Review Article

Emerging drivers in non-small cell lung cancer, is there a role for immunotherapy?—a narrative review

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Background and Objective: Immunotherapy and novel targeted therapies are revolutionizing the outcomes for patients with non-small cell lung cancer (NSCLC). Immune checkpoint inhibitors (ICIs) historically had a marginal role in treating patients with "common" oncogenic drivers, however there's still little evidence when it comes to uncommon and emerging molecular targets. The aim of this narrative review is to analyze the impact of immunotherapy in NSCLC harboring uncommon and novel driver mutations.

Methods: All searches were performed on MEDLINE/PubMed matching the keywords of NSCLC, immunotherapy, and the single mutations in order to obtain an oncogene-specific literature. We excluded from our research EGFR, ALK and ROS-1 mutations due to the already established role of target therapy in tumors bearing these driver mutations. We also excluded all those mutations with no target-specific therapy approved, for it was impossible to compare immunotherapy with other specific treatments. Non-English literature was excluded. All searches were conducted between May and September 2022.

Key Content and Findings: The immunologic environment and the smoking signature are predominant features in determining response rates and survival outcomes for patients treated with immunotherapy. Consistently with this statement, data from literature underline that among the oncogene-addicted family, patients carrying KRAS G12C or BRAF mutation gather better results with ICIs. On the contrary, patients harboring mutations such as RET, NTRK or EGFR's Insertion of exon 20, with classical oncogene-addicted presentation (i.e., non-smoker, young females), tend to be refractory to immunotherapy. Many questions remain unsolved for other druggable mutations such as cMET, where the type of alteration seems to be related to the immune-sensitivity, or HER-2 with contrasting results from one study to another.

Conclusions: Target therapy still plays the main role in oncogene-addicted NSCLC's treatment, although a deepened understanding of molecular profiling could probably open new perspectives for the use of immunotherapy even in this setting, given the promising results obtained with some specific mutations. New prospective studies could solve this challenging question.

Keywords: Non-small cell lung cancer (NSCLC); oncogene-addicted; immunotherapy; immune checkpoints

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Introduction

The treatment scenario in non-small cell lung cancer (NSCLC) is rapidly evolving thanks to the advent of immunotherapy and novel targeted therapies, which has led to the increasing use of driver mutations and predictive biomarkers to guide therapeutical choices: in the last decade, the progress in the knowledge of molecular biology has led to the identification of new oncogenic drivers and therapeutic targets for tyrosine kinase inhibitors (TKIs). The biggest part of molecular drivers is found in young non-smoker patients affected by the adenocarcinoma subtype, but this assumption is less valid for KRAS mutations, which are more frequent in adenocarcinomas but are consistent also in squamous cell carcinomas and in patients with smoking history. In this context, molecular testing has acquired a critical role due to the several proofs of the efficacy of TKIs when compared with chemotherapy: gene-specific treatments including *EGFR* mutations (anti-EGFR TKIs) and *ALK* and *ROS1* rearrangements (ALK inhibitors), already demonstrated prolonged survival and significantly higher response rates where chemotherapy and immunotherapy have limited effects. Immune checkpoint inhibitors (ICIs) are ineffective in most patients with "common" oncogenic drivers (1), consequently patients harboring EGFR or ALK oncogene-addiction are usually excluded from immunotherapy-based studies while lots of studies already demonstrated the efficacy of TKIs such as Crizotinib and Entrectinib in patients carrying ROS-1 fusions. The potential role of immunotherapy in emerging molecular targets, such as BRAF, KRAS G12C, EGFR insertions of exon 20, HER2, MET, RET and NTRK mutations, is still debated (2) and unexplored.

An immunosuppressive tumor environment as well as a lower number of neo-antigens (3,4), which are the most credited reason for the inefficacy of ICI treatment (5), often characterize tumors harboring a driver mutation. However, not all the molecular targets are equal when faced with immunotherapy (4), especially considering the different characteristics of patients and that smoke-induced mutations may promote pro-inflammatory cancer subtypes and have improved response patterns (6).

In this review we summarize the main evidence on the role of immunotherapy in NSCLC harboring uncommon and emerging driver mutations. We considered "emerging" driver all those mutations for which targeted therapies are under development or approval. We present this article in accordance with the Narrative Review reporting checklist (available at https://pcm.amegroups.com/article/view/10.21037/pcm-22-33/rc).

Methods

We searched MEDLINE/PubMed for English-language literature using the terms "non-small cell lung cancer", "NSCLC", "immunotherapy", "oncogene addicted", "checkpoint inhibitors", "KRAS", "BRAF", "RET", "NTRK", "HER-2", "EGFR Exon-20", "MET" (*Table 1*). We differently matched the keywords on the basis of the single mutation in order to gather oncogene-specific literature and data. We excluded from our research EGFR, ALK and ROS-1 mutations because there are already validated target-therapies and literature data showing poor response to immunotherapy. We also excluded all those mutations with no target-specific therapy approved, for it was impossible to compare immunotherapy with other specific treatments. All searches were conducted between May and September 2022. Non-English and pre-2015 publications were excluded.

Discussion

KRAS mutations

KRAS mutations are the most frequent proto-oncogene mutations in NSCLC, with a prevalence of 20% to 30% of non-squamous NSCLC depending on the regional variations (7). Mutations in the KRAS gene often occur in codons 12 and 13, with the G12C, G12D and G12V mutations together responsible approximately for the 70% of the events.

The vast heterogeneity found in KRAS mutations and co-mutational status is the main reason for the several failures in developing a target-therapy. The CodeBreaK100 (8) trial recently changed this trend with the introduction of Sotorasib, a mutation-specific drug targeting KRAS G12C mutated NSCLC. In a population of heavily pre-treated patients, Sotorasib achieved an 80% of disease control rate (DCR) with a median progression-free survival (PFS) of 6.8 months; these results were confirmed with the recent presentation of CodeBreaK200 (9), where Sotorasib was tested versus Docetaxel with a 1:1 randomization in patients with KRAS G12C mutation who progressed after prior platinum-based chemotherapy and a checkpoint inhibitor. At a median follow-up of 17.7 months, hazard ratio (HR) for PFS was 0.66 with an overall response rate (ORR) of 28.1% *vs.* 13.2%. Although delivering worse performances if compared to other gene-directed treatments, these results

Table 1 Systematic search strategy

Items	Specification
Date of search	May 1st, 2022 to September 21st, 2022
Databases and other sources searched	MEDLINE/PubMed
Search terms used	"non-small cell lung cancer", "NSCLC", "immunotherapy", "oncogene addicted", "checkpoint inhibitors", "KRAS", "BRAF", "RET", "NTRK", "HER-2", "EGFR Exon-20", "MET"
Timeframe	January 1st, 2015 to September 21st, 2022
Inclusion and exclusion criteria	Excluded non-English and pre-2015 publications
Selection process	LB, VS and MR independently reviewed and selected studies from PubMed/Medline

NSCLC, non-small cell lung cancer.

have granted the approval for KRAS G12C pre-treated NSCLC. In the same context, the KRYSTAL-1 (10) trial investigated the efficacy of the G12C-targeted Adagrasib.

Differently from the classic non-smoker pattern in the family of non-squamous cell Lung Cancers bearing driver mutations, KRAS G12C mutations usually have a stronger correlation with the smoking status, as also confirmed by their strict association with tobacco-induced mutations. Consistently with this finding, patients harboring KRAS mutations often show higher tumor mutation burden (TMB) values when compared with other tumors with oncogenic driver alterations. It has been theorized a possible role for G12C mutations as a predictor of better ICI-related outcomes (11,12), but there is also evidence that response rates mostly depend on the programmed death-ligand 1 (PD-L1) expression (7,13) and above all on the smoker/non-smoker status. According to the IMMUNOTARGET registry, in the subgroups of patients with oncogene-addicted disease treated with ICIs, the KRAS one was the most performing, with a 26% response rate versus an average of 12.7% in the population including all the other targetable mutations (2). Moreover, KRAS mutations often occur with co-mutations that characterize specific patterns: Skoulidis *et al.* classified KRAS-mutated NSCLC into three subgroups (14): the KL expressing STK11 and KEAP co-mutations, the KP with TP53 and the KC with CDKN2A/B and with lower TTF-1 expression. Each of these groups has a specific behavior towards ICIs: the KP sub-type often comes with high tumor-infiltrating lymphocytes (TILs) levels and higher PD-L1, resulting in better ICI-related results and overall outcomes, while KC and mainly KL subgroups represent "colder" tumors with lower response rates and overall survival (OS) (15), also due to the role STK11 as an independent inflammatory down-regulator and a predictor of worse performances when treated with ICIs.

To date, in such a complex context, immunotherapy-based regimens (single agents or combined with platinum-based chemotherapy) are the best option in first line treatment of metastatic KRAS G12C NSCLC, also due to the modest effective target-therapies. In this context, a recent safety report of the phase Ib CodeBreak 100/101 trials, showed controversial results about the possible combination of Sotorasib with immunotherapy (16): a total of 58 patients were randomized to receive a lead-in dose of Sotorasib and a subsequent immunotherapy (Atezolizumab or Pembrolizumab) or a combination therapy of Sotorasib plus Atezolizumab or Pembrolizumab. Even though across all the cohorts the combination therapy achieved a 29% of ORR and an 83% of DCR with a duration of response (DoR) of 17.9 months in a pre-treated population, the safety reports showed worrying toxicity rates, with high incidence of grade ≥3 treatment-related adverse events (TRAEs) the most common grade ≥3 TRAE was the hepatotoxicity, with a median onset of approximately 2 months after the beginning of the treatment. Interestingly, the lead-in cohort gathered minor toxicity rates than the combination arms, making it a possible strategy to investigate in the future. Further studies are needed to better select the population who could best benefit from ICIs and to possible combination treatments.

RET fusions

RET fusion is one of the rarest targetable mutation in NSCLC, representing the 1–2% of cases. As the result of the cancerogenic hit is a fusion-gene, lots of rearrangements may happen, with the *KIF5B* gene representing most of the fusion partners (about 50% to 60% of the cases) (17).

Targeting the fusion of RET has been challenging in the past, with the main attempts regarding multikinase inhibitors such as Vandetanib and Cabozantinib which showed some clinical activity but without solid results. The landscape recently changed with the results of the phase II studies LIBRETTO (18) and ARROW (19) which led to the introduction of RET-specific drugs, Selpercatinib and Pralsetinib, respectively. With an ORR of respectively 85% and 70% in treatment-naïve patients, these TKIs could represent the best answer to an unmet clinical need for these patients, historically characterized by poor prognosis.

Given the nature of "emerging and rare" NSCLC mutation, data from ICIs effectiveness in RET-positive cancers mostly come from retrospective studies and case reports (20). According to literature, tumors harboring this fusion gene appear to be among the "coldest" lung cancers, with a median TMB of 1.75 mutations/MB (*vs.* 5.27 in RET-wt) (21). The tumor environment presents the classic pattern of non-smoker oncogene-addicted patient with a low production of neoantigens and an intrinsic resistance to immunostimulating-factors, possibly explaining the poor results obtained by immunotherapy across the studies regardless of the line of treatment and the PD-L1 expression: median PFS range from 2.1 months in the IMMUNOTARGET trial (2), to 7.6 months in the real-world experience from Guisier *et al.* (22).

The advent of new specific TKIs and the historical role of Pemetrexed-based chemotherapy, probably confine the use of ICIs in this setting as ancillary to chemotherapy.

BRAF mutations

BRAF mutations account for about the 5% of the oncogenic driver mutations in NSCLC.

The mutational status in this family is complex and various, with most of the clinical studies dividing the court into two main groups: V600 (gathering circa the 50%) and non-V600 mutations, mostly occurring respectively in non-smokers and former/current smokers, with the already known different ICI sensibility. A more recent pre-clinical classification better expresses the high level of mutational subtypes, differentiating three subgroups: class I including all the codonic substitutions generating constitutively active kinases and therefore all the V600 types, which are already proven to be sensible to TKIs, class II comprising the mutations or fusions and an intermediate/high kinase activity and class III paradoxically characterized by kinases with little or no residual activity (23).

The approval of TKI combination therapy with Dabrafenib-Trametinib comes from different phase-II studies where the doublet of BRAF and MEK inhibitors showed great PFS and OS outcomes (24,25) with a median PFS of 17.5 months and an OS of 25.5 months assessed in the retrospective French real-world study of BRAF-mutant metastatic NSCLC, in a group of patients historically characterized by poor outcomes. Data coming from real-world and retrospective analyses confirmed the sensitivity to TKIs mostly for patients bearing V600 mutations, with insufficient results when applied to non-V600.

The limited number of cases and the difficulty in recruiting patients for clinical studies make the role of immunotherapy in this family pretty much debated (26). Among the oncogene-addicted NSCLC, BRAF-mutated tumors show a higher response rate (23), with survival performances that tend to be like those obtained in the KRAS subgroup (27). Moreover, across the retrospective literature quite a few patients were smokers or former-smokers (28), with significative differences in survival outcomes and sharp benefit for the smokers, as often seen for all NSCLC treated with immunotherapy.

While TKIs doublet of Dabrafenib-Trametinib still plays the main role in V600 bearers, ICIs may have some activity especially in non-V600 tumors and above all in smokers (29). In the view of identifying those who best benefit from immunotherapy, further analyses are also required on the basis of melanoma-derived experience, since ICIs seems to be better performing when administered in first line, with TKIs keeping their efficacy in second line too.

NTRK fusions

NTRK fusion genes coming from its three forms (NTRK1, 2 and 3) are responsible for a very low number of NSCLC with a prevalence standing below the 1%, with even lower numbers in several other cancers such as gastro-intestinal (GI) tract (30).

Entrectinib and Larotrectinib are the main players in first line NTRK-mutated lung cancers. Their registration phase II studies, STARTRK-1 (31) and NAVIGATE (32) respectively, showed improved PFS and OS with feasible safety results, and obtained the agnostic approval for patients bearing NTRK fusion gene.

The only notions regarding the relation between NTRK and ICIs come from small case series (33). Previous reports documented some clinical efficacy in NTRK-fusion positive patients (34), but data are too limited to state if this finding

has any statistical confirmation. Of note, an interesting correlation between NTRK fusions and microsatellites instability-high (MSI-H) as well as elevated levels of TMB was found in some samples (30), creating a rationale for a possible response to ICIs and representing a fascinating area for clinical research. However, the lack of evidence on the benefit form immunotherapy, the results gained by first generation TKIs and the pathological proof of a hostile tumor environment to immune stimulation, make ICIs a second-to-third line option, only in presence of multidrug TKI-resistance.

HER-2 alterations

HER-2 gene expression alterations include mutations, amplifications and overexpression which globally characterize about the 3% of non-squamous NSCLC. Among these, the most common mutation is the insertion of exon 20 (80% of cases).

After several failed attempts at targeting HER-2 positive lung cancers, in the phase II Destiny-Lung-01 trial (35) the Trastuzumab-Deruxtecan obtained durable responses and effective results with feasible safety.

Efficacy of immunotherapy is largely unknown due to the small number of patients and trials. HER-2 cancers appear similar to EGFR-mutated tumors (36), characterized by very little sensitivity to ICIs as a result of a cold tumor microenvironment (34). A Chinese case-series documented some clinical responses to the combination of chemo-immunotherapy (37), suggesting a possible role as first line, with due limits of the small number of treated patients.

HER-2 lung cancer remains among the most difficult to treat. Chemo-immunotherapy combination seems to be the best option as front-line treatment, even if the promising results coming from Trastuzumab-Deruxtecan may change this paradigm in the next future. ICIs should be probably considered in combination with chemotherapy or in later lines of treatment.

MET amplification and exon 14 skipping mutation

MET amplification and exon 14 skipping are globally found in 3–4% of lung cancers. The type of alteration of MET currently distinguishes three different groups with different treatment sensitivity: the already described exon 14 skipping and the MET amplification group, divided into high and low amplified, with therapeutic gene copy number (GCN) cutoff set at 10. The differences between the subgroups are vast: if MET exon 14 mostly acts as a typical oncogene-addicted disease, generally harboring in non-smoker patients, with little or no co-mutation and bearing low levels of TMB, MET amplification incorporates frequently high TMB levels together with many co-occurring mutations with particular effect on the GCN-high group. Of note, there's been reports about the tendency of non-squamous NSCLCs carrying the MET exon 14 skipping to be often PD-L1 enriched (38,39), even though with no therapeutic improvements.

Historically, MET-mutated NSCLC are chemorefractory but can now benefit from gene-specific therapies [such as Capmatinib (40) and Tepotinib (41)], being mainly effective on MET exon 14 and MET amplification cancers with high GCN (>10).

ICIs-related outcomes are generally unsatisfying (42), even if with little evidence and some exceptions (43). In a German study evaluating the impact of immunotherapy in MET-altered disease, a clear difference emerged between MET exon 14 and MET amplification family (44), with the second gaining significant improvements in PFS when treated with ICIs, confirming the clearly different nature of these two alterations (45). A recent work by Guisier *et al.* (46), retrospectively explored the activity of first-line Pembrolizumab in NSCLCs with MET exon14 skipping and PD-L1 ≥50%. Among the 24 patients enrolled, the ORR was 43%, while the PFS and OS where 3.5 and 12.1 months respectively, with better outcomes for patients whose histology was adenocarcinoma. Taken together, even if with the limits of the numerical sample and the retrospective nature of the study, this study showed some activity in these patients, with due limitations if again compared with the emerging targeted strategies.

MET-altered NSCLCs demonstrated to be highly sensitive to specific TKIs, however the subgroup of GCN-low in MET amplification still shows no benefit when treated with targeted-therapy. In a context that seems to be favorable, ICIs, possibly combined with CT, may be an option for these patients.

EGFR exon 20 insertions (Ex20ins)

EGFR Ex20ins occurs in the 7% of the EGFR mutated NSCLC and represents the main insensitive mutation to anti-EGFR TKIs. As this is an important unmet clinical need, ongoing trials are investigating the efficacy of targeted therapies such as the bi-specific conjugate antibody Amivantamab (47) and the exon-20-specific TKI Mobocertinib (48). Phase II trials already achieved satisfying

results in term of objective response and DCR.

The lack of large clinical immunotherapy-related studies involving EGFR-mutated patients, also affects this subpopulation with the result of the absence of large cohorts covering ICI-related outcomes in EGFR Ex20Ins. Since the prototype patient carrying this mutation reflects the cancer-dependent nonsmoking phenotype, most studies on ICI role show limited results (49). Likewise, it is unclear whether adding ICI to platinum-based chemotherapy improves outcomes (50). In this regard, a retrospective study from Lau *et al.* recently documented a clinical benefit in the Ex20Ins of EGFR and HER-2 from immunotherapy (51), pointing out the need of larger scale trials to evaluate this subset.

To date, platinum and pemetrexed-based regimens are the most effective first-line treatments. The adding of ICIs has doubting benefits. Newly introduced targeted therapies will probably change the landscape in this setting.

Conclusions

The efficacy of immunotherapy in NSCLC expressing the emerging drivers is still little unclear. Undoubtedly, the most promising and reliable results come from the trials with target therapies. However, the paradigm according to which immunotherapy is ineffective in oncogene-addicted disease could be disproved, since some mutations can be associated with good responses to ICIs, making the choice of the best treatment for the single patient even more challenging in the future.

Large-scale prospective studies exploring the real role of ICIs are needed in order to optimize therapeutic choices and patient selection.

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