



Is there any place for immune-checkpoint inhibitors in the treatment algorithm of fusion-driven non-small cell lung cancer? – a literature review

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Abstract: The advent of immune-checkpoint inhibitors (ICIs) targeting the programmed death-1 (PD-1)/programmed death ligand-1 (PD-L1) axis, produced a paradigm change of the treatment algorithm for metastatic, non-oncogene addicted, non-small cell lung cancer (NSCLC). However, the majority of patients with oncogene-addicted disease have been excluded from the “immunotherapy revolution”, thus the clinical efficacy of these agents in this subset of patients remains largely unknown. Although pre-clinical evidence provided a good rationale to pursue the investigation of ICI treatment in specific subgroups of oncogene-addicted NSCLC, current available evidence suggested that tumors harboring molecular alterations likely do not represent the best candidate to single agent ICI therapy. Furthermore, the prospect of further improving overall survival (OS) with the combination of tyrosine kinase inhibitors (TKIs) and ICIs led to unexpected poor results and safety issues in recent phase I trials exploring different therapeutic associations. Conversely, the combination of immunotherapy and chemotherapy is emerging as a potential effective strategy in specific subsets of NSCLC patients harboring oncogenic drivers. In this review we particularly focus on the subgroup of patients whose disease harbor oncogenic rearrangements, summarizing current evidence from preclinical and clinical studies and discussing their practical implications, in order to define the potential role of ICIs in the clinical management of fusion-driven NSCLC.

Keywords: Immune-checkpoint inhibitors (ICIs); programmed death-1/programmed death ligand-1 (PD-1/PD-L1); rearrangements; fusion; non-small cell lung cancer (NSCLC)

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Introduction

The advent of targeted therapies and immune checkpoint inhibitors (ICIs) has radically changed the therapeutic landscape of non-small cell lung cancer (NSCLC) over the last years, certainly contributing to the increase of 5-year survival rate, reported to be 21.7% nowadays, compared to 17.2% about a decade ago (1). Although the efficacy of tyrosine kinase inhibitors (TKIs) is limited to a subset of NSCLC patients harboring specific oncogenic

drivers, their implementation in the clinical practice dramatically improved patients' survival and quality of life in stage IV diseases (2), delaying the use of less tolerated chemotherapeutic agents. Alongside epidermal growth factor receptor (*EGFR*), v-Raf murine sarcoma viral oncogene homolog B (*BRAF*), Kirsten rat sarcoma 2 viral oncogene homolog (*KRAS*) and c-*MET*-exon 14 mutations (hepatocyte growth factor receptor), oncogenic fusions involving anaplastic lymphoma kinase (*ALK*), v-ROS avian

UR2 sarcoma virus oncogene homolog 1 (*ROS1*), rearranged during transfection (*RET*), and tropomyosin receptor kinase A (*NTRK*) genes represent the most successfully druggable targets in NSCLC, with new-generation TKIs already available or coming soon in the clinical setting. This means to progressively extend the number of potential candidates to personalized treatment strategies in the upcoming years. Conversely, the majority of patients with oncogene-addicted NSCLC have been excluded from the “immunotherapy revolution”, due to the anticipated poor response from preclinical data (3) and the lack of activity observed in the small group of EGFR-positive patients included in the second-line ICIs clinical studies (4). As a consequence, the clinical development of ICIs, both as single agent and in combination with first-line platinum-based chemotherapy has been exclusively limited to the EGFR/ALK wild-type NSCLC population. In absence of prospective data on immune-chemotherapy combinations in oncogene-addicted NSCLC, a subgroup analysis of the phase III IMpower-150 trial showed that the survival benefit derived from the addition of atezolizumab to the bevacizumab-chemotherapy combination regimen in advanced non-squamous NSCLC, was extended also to the EGFR-mutant population [hazard ratio (HR): 0.60; 95% confidence intervals (CIs): 0.31–1.14] (5). This evidence has driven the regulatory approval of this treatment regimen after EGFR-TKI failure, but the low number of evaluated patients and the lack of detailed information regarding tumor molecular alterations and previous TKI lines reduced the scientific reliability and the clinical value of such data. Conversely, the prospect of further improving overall survival (OS) with the combination of TKIs and ICIs lead to unexpected poor results and safety issues in recent phase I trials exploring different drug associations. Based on current available clinical evidence, immunotherapy and TKIs are emerging as two different therapeutic approaches with clinical efficacy limited to two distinct, separate subsets of NSCLC patients. However, preclinical studies and translational data revealed interesting dynamic molecular networks between tumor cells intrinsic oncogenic signaling and immune microenvironment, with potential influence on immunomodulating process, which provide a strong rationale to pursue the investigation of ICI treatment efficacy in particular subsets of oncogene-addicted NSCLC. This review will particularly focus on the subgroup of patients whose disease harbors oncogenic rearrangements, summarizing current evidence from preclinical and clinical studies and discussing their practical implications, in order to define the potential role of ICIs therapy in the clinical

management of fusion-driven NSCLC. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at <http://dx.doi.org/10.21037/tlcr-20-710>).

Search strategy

The literature search was conducted using PubMed database. For each rearrangement analyzed in this review the following terms were used: “‘Rearrangement’ and PD-L1 expression”, “‘Rearrangement’ and immunotherapy”, “‘Rearrangement’ and checkpoint inhibitors” and “NSCLC Fusions” (e.g., “ALK and checkpoint inhibitors”). Relevant studies published between January 2015 and May 2020 were selected. Literature citations within selected studies were also searched to find other potentially relevant studies.

ALK

The introduction of second-generation ALK inhibitors into clinical practice has dramatically improved the survival outcomes of ALK-positive NSCLC, with unmatched results even compared to other oncogene-addicted NSCLC. Alectinib and brigatinib have largely replaced crizotinib as first line treatment in ALK-positive patients with advanced disease, based on the results of the phase III ALEX (6) and ALTA-1L (7) trial, respectively. Lorlatinib is the first third-generation ALK inhibitor that has been approved as a second line treatment after ALK-TKI progression in this subgroup of patients, based on the B7461001 phase II trial results (8). Nowadays, the treatment algorithm for advanced ALK-positive NSCLC should include a second-generation TKIs (alectinib or brigatinib preferred over ceritinib) in first line therapy, eventually followed by lorlatinib or platinum-based chemotherapy at disease progression. Immunotherapy represent a potential option in heavily pre-treated patients who maintain a good performance status.

Pre-clinical background

Several studies illustrated the correlation between ALK-rearrangements and programmed death ligand-1 (PD-L1) expression. PD-L1 mRNA and surface protein expression are significantly higher in EML4-ALK-positive lines compared to both EGFR and ALK wild-type cells. Moreover, wild-type cells transfected with an EML4-ALK expression vector showed an increase of PD-L1 levels, while alectinib downregulated PD-L1 expression in EML4-ALK-

positive models (9). PD-L1 TPS score usually increased in repeated biopsy after ALK-TKIs therapies, reaching about 57% in heavily pre-treated samples (10).

It has been largely demonstrated that ALK-rearrangements upregulates PD-L1 expression via STAT3 signaling in both anaplastic large cell lymphoma (11) and lung cancer (12). Indeed, PD-L1 expression significantly decreased in EML4-ALK-positive cell lines when treated with STAT3 inhibitors. Data from protein-DNA binding assays suggest that STAT3 exerts its activity by directly binding to PD-L1 promoter region. Marzec *et al.* used CRISPR/Cas9 library screening to find other nuclear proteins (GRB2/SOS1, IRF4, BATF3) that play a crucial role for ALK-mediated PD-L1 expression in NPM-ALK-positive anaplastic large-cell lymphoma (11). Indeed, these transcription factors seem to be equally involved for the PD-L1 upregulation in EML4-ALK-positive adenocarcinomas (ADCs). HIF-1 α cooperates with STAT3 to increase PD-L1 levels under hypoxia. While HIF-1 α is known to act as a transcription factor for PD-L1 in different tumor types (13), its effect seems to be amplified in EML4-ALK-positive lung cancer. The interaction between STAT3 and HIF-1 α might be critical to enhance PD-L1 expression in EML4-ALK-positive cell lines (12). Recently, Nouri *et al.* identified ALK as a critical regulator of the Hippo pathway, which seems to be involved in both tumorigenesis and immune evasion processes (14). The interaction between EML4-ALK and the yes-associated protein 1/transcriptional co-activator with PDZ binding motif (YAP/TAZ) complex resulted in a STAT3 independent PD-L1 upregulation (14).

Correlations between ALK-rearrangements and other known immune-related biomarkers, such as CD8⁺ T cell infiltration, HLA-class I receptor expression and total mutation burden (TMB), have been also investigated. The combination of PD-L1 expression on tumor or stromal cells and intratumoral infiltration by PD-1⁺CD8⁺ T cells tended to be more frequent in ALK-positive than in non-ALK-rearranged ADCs. In addition, high HLA-class I expression on tumor cells with intratumoral infiltration by PD-1⁺CD8⁺ T cells appeared to be more frequent in ALK-positive ADCs (15). Interestingly, a positive correlation between intratumoral infiltration by CD8⁺ T cells and ALK-rearrangements was not constantly observed in other tumors (16). Conversely, TMB level was significantly lower (mean 3.1 mutation/Mb) in ALK-positive lung cancer compared to that observed in unselected NSCLC patients (17). Although a prognostic role of these biomarkers in ALK-rearranged NSCLC has not been demonstrated

yet (15), in a large retrospective database including 715 EGFR/ALK-positive lung cancer samples, with only 10% reporting ALK-rearrangement, the detection of PD-L1⁺/CD8⁺ cells in the tumor microenvironment was associated to worse OS (44.3 months compared with 93.4 months in PD-L1⁻/CD8⁻ group) (18). Finally, pre-clinical data showed that the therapeutic inhibition of ALK oncogenic signaling increased T-cells interactions, proliferation and tumor infiltration, as well as inflammatory cytokine release, thus providing biological rationale for immune-target combination strategies (19).

Clinical evidence

Despite the theoretically favorable preclinical background, available evidence from different trials testing ICIs for ALK-rearranged ADCs have so far been disappointing. ICIs have been investigated either alone (prospectively and retrospectively) or in combination with chemotherapy or ALK-TKIs (*Table 1*).

ALK-positive ADCs, as well as other oncogene addicted NSCLC, were poorly represented in the majority of prospective clinical trials investigating single agent ICI both in second and first-line setting (20-22). The ATLANTIC study was a single arm trial investigating durvalumab in NSCLC patients who received at least two previous lines of treatment. In the Cohort 1, 111 patients with ALK and/or EGFR positive NSCLC were enrolled, including 16 patients with ALK-positive ADCs. Exclusive analysis for OS in the ALK-positive subgroup was not performed, but an exploratory post-hoc analysis showed that all objective responses in the cohort 1 occurred in EGFR⁺ patients (9%; 10 out of 111) (23). Only five EML4-ALK-positive patients were included in the OAK trial, comparing atezolizumab *vs.* docetaxel in previously treated NSCLC, while about 50% of the entire population was untested for ALK-rearrangements (24). Thus, any evaluation about the efficacy of atezolizumab in this subgroup is meaningless. The Impower-150 investigated the association between atezolizumab and bevacizumab with standard platinum-based chemotherapy in non-squamous NSCLC. Thirty-four patients with EML4-ALK-positive disease, experiencing disease progression to at least one previous treatment, were enrolled in the trial (13 in the experimental arm). In EGFR/ALK-positive population progression-free survival (PFS) and OS were longer within the chemo-immunotherapy combination compared to control arm (PFS: median, 8.3 *vs.* 6.8 months; HR, 0.61; 95% CI, 0.52 to 0.72; OS: median,

Table 1 ICIs activity and safety in fusion-driven NSCLC patients

Authors [year]	N. patients	Treatment	ORR	AEs grade ≥ 3
<i>ALK</i>				
Mazieres <i>et al.</i> [2019]	23	PD-1/PD-L1 inhibitors	0%	NR
Ng <i>et al.</i> [2019]	13	PD-1/PD-L1 inhibitors	0%	NR
Gainor <i>et al.</i> [2016]	6	PD-1/PD-L1 inhibitors	0%	NR
Heo <i>et al.</i> [2019]	14	PD-1/PD-L1 inhibitors	14.3%	NR
Bylicki <i>et al.</i> [2020]	8	PD-1/PD-L1 inhibitors	25%	8%**
Chalmers <i>et al.</i> [2019]	3	Crizotinib-ipilimumab	NR*	33%
Spigel <i>et al.</i> [2018]	13	Crizotinib-nivolumab	38%*	38%
Patel <i>et al.</i> [2020]	9	Crizotinib-pembrolizumab	55.6%	44%
Felip <i>et al.</i> [2020] (TKI naïve)	16	Ceritinib-nivolumab	69%	36%
Felip <i>et al.</i> [2020] (pre-treated)	20	Ceritinib-nivolumab	35%	
Kim <i>et al.</i> [2018]	21	Alectinib-atezolizumab	85.7%	57%
Shaw <i>et al.</i> [2018]	28	Lorlatinib-avelumab	46.4%	53.6%
<i>ROS1</i>				
Mazieres <i>et al.</i> [2019]	7	PD-1/PD-L1 inhibitors	17%	NR
Park <i>et al.</i> [2018]	12	CTLA4/PD-1/PD-L1 inhibitors	25%	NR
<i>RET</i>				
Offin <i>et al.</i> [2019]	16	CTLA4/PD-1/PD-L1 inhibitors	0%	NR
Mazieres <i>et al.</i> [2019]	16	PD-1/PD-L1 inhibitors	6%	NR
Guisier <i>et al.</i> [2020]	9	PD-1/PD-L1 inhibitors	37.5%	10%**
Sarfaty <i>et al.</i> [2017]	2	Pembrolizumab	0%	NR
Lu <i>et al.</i> [2020]	10	CTLA4/PD-1/PD-L1 inhibitors	20%	NR
<i>NRG1</i>				
Duruiseaux <i>et al.</i> [2019]	6	PD-1/PD-L1 inhibitors	0%	NR

*, treatment discontinued due to safety issues; **, overall population enrolled in the trial, included but not limited to ALK/RET positive NSCLC. ICI, immune-checkpoint inhibitor; NSCLC, non-small cell lung cancer; N., number; ORR, objective response rate; AEs, adverse events; PD-1, programmed death-1; PD-L1, programmed death ligand-1; CTLA-4, cytotoxic T-lymphocyte antigen 4; NR, not reported.

9.7 vs. 6.1 months; HR, 0.59; 95% CI, 0.37 to 0.94) (25). Considering the low number of included patients and the lack of efficacy analysis specifically devoted to ALK-positive subgroup, the exact efficacy of this combination in TKI-pre-treated patients with ALK-rearrangements remains currently controversial. A phase II prospective study is currently evaluating the efficacy of pembrolizumab in combination with platinum-based doublet chemotherapy in patients with ALK-rearranged NSCLC with progressive disease following prior TKIs (NCT03242915).

Additional data were available from retrospective studies and small case series. Among 551 pre-treated patients with advanced NSCLC included in the IMMUNOTARGET registry, 23 harbored ALK-rearrangements. All patients received a programmed death-1 (PD-1) or PD-L1 inhibitor at some point of their disease history, especially as a second- or third-line treatment (67%), and objective responses were not observed in anyone of the ALK-positive patients (26). These results are consistent with another retrospective series of 13 ALK-positive patients collected by Ng *et al.*,

where no response were achieved (27). Similar findings from other small series were reported, with overall response rate (ORR) to PD-1 blockade overall ranging from 0% to 25% in the ALK-rearranged population (28-30).

Despite a strong biological rationale and the high expectations regarding the association between TKI and immunotherapy, phase I clinical trials disappointing results discouraged to pursue this treatment strategy. In a phase 1 trial the CTLA4 inhibitor ipilimumab was studied in combination with erlotinib or crizotinib in EGFR and ALK-positive NSCLC, respectively. Both treatment arms were associated to unacceptable toxicity, with two of three ALK-positive patients developing hypophysitis and grade 2 pneumonia, respectively (31). Combinations of TKIs and PD1/PDL1 inhibitors were also characterized by high grade adverse events. CheckMate 370 was a 5-cohort, open-label phase 1/2 study investigating nivolumab in different settings. Within the cohort E, nivolumab (240 mg every 2 weeks) was associated with crizotinib (250 mg twice daily) as a first line therapy for advanced ALK-positive NSCLC. Among the 13 patients enrolled in the study, 5 (38%) developed severe hepatic toxicities, including two grade 5 toxicities. Hepatic adverse events were reported to be less common with single agent nivolumab (0.3% to 1.5%) (20,32) and crizotinib (2.3%) (33), suggesting an additive and synergistic toxic effect for the combination. Enrolment was closed and treatment discontinued in all other patients included in this cohort (34). Another trial investigating the association of pembrolizumab and crizotinib was terminated early due to the very slow accrual. Elevations in transaminase levels was the most common adverse event, but bilirubin increase or hepatic failure was not observed in this study, as toxicities were reversible with pembrolizumab discontinuation (35). Ceritinib and nivolumab combination was evaluated in an open-label, phase 1B study. The trial enrolled 16 TKI-naïve and 20 pre-treated ALK-positive patients to receive nivolumab (3 mg/kg every 2 weeks) plus ceritinib (three different dose levels, administered once daily with a low-fat meal). Despite the study planned a maximum dose of 600 mg/day for ceritinib, all patients received 300 mg/die (n=22) or 450 mg/die (n=14). Once again, a high rate (83%) of grade ≥ 3 adverse events was reported, with increase in AST/ALT or lipase levels, and rash being the most common. ORR and PFS were 69% and 16.6 months in the TKI-naïve and 35% and 4.6 months in the pre-treated subgroups, respectively (36). Although the combination showed some level of activity, particularly in presence of high PD-L1 expression, overall results were

comparable to those obtained with ceritinib monotherapy in the ASCEND-4 and ASCEND-5 trials, with the drawback of augmented toxicities (37,38). In another phase I trial, induction therapy with alectinib at the standard dose of 600 mg BID for a week was followed by the association of alectinib (600 mg BID) and atezolizumab (1,200 mg every 3 weeks) (39). Twenty-one ALK-positive patients who had not received any previous treatment were enrolled in the study. Since the median follow-up at the time of data cut off was just 13 months and considering the impressive outcome in terms of PFS reported with alectinib monotherapy in the ALEX trial (40), any assumption about the activity of this combination remains speculative. Conversely, the tolerability profile of the association was really poor, compared to single agent TKI, with 14 patients (67%) experiencing alectinib dose interruptions or modifications due to grade 3 adverse events (57.1% treatment-related, mainly rash and liver toxicity). Lastly, Javelin Lung 101 trial evaluated the combination of avelumab with crizotinib or lorlatinib in two different cohorts. The combination of avelumab and crizotinib was investigated in the ALK wild-type population. The avelumab-lorlatinib cohort included 28 ALK-positive patients, reaching an ORR of 46.4%, which could be considered a promising result in a population with unfavorable prognostic factors (36% had untreated brain metastasis, 71.4% received two or more previous TKIs) (41). The safety was again the main issue with grade ≥ 3 adverse events occurring in 53.6% of cases.

ROS1

ROS1 tyrosine kinase domains present high affinity with the ALK ones, therefore TKIs targeting ALK-rearrangements, crizotinib and lorlatinib, showed great levels of activity also in ROS1 positive patients (42,43). Entrectinib is a novel TKI that inhibits both ROS1 and NTRK fusion products, showing great efficacy in a heterogeneous group of ROS1 positive NSCLC included in an integrative analysis of three phase I/II trials. (44). Promising results were reported in early-phase clinical trials for repotrectinib and DS-6051b (45,46). Since crizotinib represents the current first-line standard of care in this subgroup of patients, single agent immunotherapy could be considered in patients progressed to previous TKI and chemotherapy.

Pre-clinical background

The correlation between ROS1 rearrangements and PD-

L1 expression or immunotherapy response is the least investigated so far among the druggable translocations in NSCLC. While ROS1 and ALK present high homology in their kinase domains, suggesting a similar effect on PD-L1 expression, there are current no preclinical data confirming this hypothesis. ROS1 positive tumors were poorly represented even in retrospective case series (27,47,48), preventing any conclusion about PD-L1 expression in this subgroup of patients. Importantly, ROS1 positive NSCLC shares with ALK- and RET- positive counterparts a lower TMB compared to wild type or EGFR-mutated adenocarcinomas (49).

Clinical evidence

Seven ROS1 positive NSCLC patients were enrolled within the IMMUNOTARGET cohort. ORR was 17%, while PFS and OS data were not available (26). In a retrospective Korean study 12 ROS1 positive NSCLC patients (among 103, 67% stage IV) received ICIs at some point of their treatment history. ORR was 25% and PFS ranged from 1.1 to 10.7 months (50) (Table 1). The presence of ROS1 positive NSCLC in prospective phase III trials investigating ICIs both as single agent and as combination with chemotherapy was not assessed, while phase I trials investigating crizotinib/lorlatinib and ICIs combinations were limited to ALK-positive patients.

RET

RET-rearranged NSCLC is getting more and more interest among clinicians with the upcoming advent of new selective RET inhibitors. Thus, searching for RET fusions is becoming more common in clinical practice alongside EGFR and BRAF mutations and ALK and ROS1 rearrangements. Pralsetinib (BLU-667) and selpercatinib (LOXO-292), are the two major compounds currently under clinical development, with promising activity emerging from the ARROW (51) and the LIBRETTO-001 (52) phase I trials, respectively. A phase III trial comparing selpercatinib to platinum-based chemotherapy with or without pembrolizumab as a first line treatment in RET positive NSCLC is currently ongoing (LIBRETTO-431, NCT04194944). Where clinical trials for selective RET inhibitors are not available, chemotherapy and/or immunotherapy remains the current standard first line treatment for RET positive NSCLC.

Pre-clinical background

As a recent molecular alteration for NSCLC, potential correlation between RET and PD-L1 expression has not been investigated yet on molecular basis. However, RET signaling pathway includes STAT family members (STAT1/3/5) (53), which are known to increase PD-L1 expression, as already stated above. In addition, data from studies on multiple endocrine neoplasia type 2 showed that RET positive papillary thyroid carcinoma display a significant immune infiltrate in the tumor microenvironment (54). Whether these results are applicable also to NSCLC remains uncertain. RET positive NSCLC presented significant PD-L1 expression in different case series (49,55-57), with PD-L1 positive (TPS $\geq 1\%$) RET-rearranged tumors accounting for 40–50% of all cases. Conversely, median TMB was significantly lower in RET positive as compared to wild type NSCLC (49,56), but similar to that reported for ALK and ROS1 positive NSCLC (49).

Clinical evidence

Screening for RET rearrangements was not required in the main prospective NSCLC trials with single agent ICIs or chemo-immunotherapy combinations, thus the number of RET positive cases enrolled, if any, as well as potential ICI efficacy in this subgroup of enrolled patients, remains currently unknown. Several retrospective series reported generally poor response to ICIs. Offin *et al.* collected 74 RET positive NSCLC patients, with 16 of them receiving PD-1/PD-L1 inhibitors at some point of their treatment history. No objective response was observed among the 13 patients assessed for clinical and/or radiological response and overall PFS was 3.4 months (56). These results are consistent with the RET cohort included within the IMMUNOTARGET registry, where only one of 16 evaluated patients achieved PR, with median PFS reaching 2.1 months (26). In another retrospective case series, two RET positive patients (out of 14 total cases) with PD-L1 TPS $>50\%$ received pembrolizumab as first line therapy. PD was observed for both patients after 1 and 2 months respectively (58). Baglivo *et al.* reported two cases of RET positive NSCLC with PD-L1 expression $>50\%$ who experienced hyper-progression under Pembrolizumab first line therapy, suggesting that knowing RET status at baseline could be crucial to exclude these patients from immunotherapy treatment (59). More encouraging

results were obtained by Guisier *et al.* in a small subgroup of nine RET-positive NSCLC patients who received pembrolizumab or nivolumab (89% as a second- or third-line therapy). Three patients achieved partial response and the disease control rate and PFS were 60% and 7.6 months respectively (57). Lastly, 11 patients received ICIs among 129 RET-rearranged NSCLC collected in 13 Chinese centers. Among 10 patients with evaluable response, disease control rate was 60%, and ORR was 20%. PFS was overall poor (3.8 months), but two patients had durable response of 10.4 and 11.5 months at data cut off. Interestingly, both patients harbored KIF5B-RET fusion and presented high PD-L1 expression (TPS >50%) (49) (Table 1). Efficacy of combinations between immunotherapy and selective RET inhibitors have not been assessed yet. As far as we know, there are not ongoing clinical trials evaluating this treatment strategy.

Emerging oncogene rearrangements

Neurotrophic tyrosine kinase- (NTRK), neuregulin 1- (NRG1), and fibroblast growth factor receptor 3- (FGFR3) fusions have been recently proposed as novel oncogene drivers for a small percentage of NSCLC (60-63). Selective TKIs targeting NTRK rearrangements, like entrectinib and larotrectinib, are currently being tested for several tumor types, (60) with both agents showing exciting activity also for NTRK positive NSCLC (64,65). However, where clinical trials for NTRK inhibitors are not available, chemotherapy and/or immunotherapy remains the standard first line treatment options for NTRK positive NSCLC. Alongside c-MET amplification and exon 14 skipping mutation, KIF5B-MET, HLA-DRB1-MET, and MET-ATXN7L1 fusions have also been recently reported as oncogenic drivers in NSCLC (66-68). The clinical relevance of these rearrangements is still unclear, but their onset could be unrelated to other oncogene alterations and previous TKI treatments. Although novel TKIs are currently being tested for the different c-MET alterations, MET fusions have been excluded from the majority of these clinical trials (e.g., NCT02864992, NCT04077099, NCT03940703, NCT03911193).

Pre-clinical background

Comprehensive genomic profiling showed a higher TMB and PD-L1 expression for NTRK rearranged NSCLC compared to other oncogene addicted tumors harboring

EGFR mutations, ALK or ROS1 rearrangements (69). However, NTRK fusions in NSCLC often co-exist with STK11 mutations, which have been associated to poor immunotherapy response in KRAS mutant disease (70). A global, multicenter network of thoracic oncologists (6 countries, 13 institutions) identified 80 patients with pathologically confirmed NRG1 fusion-positive NSCLCs; when tested, PD-L1 was found negative in most of these tumors (79%, 26/33) (71). Qin *et al.* evaluated TMB in FGFR rearranged NSCLC, showing relatively low levels (5.2 Mb), in the majority of tested adenocarcinomas, consistently with the results obtained for other oncogene addicted NSCLC. As expected, TMB was higher in squamous cell carcinomas (9.6 Mb) (63). c-MET activation induces PD-L1 expression regardless from JAK/STAT signaling pathway (72,73). It was associated also to the upregulation of other immunosuppressive genes and transcripts involved in angiogenesis and cell proliferation (72). Moreover, Wang *et al.* demonstrated that the inhibition of c-MET decreased indoleamine-2,3-dioxygenase expression (74), which exerts immunosuppressive effects on T-cells and natural killer cells (75). These data suggest that MET activation could be involved in the tumors immune escape process, likely contributing to an immunosuppressive microenvironment (76). Although specific conclusions for MET fusions cannot be currently drawn, it is likely that the high PD-L1 expression and low-TMB level found in c-MET exon 14 skipping mutated NSCLC samples (77) may be likely applied also to other MET alterations, including oncogenic rearrangements.

Clinical evidence

Duruisseaux *et al.* observed no ORR among 6 NSCLC patients harboring NRG1 fusions who were treated with anti-PD-1 or anti-PD-L1 therapy (71). Although the high frequency of high PD-L1 expression, single agent ICIs activity in c-MET exon 14 skipping mutated NSCLC patients was very poor within different retrospective series (26,77), while favorable outcomes to ICIs therapy have been observed in patients with high c-MET expression (78). No evidence is currently available regarding the clinical efficacy of ICIs in MET, NTRK, or FGFR3 rearranged NSCLCs.

Conclusions

The potential role of ICI therapy in NSCLC patients harboring oncogenic fusions represents an actual and

controversial topic which requires further investigation in dedicated studies. Pre-clinical data revealed that ALK/ROS1/RET rearranged NSCLC are mostly characterized by low TMB level, suggesting that high PD-L1 expression may just be an epiphenomenon of the oncogene pathway activity rather than a crucial mechanism of cancer immune-escape. Current available evidence (Table 1) overall showed that tumors harboring oncogene rearrangements likely do not represent the best candidate to single agent ICI therapy, with poor clinical responses to PD1/PD-L1 inhibitors reported across different retrospective studies including TKI pre-treated populations. The higher incidence of rare oncogene rearrangements may likely explain also the lower efficacy of first-line ICIs in never smoker patients with high PD-L1 expression (79), highlighting the issue of adequate molecular testing for upfront treatment selection. Despite a strong biological rationale and the high expectation regarding the association between TKI and immunotherapy, early clinical trials disappointing results discouraged to pursue this treatment strategy. Combination therapy with next-generation TKIs, which are usually associated to a lower toxicity, could still represents a viable option, worthy of investigation in dedicated trials. However, the specific impact of immunotherapy on already long-lasting TKI-related response might be difficult to prove and a serious evaluation of cost/effectiveness ratio, also in terms of financial toxicities, is mandatory. Considering the recent advent of immune-chemotherapy regimens in clinical practice, exploring the potential efficacy of this treatment strategy in specific subsets of NSCLC patients harboring oncogenic fusions represents a major topic for clinical research. Although the occurrence of ALK/ROS1 secondary mutations represent the main resistance mechanisms emerging under TKI therapy (80,81), however, a significant subgroup of ALK/ROS1+ NSCLC patients treated with second/first-generation TKI, and most of those treated with third-generation TKI develop a non-oncogene driver dependent mechanism of resistance, being the best candidate for a combination approach (82). Furthermore, the recent evidence that lorlatinib activity after second-generation TKI resistance is strictly dependent from the presence of secondary ALK mutations (83) is leading to the development of genomic-driven therapeutic sequences in ALK/ROS1 positive NSCLC patients, ultimately favoring the investigation of alternative strategies in mutation-negative subgroups. The large-scale spreading of next generations sequencing panels will likely lead to an increased detection of rare oncogene

rearrangement in NSCLC, with a potential correlation to both PD-L1 expression and ICIs' efficacy. Considering the low prevalence of oncogenic fusions in the overall NSCLC population, the design of prospective clinical studies in this subset of patients represents a real challenge for the academic community, but remains the best way to definitively assess whether there will be any place for ICIs therapy in the treatment algorithm of fusion driven NSCLC.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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