS (mo)
Rihawi, J Thorac Oncol 2019 (138)	11 <i>BRAF</i> +	1 [9]	0	9 [82]	NA	10.3
	199 WT	39 [20]	45 [23]	108 [54]	NA	11.2
Guisier, J Thorac Oncol 2020 (139)	26 V600	6 [26]	8 [35]	9 [39]	5.3	22.5
	18 non-V600	6 [35]	3 [18]	8 [47]	4.9	12
Schouten, Lung Cancer 2018 (73)	4 V600E	0 [0]	NA	NA	NA	NA
	5 non-V600E	3 [60]	NA	NA	NA	NA
Dudnik, J Thorac Oncol 2018 (140)	12 V600E	3 [25]	NA	NA	3.7	NR
	10 non-V600E	3 [33]	NA	NA	4.1	NR
Dudnik, Lung Cancer 2018 (141)	4 V600E	1 [25]	NA	NA	1.5	NR
	5 non-V600E	1 [20]	NA	NA	2.6	NR
Mazières, Ann Oncol 2019 (68)	37 <i>BRAF</i> +	9 [24]	11 [30]	17 [46]	V600E (n 17) 1.8, non-V600E (n 18) 4.1; P=0.2	V600E (17) 8.2, non-V600E (18) 17.2; P=0.28
Ng, Cancer 2019 (61)	8 V600E	2 [25]	1 [12]	5 [63]	2.73	NA
Oya, Oncotarget 2017 (72)	1 <i>BRAF</i> +	0 [0]	NA	NA	NA	NA
Gainor, Ann Oncol 2020 (81), <i>BRAF</i> + PD-L1 ≥ 50%	4 light-never smokers	1 [25]	NA	NA	NA	NA
	12 heavy smokers	6 [50]				

WT, wild-type; CR, complete responses; PR, partial responses; SD, stable diseases; PD, progressive diseases; NA, not available; mPFS, median progression-free survival; mo, months; mOS, median overall survival.

with concomitant therapies, while sequential approaches have not been evaluated prospectively. As already noticed in *EGFR*-mutated disease, in other oncogene-driven ones the use of ICIs before target therapies may also have toxic consequences. A retrospective study evaluated patients harboring *ALK/ROS1* rearrangement or *MET* amplification/mutation treated with crizotinib. Eleven out of 453 received a TKI after a previous ICI (as single agent or in combination strategies). Patients previously treated with immunotherapy experienced higher incidence of hepatotoxicity (reversible in all cases) including grade 3/4 ALT or AST increase reported in 45.5% and 36.4% of patients, respectively, suggesting the importance of a careful surveillance in a sequential regimen (135). Still, the reverse strategy in *ALK*-driven disease has not been evaluated.

### *BRAF*-driven NSCLC and ICIs

*BRAF* mutations account for approximately 5% of lung adenocarcinomas, half of them occurs in codon V600 in exon 15 (namely V600E), the others in codons other than

V600 in exon 11 or 15 (136). While dabrafenib-trametinib combination is the novel standard of care for *BRAF*<sup>V600E</sup> mutant NSCLC, scant data are available concerning activity and efficacy of *BRAF*/*MEK* inhibitors in non-V600E *BRAF* mutations (136,137). The repartition between these two groups of *BRAF*-mutated patients has frequently been maintained in retrospective reports dealing with ICIs (Table 9). Activity and efficacy of immunotherapy in *BRAF*-positive disease are satisfactory, recapitulating results observed in *KRAS*-driven and WT disease. The global limited number of patients in the respective V600 and non-V600 subgroups, as well as the contradictory results reported in some series (68,139), precludes any conclusion regarding a potential differential benefit derived from ICIs. The positive smoking history, frequently observed in *BRAF*-mutant NSCLC (137,139,140), likely contributes to the better outcomes observed (Table S10).

In the largest series published so far, Guisier and colleagues reported slight differences in outcomes in *BRAF*<sup>V600</sup> (n=26) and *BRAF*<sup>non-V600</sup> (n=18) patients (139). Half of them received single-agent ICI as a second-line

of treatment; PR and disease control were observed in approximately 30% and 60% of the cases. Median PFS was 5 months, with approximately 50% and 30% of the patients not progressing at six and 12 months, respectively at the same landmark time-points, proportions of progression-free patients were 32% and 18% in the series of Mazières and colleagues (68). Median OS was 22.5 months in the V600 group and 12 months in the non-V600 one, nevertheless 12-months OS rates were overlapping (~50%). The lack of a specific report of post-ICI treatment does not allow to contemplate the contribution of targeted agents in engendering such positive OS outcomes in *BRAF*<sup>V600</sup> patients.

### *ICIs in patients suffering from NSCLC driven by additional oncogenes*

The immune context in which lung tumors harboring other oncogenic aberration arise has not been deeply characterized, nevertheless some information is already available.

Sabari and colleagues reported that, out of 111 *MET* exon 14 mutated tumors, 37%, 22%, and 41% expressed PD-L1 in 0%, 1–49% and ≥50% of tumor cells, respectively, globally in line with molecularly unselected cohorts of non-squamous NSCLC (142). TMB, on the other hand, was lower in this population of *MET*-activated NSCLC compared to unselected cases (143).

Among 26 NSCLC cases harboring *RET* rearrangements, 58%, 23% and 19% expressed PD-L1 in 0%, 1–49% and ≥50% of tumor cells, while TMB in *RET*-positive diseases was lower compared to *RET*-negative ones (11).

*Table 10* gather the information concerning activity and effectiveness collected in retrospective series of ICI administration to patients suffering from NSCLC driven by *MET* or *HER2* abnormalities, *RET* or *ROS1* rearrangements. Again with limited global patients' numbers, across these molecular subgroups, the outcomes obtained with ICIs appears globally disappointing (*Table S11* for meta-analysis of ORR in *RET*-positive patients), with the putative exception of *MET*-driven diseases, where satisfying activity signals can be observed (*Table 10*), with 36% and 23% of the patients not experiencing progression at 6- at 12-month analyses in the series of Mazières and collaborators (68). At the same landmark time-points, PFS-rates were 23% and 14% for *HER2*-positive NSCLC, 14% and 7% for *RET*-rearranged diseases (68).

The positive median OS estimations suggest that a

meaningful proportion of patients have been exposed to targeted agents after ICIs failure.

Finally, two patients with *NTRK* mutations were exposed to ICIs, one of them experiencing disease response (140); nevertheless, the assumption that *NTRK* is known as an actionable and targetable driver in the case of gene rearrangement, question the relevancy of these data.

## Conclusions

Although tremendous progresses over the last years, NSCLC treatment is still plagued by resistance issues. In oncogene-addicted NSCLC, the increasing number of target therapies available cannot guarantee a persistent disease control, due to the emergence of acquired resistance, and the recourse to different treatment strategies is almost unavoidable. Immunotherapy, that revolutionized management of thoracic disease, has a controversial role in this setting, as primary resistance frequently turns this disease into refractory to ICIs. Within each specific group of oncogene-addicted NSCLC, additional pathological or molecular characteristics, that may help to select patients more likely to respond to ICIs, have been suggested, while a clear view on this issue of major clinical relevance is required.

Apart from isolated good responses, evidence suggest that *EGFR* mutations may be a biomarker of poor response to single-agent immunotherapy. On the contrary, in *EGFR*-positive patients, the combination of atezolizumab + bevacizumab + chemotherapy at the failure of previous TKIs, merges its effectiveness with an acceptable safety profile (85).

*KRAS*-mutated disease usually shows different clinical and pathological characteristics, but co-existing mutations may influence tumor microenvironment and response to single-agent ICIs (119,122).

As already demonstrated with *EGFR*-positive disease, synergistic effects of chemotherapy, antiangiogenic agents and immunotherapy improve outcome of oncogene-addicted patients (85). At the failure of target therapies, combination strategies are probably the best way to exploit immunotherapy effects, but a careful selection of patients is necessary, considering increased treatment toxicities (85).

Moreover, it is quite common in this setting to use single-agent immunotherapy as last treatment option, when patients' performance status has already worsened, and this may limit its efficacy (145). Moving ICIs in an earlier setting in patients' disease history could favorize their action.

**Table 10** Clinical evidence of immune checkpoint activity and effectiveness in non-small cell lung cancer patients harboring *MET* or *HER2* alterations, *RET* or *ROS1* rearrangements

Reference	Patients	CR+PR [%]	SD [%]	PD [%]	mPFS (mo)	mOS (mo)
<i>MET</i>						
Mazières, <i>Ann Oncol</i> 2019 (68)	36 ex14 or ampl	5 [16]	11 [34]	16 [50]	3.4	Ex14 (n 23): 25; No ex14 (n 10): 8; P<0.01
Guisier, <i>J Thorac Oncol</i> 2020 (139)	30 ex14	10 [36]	10 [36]	8 [28]	4.9	13.4
Sabari, <i>Ann Oncol</i> 2018 (143)	24 ex14 <sup>a</sup>	4 [17]	NA	NA	1.9	18.2
Dudnik, <i>Lung Cancer</i> 2018 (141)	8 ex14	1 [12]	NA	NA	4.0	NR
	4 ampl	1 [25]	NA	NA	4.9	NR
Reis, <i>Clin Lung Cancer</i> 2018 (144)	2 ex14 PD-L1 >50%, light smokers	0	0	2 [100%]	NA	NA
Gainor, <i>Ann Oncol</i> 2020 (81), <i>MET</i> ex14 PD-L1 ≥50%	7 light-never smokers 5 heavy smokers	3 [43] 2 [40]	NA	NA	NA	NA
<i>HER2</i>						
Mazières, <i>Ann Oncol</i> 2019 (68)	27 ex20	2 [7]	7 [26]	18 [67]	2.5	20.3
Guisier, <i>J Thorac Oncol</i> 2020 (139)	23 mut	6 [27]	5 [23]	11 [50]	2.2	20.4
Dudnik, <i>Lung Cancer</i> 2018 (141)	7 mut	1 [14]	NA	NA	3.4	17.5
	5 ampl	1 [20]	NA	NA	6.3	10.4
Ng, <i>Cancer</i> 2019 (61)	2 ex20	0 [0]	1 [50]	1 [50]	1.9	NA
Takeda, <i>Oncotarget</i> 2018 (78)	2 ex20	0 [0]	2 [100]	0	3.0	NA
Fang, <i>Clin Cancer Res</i> 2018 (67)	7 mut	1 [14]	0	6 [86]	NA	NA
<i>RET</i>						
Mazières, <i>Ann Oncol</i> 2019 (68)	16	1 [6]	3 [19]	12 [75]	2.1	21.3
Offin, <i>JCO PO</i> 2019 (11)	13	0 [0]	3 [23]	8 [62]	3.4	NA
Guisier, <i>J Thorac Oncol</i> 2018 (139)	9	3 [37]	2 [25]	3 [37]	7.6	NR
Dudnik, <i>Lung Cancer</i> 2018 (141)	5 <sup>b</sup>	0	NA	NA	3	14.9
Ng, <i>Cancer</i> 2019 (61)	2	0	1 [50]	1 [50]	2.73	NA
<i>ROS1</i>						
Mazières, <i>Ann Oncol</i> 2019 (68)	6	1 [17]	0	5 [83]	NA	NA
Bylicki, <i>Med Baltimore</i> 2020 (58)	1	NA	NA	1	1.4	2.8
Dudnik, <i>Lung Cancer</i> 2018 (141)	1	NA	NA	NA	0.1	0.1

<sup>a</sup>11 received immunotherapy as first-line treatment, two received anti-PD-1/anti-CTLA-4 combination treatment. <sup>b</sup>One patient with RET-mutated disease. ex 14, Exon 14 skipping mutations; ampl, Amplified; ex 20, Exon 20 mutations; mut, mutated; CR, complete responses; PR, partial responses; SD, stable diseases; PD, progressive diseases; NA, not available; mPFS, Median progression-free survival; mo, months; mOS, median overall survival; NR, not reached.

With regard to further molecular alterations, such as ALK, BRAF, MET, HER2, RET and ROS1, perspective evidences are lacking. ICIs in *ALK*-rearranged disease have

been marginally considered prospectively, but retrospective evidences are not encouraging. Given similarities between *ALK* and *ROS1* rearrangements, it is conceivable that

immunotherapy in this subgroup may lack of effectiveness. Differently, in *BRAF* or *MET*-driven NSCLC some signals of activity have been reported (68,139). Patients suffering from advanced, oncogene-addicted NSCLC suitable for targeted treatment should be exposed to all available lines of potentially active and effective kinase inhibitors, and then evaluated for the best setting of ICIs administration. Leaving immunotherapy in the post-TKI setting reduces in addition the risk of unexpected toxicities, as they are far more common when ICIs are administered before targeted therapies (89).

ICIs and TKIs will likely contribute as game changers also in the management of early stage NSCLC in the next future (146-150), with immunotherapy already being the standard of care in locally advanced NSCLC after chemoradiotherapy (42,43) regardless of mutational status. Molecular characterization will become fundamental even in early stage disease, to define the best treatment strategy and its integration with loco-regional treatments, especially in oncogene-addicted disease.

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