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# Immunotherapy in non-small cell lung cancer harbouring driver mutations

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## Introduction

Lung cancer is the leading cause of cancer-related death globally [1]. Non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers, and lung adenocarcinoma (LUAD) is the major subtype of NSCLC [1]. The majority of patients with NSCLC are diagnosed at advanced stages, where chemotherapy has only limited efficacy, at the price of significant toxicity [2]. The advent of molecular targeted therapies against driver oncogenes such as EGFR mutations and ALK fusions have altered the therapeutic landscape of subsets of oncogene driven NSCLC [3] (Fig. 1). Despite these life-prolonging advances in NSCLC, the majority of patients ultimately acquire resistance to targeted therapies through a variety of mechanisms, resulting in cancer progression [3]. The recent introduction of immune checkpoint inhibitors (ICIs), including antibodies against programmed cell death-1 (PD-1), programmed cell death ligand-1 (PD-L1) and cytotoxic T-cell lymphocyte antigen-4 (CTLA4), can confer a durable response in a subset of patients, raising the hope of a "cure" [4-6]. However, the therapeutic role of ICIs in oncogene-driven NSCLC remains unclear, as the vast majority of trials was conducted without patients harbouring established oncogenic mutations [7-9].

Whether ICIs have a role among these patients, and if so, when, is controversial. Most of the evidence currently available pertaining to immunotherapy in patients with oncogene-driven NSCLC comes from either subgroup analyses of clinical trials, small phase I or II non-controlled trials with combination regimens (generally including a targeted TKI as a backbone), or retrospective analyses from real-world data. In most ICI trials, patients with *EGFR* or *ALK* alterations are excluded, but the presence of other oncogenic drivers (e.g. *MET*, *RET*, *ROS1*, *BRAF* or *KRAS*) are neither detailed nor considered exclusion criteria. Consequently, the level of evidence supporting the use of immunotherapy in patients with NSCLC and driver mutations is quite low, and clinical decisions require a rigorous judgment balancing the benefit and harm to the patient.

The evolution of tumours bearing a molecular alteration usually depends on a single dominant mechanism following the principle of oncogenic addiction, which has been described as the dependence of tumour cells upon the specific activity of an activated oncogene [10]. A single mutation or translocation is supposed to confer a survival advantage to the respective cells, and it is usually isolated, explaining the low tumour mutation burden (TMB) observed in these tumours [11], and a less inflammatory tumour microenvironment, poor in tumour-infiltrating $CD8^+$ lymphocytes. These facts might, therefore play a role in the lack of sensitivity to ICIs in oncogene-driven lung cancer [12].

Herein, we explore the role and impact of ICIs in NSCLC harbouring other oncogenic driver alterations and discuss the possible biological rationale to explain the lack of sensitivity to ICIs in these diseases

## EGFRxxx

The monomeric transmembrane epidermal growth factor receptor, *EGFR*, is a receptor tyrosine kinase involved in major cell proliferation pathways. It primarily exerts this function through the RAS-RAF-MAPK-MEK, PI3K-AKT-mTOR and STAT pathways. EGFR activating mutations are among the most frequent oncogenic alterations in NSCLC. In lung cancer, they are most prevalent among never or light smokers and young, Asian, female patients. The incidence of EGFR mutations varies significantly by ethnicity. Among Caucasians with any stage of lung adenocarcinoma, they occur in 15% to 27% of patients, depending on the stage, while this can reach 62% in East Asians with advanced disease [13,14]

The efficacy of ICIs among patients with EGFR activating mutations in NSCLC appears to be quite limited, though most data are from early phase or retrospective trials [14]. In the phase I CA209-012 and Keynote 001 trials, front-line ICIs provided lower response rates (14% versus

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30% and 16% versus 37%, respectively) in patients with EGFR mutant versus wild-type advanced NSCLC [15]. The poor response was independent of PD-L1 status. Similarly, survival results were inferior in the EGFR subgroups.

In a phase II trial of upfront pembrolizumab in TKI-naïve EGFR mutated lung cancer patients, the RR was 0% after the first 11 patients, leading to early trial discontinuation [15]. Furthermore, two patients who were subsequently treated with EGFR TKIs therapy died within 6 months, one from toxic pneumonitis [15].

The phase II BIRCH trial, assessing the PD-L1 inhibitor, atezolizumab, in different lines of therapy in NSCLC, included a subgroup analysis about EGFR mutant patients. In first-line, the response was similar among the 13 EGFR mutant patients (19%) was similar to that among wild-type (23%) patients, though the small numbers makes interpreting these results difficult. Among the 32 remaining EGFR mutant patients in second-line or above, there was almost no response and outcomes were far inferior to those of wild-type patients [16].

In the phase II, single-arm, ATLANTIC trial durvalumab was assessed among pretreated NSCLC patients. Among EGFR or ALK altered patients, outcomes were inferior to wild-type patients, independently of PD-L1 expression [17]. The only randomised data available on the efficacy of ICIs in *EGFR* mutated NSCLC patients come from the IMpower 150 trial, a randomised phase 3 study in first-line treatment with patients randomised (1:1:1) to receive atezolizumab-bevacizumab-carboplatin-paclitaxel (ABCP), atezolizumab-carboplatin-paclitaxel (ACP), or bevacizumab carboplatin-paclitaxel BCP every three weeks [18]. Efficacy was assessed in key subgroups within the intention-to-treat population, including patients with EGFR mutations (both sensitising and non-sensitising; EGFR-positive) previously treated with one or more tyrosine kinase inhibitors. The analysis showed an improved OS with ABCP versus BCP in patients with sensitising EGFR mutations (median overall survival not reached with ABCP [26/400] vs 17·5 months with BCP [32/400]; HR 0·31 [95% CI 0·11–0·83]). Despite its limitations, IMpower 150 remains the only study that included and clearly analysed data on an *EGFR* mutated population treated with a combination of chemotherapy and ICIs.

**ALKxxx**

*ALK* is a transmembrane receptor tyrosine kinase that consists of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain [19]. Since the initial Nucleophosmin (*NPM*)-*ALK* fusion protein described in anaplastic large cell lymphoma (ALCL) in 1994 [20], several *ALK* gene alterations have been identified across different tumour types, including point mutations, deletions, insertions and rearrangements leading to *ALK* reactivation. The Echinoderm Microtubule-associated protein-Like 4 (*EML4*)-ALK is the most prevalent in NSCLC [21]. When tumour growth is driven by constitutive activation of the *ALK* fusion oncogene, they are susceptible to an ATP analogue inhibitor of *ALK*. There are actually 5 *ALK* tyrosine kinase inhibitors (TKIs) that have shown superior efficacy and a more tolerable toxicity profile than chemotherapy in first-line in patients with advanced NSCLC and an *ALK* [22,23].

The data about ICI efficacy in patients with NSCLC harbouring an *ALK* rearrangement are scarce but suggests very poor activity of single agent ICIs. In the phase 2 ATLANTIC trial, the efficacy of durvalumab was evaluated in NSCLC patients who had received at least two prior lines systemic therapy. Fifteen patients harboured *ALK* alterations, and no response was registered in that group [17]. Similar data were published on the IMMUNOTARGET study where 23 *ALK*-rearranged patients were treated with ICIs, without any responses. Further supporting these results, the Massachusetts General Hospital oncologist group published a retrospective analysis on 6 patients with *ALK-rearranged* NSCLC treated with ICIs, showing again no response [13]. Further data were presented in a retrospective multicenter French study in which 2 out of 8 *ALK*-positive patients, treated with ICIs, achieved a partial response [24].

Finally, an arm of the phase 3 IMpower150 trial evaluated the safety and efficacy of chemotherapy with atezolizumab and bevacizumab in non-squamous metastatic NSCLC [25]. Thirteen percent of patients harboured *ALK* rearrangements or EGFR mutation, all pre-treated with TKIs. For the analysis, *ALK-positive* patients were grouped together with patients harbouring an EGFR mutation, making any interpretation quite difficult. In the 34 ALK-positive patients included in the study, no statistically significant differences were observed in PFS for the quadruplet combination compared with the bevacizumab/chemotherapy arm (8.3 vs 5.9 months; HR, 0.65; nonsignificant) [25]. Similar findings were seen in the IMpower130 trial, in which 44 patients with NSCLC had *ALK*-rearranged tumours, and the *EGFR/ALK* group obtained similar outcomes in both treatment groups of chemotherapy with and without atezolizumab [26].

Though these data are scant, ICIs as single agents do not appear

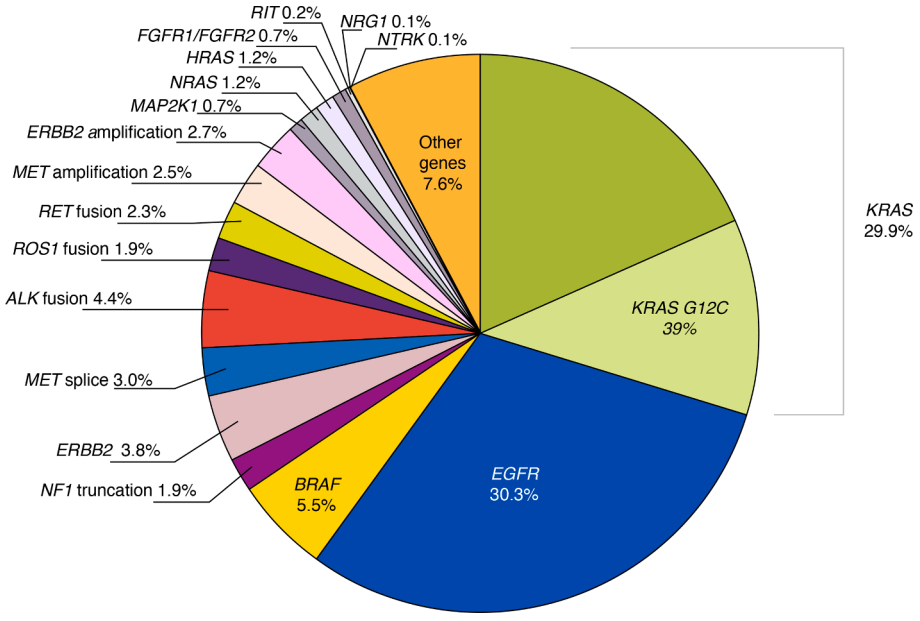


**Fig. 1.** Prevalence oncogenic-drivers NSCLC, image adapted from Skoulidis et al. [92].

promising in *ALK-rearranged* NSCLC. Chemotherapy remains the standard of care after exhaustion of *ALK* TKIs. Whether to add ICIs to chemotherapy or even consider a quadruplet, as per IMpower 150, remains unclear and further prospective data are warranted to address the question.

**ROS1xxx**

The *ROS1* gene belongs to the subfamily of tyrosine kinase insulin receptor genes [27]. *ROS1* fusions are identified in about in 2.5% of the patients with lung adenocarcinoma and at even higher frequencies in spitzoid neoplasms and inflammatory myofibroblastic tumours [28]. So far, 26 genes have been identified as fusion partners for *ROS1*. Interestingly, some of them can fuse with *RET* and *ALK*. All the fusion proteins retain the *ROS1* kinase domain, but rarely its transmembrane domain. Most of the partners have dimerization domains that are retained in the fusion, presumably leading to constitutive *ROS1* tyrosine kinase activation. Some partners have transmembrane domains that are retained or not in the chimeric proteins. Several drugs that bind to the ATP-binding site of their target enzymes are now used or under development. There are several tyrosine kinase inhibitors approved by the Food and Drug Administration (FDA) for the treatment of *ROS1* positive NSCLC: crizotinib, lorlatinib, entrectinib [29]. The efficacy of ICIs in patients with *ROS1* fusion-positive metastatic NSCLC patients is unclear. However, the IMMUNOTARGET registry offers a pessimistic outlook, with 5 of the 6 included patients presenting with progressive disease to single-agent ICIs, and a response rate of 17% (1 patient), with a median OS of 18.4 months [7.0; NR [14]].

A case report about a 52-year-old male former (15 pack-years) smoker, diagnosed with metastatic lung adenocarcinoma, was recently published. He received first-line treatment with carboplatin-pemetrexed and bevacizumab with a good response, followed by maintenance with pemetrexed and bevacizumab for more than one year. Due to progression, the patient was started on nivolumab (anti-PD-1) achieving partial response. Seven months thereafter, the original lung biopsy specimen was sent for screening as part of a clinical trial, and a ROS1 gene rearrangement was identified. Given the excellent response, nivolumab was continued and a scan performed a few months later showed a complete radiographic response, sustained for more than two years at the time of the publication. This patient was found to have a novel ROS1 fusion with non-muscle heavy chain 9 gene (MYH9) [30]. The breakpoint occurring in ROS1 exon 36 had not been previously reported. Both wild-type and fusion ROS1 transcription were found in this patient. It was the first report of a ROS1-rearranged lung adenocarcinoma demonstrating a complete radiographic response to ICIs, with a progression-free survival of 3.5 years. This unique case highlights the potential role of ICIs in ROS1 fusion-positive NSCLC. From these anecdotal cases, it may be possible that at least a subset of patients with ROS1 rearrangements may be immunogenic, with the sensitivity to ICIs based on the interaction between tumour microenvironment and immune specific factors and not simply the interaction between the PD-1 and PD-L1 axes.[31] Furthermore, it is possible that *MYH9*-ROS1 may not be associated with constitutive kinase activation, explaining the efficacy of immunotherapy in this context. However, given the lack of data, and effective alternatives, we do not consider ICIs to be standard front-line therapy in NSCLC with *ROS1* rearrangements and would reserve this option for late treatment lines, after targeted agents.

***BRAF* p.V600Exxx**

*BRAF* p.V600E mutation are seen in 2% of NSCLC. *BRAF* inhibitors either as monotherapy or in combination have shown substantial antitumour activity in both treatment naïve and treatment-refractory NSCLC harbouring *BRAF* p.V600E mutation [31,32-34]. Dabrafenib and trametinib are currently FDA approved for *BRAF* p.V600E alteration. Several *MAPK* and *ERK* inhibitors are in development for non-*BRAF* V600 alterations. Conflicting data surround the role of ICIs among NSCLC patients harbouring *BRAF* V600 mutations [35]. Two multicentre retrospective cohorts of 39 and 38 patients, respectively, support the clinical efficacy of ICIs in *BRAF* mutant NSCLC [36,37]. In the first, of 21 evaluable patients treated with ICIs, 12 had the most common *BRAF* variant, p.V600E, and 9, non-p. V600E mutations. The median PFS was of 3.7 and 4.1 months among patients with p.V600E and non-p. V600E variants, respectively. At the time of publication, the median OS was not reached. The objective response rate (ORR) was 25% among patients with p.V600E mutations and 33% among the others. These results mirrored those reported in the second retrospective analysis, this time on 38 patients with *BRAF* mutations. It found an ORR of 28%, a median PFS of 3.0 months, and an OS of 13.1 months.

A smaller retrospective study reported the efficacy of ICIs among 3 NSCLC patients with *BRAF* mutations. These patients exhibited a numerically inferior OS compared to similar patients receiving front-line chemotherapy [38]. While front-line ICIs in *BRAF* mutant NSCLC do not appear to be very promising, their efficacy in second or greater line seems to be comparable to that of ICIs in non-oncogene driven NSCLC [39]. Among 44 BRAF-mutated NSCLC patients, comprising 26 with p.V600E variants and 18 with others subtypes, the ORR was roughly 30%, with 26% ORR for p.V600E variants and 33% for other variants. While patients' numbers are small and data are not prospective, these results nonetheless suggest that patients with NSCLC and *BRAF* mutations exhibit some degree of sensitivity to ICIs. BRAF mutations, more commonly found among smokers in NSCLC, could more closely mirror the impact and behaviour of KRAS mutations than those of *EGFR* or *ALK* alterations. From a biological point of view, given *BRAF*'s association with smoking, PD-L1 expression and a higher mutational burden, there is a rationale for a higher sensitivity to ICIs compared to some other oncogenic alterations [4,40-42].

In clinical practice, we favour front-line targeted therapy for *BRAF* p.V600E mutation but if this is unavailable, we would use chemo-immunotherapy among these patients.

**NRG1xxx**

Neuregulin 1 (NRG1) fusions are detected in roughly 0.3% of NSCLCs [43]. In a recent retrospective analysis of 117 patients with NSCLC and *NRG1* fusions, 95% of cases were among adenocarcinoma, most frequently of the mucinous subtype, almost half of the patients were non-smokers and there was slight over-representation among female patients. Anecdotal and retrospective of *NRG1* gene fusions positive NSCLC treated with *HER2/HER3* inhibitors reveal the sensitivity of this fusion to agents like afatinib [44]. Several other agents are in clinical development. Among 18 responsive-evaluable patients treated with a platinum-doublet chemotherapy, there was an 11% ORR and 61% disease control rate. On the other hand, among the 6 patients treated with ICIs alone and 5 patients treated with chemo-immunotherapy, no responses were observed [45]. While the numbers are small, these results and the contrasting promising results of targeted therapy with afatinib among these patients [46] do not support routine use of ICIs, especially if alternatives are available. Today, we would reserve ICIs for late treatment lines.

**NTRKxxx**

NTRK gene fusions have the peculiarity of occurring in adenocarcinoma, squamous and even neuroendocrine lung cancers. In NSCLC, it can be detected in roughly 0.2% of cases. No particular clinical characteristics have been identified, namely there does not appear to be a correlation with sex, age, nor smoking status [47]. These fusions are true oncogenic drivers and are mutually exclusive with other drivers. The FDA has approved Larotrectinib and entrectinib for *NTRK* fusion-positive tumors. In NSCLC, NTRK gene fusions are associated with higher TMB and PD-L1 expression than EGFR, ALK and ROS1 alterations

[44]. Unfortunately, there are currently no data about the efficacy of ICIs among these patients. In practice, if an NTRK inhibitor is available, we would favour this option, and if it is not, we would give patients combined chemo-immunotherapy to avoid potentially undertreating patients.

**METxxx**

MET is a high-affinity proto-oncogene receptor tyrosine kinase playing an important role in cell proliferation, survival, and metastases [48]. Select somatic alterations in MET lead to an alternatively spliced transcript that is a result of exon 14 skipping occurring in 3%–5% of lung cancers, while de novo amplifications are found in 1–5% of NSCLC patients [49]. Crizotinib, capmatinib, savolitinib and tepotinib all have shown activity in this subset. Capmatinib was recently FDA approved for this mutation.

To date, the response to ICIs has not been well characterized. Recently, a retrospective study has investigated the outcomes of patients with MET exon 14-altered lung cancers treated with ICIs, showing an ORR of 17% (4/24) and median PFS of 1.9 months (95% CI 1.7–2.7). Although some responses to ICIs were reported, the overall clinical efficacy of ICIs was quite modest [50].

The relationship between ICIs and *MET* alterations was also explored in the IMMUNOTARGET registry [14]. Patients with *MET* alterations (n = 36) were included, of which 23 with exon 14 skipping and 13 with amplifications. The ORR was 17%, the median PFS was 3.4 [1.7; 6.2] months, and the MET exon 14 cohort showed a numerically better PFS of 4.7 months, though this was not statistically significant [14]. Neither PD-L1 nor TMB was associated with outcomes. One noteworthy result was that 23.4% of patients with *MET* alterations were long-term responders to ICIs, second only to *KRAS* mutated NSCLC, suggesting a subset of checkpoint-sensitive patients. This result was supported by a recent limited series (n = 8*)* from Dudnik et al. in which the median PFS was 4.0 months (95% CI, 2.4–not reached) [36]. A third retrospective study mirrored these results. Among 30 patients with NSCLC harbouring *MET* mutations and treated with ICIs, there was a 35.7% ORR and 4.9-month PFS [51]. All three studies had a limited number of patients making the results difficult to interpret and failing to clarify the possible limits and benefit of using ICIs in this context.

If targeted *MET* therapy is available, we favour its use in the first-line, as using it after ICIs could increase the former's toxicity. In this case, we recommend ICIs in subsequent lines, preferring the combination with chemotherapy.

**HER2xxx**

*HER2* alterations in NSCLC include *HER2* mutations and amplifications. These are each detected in approximately 2–5% of adenocarcinomas. *HER2* pathway monoclonal antibody drug conjugates like adotrastuzumab emtansine (T-DM1), fam-trastuzumab deruxtecan-nxki (T-DXd, also known as DS8201a) and TKIs such as neritinib, afatinib, poziotinib, pyrotinib, lapatinib have shown activity in this subset. T-DXd has received FDA breakthrough therapy designation for *HER2* mutant NSCLC. PD-L1 expression among *HER2* mutant NSCLCs is lower than in unselected lung cancers, but TMB values are similar [52]. There is no prospective evidence about the efficacy of ICIs for patients with lung cancer harbouring HER2 alterations. In a retrospective study from the MSKCC, 26 NSCLC patients harbouring *HER2* mutations, treated with ICIs, had an ORR of 12%, with a median duration of response of about 3.4 months, PFS of 1.9 months and OS of 10.4 months [52]. None of the three responders had an *HER2* exon 20 mutation. In the IMMUNOTARGET registry [14] there were 29 patients harbouring *HER2* mutations. Here, there was also a low ORR, at 7.4%, with a median PFS of 2.5 months and OS of 21.3 months. Another retrospective study, this time comprising 23 patients with *HER2*-mutant NSCLC, found a 27.3% ORR to ICIs. The PFS and OS were 2.2 and 20.4 months respectively [39]. The heterogeneity of responses suggests some subtypes of *HER2*-mutant NSCLC may be sensitive to ICIs, and the results are similar to unselected populations in later treatment lines. Here, in the absence of clinical trials, we would use chemo-immunotherapy as a standard front-line approach.

**KRAS p.G12Cxxx**

KRAS mutations represent the most frequent molecular alterations encountered in advanced NSCLC. KRAS mutations are heterogeneous and can result in substitutions involving codons 12, 13, or 61[53]. The most frequent substitution, found in 41% of KRAS-mutant NSCLC, is *KRAS* p.G12C. This mutation is commonly identified in patients with a substantial history of smoking and recently, for the first time a p.G12C tyrosine kinase inhibitor has shown some efficacy [54]. In contrast, *KRAS* p.G12D substitutions are more commonly found in tumours of patients with little to no prior history of smoking. Sotorasib (AMG 510) and adagrasib (MRTX849) covalent *KRAS* G12 C inhibitors are in clinical trials and have demonstrated early activity in this subset of NSCLC.

KRAS-mutant NSCLC generally exhibits increased tumour mutation load, potentially leading to increased ICI sensitivity [55], unlike other driver mutations which tend to exhibit a cold immune-environment. This might stem from the increased incidence of select KRAS mutations in smokers, as smoking is associated with elevated somatic DNA mutations found in tumour cells [56]. Furthermore, concomitant alterations may affect the immunogenicity of KRAS-mutant tumours. Co-occurring TP53 mutations are often associated with enhanced tumour cell proliferation and inflammation, allowing for an immune-rich micro-environment. On the other hand, co-occurring STK11 mutations, present in roughly 20% of KRAS-mutant NSCLC, can reduce immune surveillance, possibly by modulating the *NF-kB* pathway. Some data suggest that concurrent KRAS and STK11 mutations in NSCLC patients may be predictive of primary resistance to ICIs [57] and a poor prognostic factor in patients treated with chemotherapy alone [58]. In contrast, co-occurring TP53 mutations seem to be associated with enhanced tumour cell proliferation and inflammation, allowing for an immune-rich micro-environment.. Cancers with concomitant KRAS-mutant and STK11-mutant are associated with decreased TILs, contributing to the suppression of immune surveillance [57,59].

Given these results from retrospective data, and conflicting results in a post-hoc analysis of Keynote 042, there is no consensus as to the current clinical implications of these mutations [60].

ICIs in *KRAS*-mutant NSCLC have consistently demonstrated clinical activity at least equivalent to that found among wild-type patients [42,61]. In a meta-analysis exploring the impact of *KRAS* mutations on the efficacy of ICIs in the second-line setting, the presence of a *KRAS* mutation appears predictive of superior outcomes of ICIs compared to docetaxel. At the same time, there is no difference between treatments in the *KRAS* wild-type population [62]. Similarly, in an exploratory analysis based on the Keynote 042 trial of front-line pembrolizumab in advanced NSCLC, the role of *KRAS* mutations appears to be predictive of numerically superior ORR (57 vs 29%), median PFS (12 vs 6 months) and OS (28 vs 15 months). The difference is even more pronounced in the *KRAS* p.G12C subset, though all of these investigations are exploratory [63]. Given their proven efficacy, we readily use ICIs in patients with NSCLC harbouring *KRAS* mutations, either as single-agent for high PD-L1 expressing tumours, or in combination with chemotherapy or other immunotherapy. We opt for targeted therapy alone in the context of clinical trials, when and if available.

**RETxxx**

*RET* (rearrangement during transfection) is a tyrosine kinase receptor that, when fused with a partner molecule, activates oncogenic activity and promotes unchecked cellular proliferation [64]. *RET* rearrangements occur in 1% to 2% of NSCLC patients [65]. It has been

demonstrated that pemetrexed-based chemotherapy and multikinase inhibitors have modest effect for patients with *RET*-rearranged lung cancers [66,67],[2,3] Recently, highly selective *RET* inhibitors, selpercatinib and pralsetinib have been FDA approved for *RET* fusion-positive NSCLC. Given the impressive response rates with TKIs [68,69], it is important to investigate the effects of ICIs in this patient population for therapy prioritization [70]. Currently, four retrospective studies have assessed the efficacy of ICIs in patients with *RET*-rearranged lung cancer. In a retrospective study that included 551 patients, 16 patients had *RET*-rearranged NSCLC [14]. The majority was diagnosed with adenocarcinoma and treated with the PD-1 inhibitors nivolumab or pembrolizumab. Approximately 66.7% of patients with *RET*-rearranged NSCLC were never-smokers, 26.7% were former smokers, and 6.7% were current smokers. The median number of cells positive for PD-L1 expression was 26%. Patients were followed for a median of 16.1 months, and the ORR among patients with *RET* rearrangements was 6%, and progressive disease was observed in 75% of patients. The median OS was 21.3 months (95% confidence interval [CI], 3.8–28.0), while the median PFS was 2.1 months (95% CI, 1.3–4.7). The modest results suggest that immune checkpoint inhibitors should not be used as single agents in patients with *RET*-rearranged NSCLC.

A retrospective, multicenter study included 107 patients who were mostly treated with the PD-1 inhibitors nivolumab and pembrolizumab.[6] Approximately 56% had PD-L1 expression $\geq$ 50%. The study specifically included nine patients with NSCLC with *RET* rearrangements, of whom the majority had adenocarcinoma. Overall, 44% of patients were never-smokers, 33% former smokers, and 22% active smokers. Patients were followed for a median of 9.2 months. Patients with *RET* rearrangements had an ORR of 37.5%, the median duration of response was 12.1 months (95% CI, 8.4-not reached [NR]), median PFS was 7.6 months (95% CI, 2.3-NR), and median OS was not reached. It is important to note that the higher response rates in this study may be related to the fact that this patient population received immunotherapy as an earlier line of treatment than in other studies [39]. Another study of 74 patients with *RET*-rearranged included NSCLC patients who were treated with pembrolizumab, nivolumab, atezolizumab, durvalumab, or ipilimumab plus nivolumab.[2] Approximately 69% of patients were never-smokers and 31% were former smokers. PD-L1 expression ranged from 0% to $\geq$50% (58% of patients had 0% PD-L1 expression; 23% had 1%-49% PD-L1 expression; and 19% had $\geq$50% PD-L1 expression).[2] Among 13 patients assessed for response, disease progression was observed in 62% of patients. The PFS was 3.4 months (95% CI, 2.1–5.6). One patient in this cohort had high PD-L1 expression (50%), and despite this, responded poorly to dual immune checkpoint inhibitor therapy. These findings are consistent with previous studies showing that immune checkpoint inhibitors have little effect in patients with *RET*-rearranged NSCLC. Finally, in a similar retrospective study of 59 patients with *RET* rearrangements in South Korea, approximately 51% of the total cohort comprised never-smokers, 28.8% were former smokers, 20.3% were current smokers, and the majority had adenocarcinoma [39]. In this cohort, 13 patients were treated with ICIs. The ORR in this patient population was 7.7%, the median PFS was 2.1 months (95% CI, 1.6–2.6), and the median OS was 12.4 months (95% CI, 2.9–21.8). Overall, patients in this study with *RET* rearrangements did not experience clinical benefit from ICIs [71]. In a single institutional study from the MD Anderson Cancer Center, among 70 patients who received systemic therapy for *RET* + malignancies, non-ICI therapy was associated with decreased risk for treatment discontinuation compared with ICI in the overall population (HR = 0.31; 95% CI 0.16–0.62; p = 0.000834 [71]).

In summary, while we lack prospective data, current evidence suggests that *RET*-rearranged NSCLCs, which are biologically cold tumours, are not very sensitive to ICIs and that, when available, targeted therapies should be preferred [71]

**TP53xxx**

*TP53* represents one of the most studied genes in humans. It is involved in cell-cycle chepoint regulation, stimulation of DNA damage repair and induction of apoptosis [72,73]. *TP53* mutations are independently correlated with longer OS in patients with advanced NSCLC. A possible explanation stems from the connection between *TP53* and TMB. Dysfunctional *TP53* could result in an accumulation of mutations, generating potentially immunogenic neoantigens and a high TMB. The presence of *TP53* mutations also appears to increase the expression of immune-checkpoint receptors and an activated T-effector and interferon-signature. It is unclear how co-mutation of *TP53* with oncogenes or other tumor suppressor genes influences the response to checkpoint inhibitors.

In a recent publication, Wang et al. [74] suggest that co-mutation of *TP53* with KMT2C, another oncogene often mutated in NSCLC, confer a favorable response to ICIs. In their cohort, co-occurring KMT2C mutations significantly enhanced the response of NSCLC patients to ICIs, serving as proof of principle that finer patient stratification is more informative to guide clinical decision. In the same study, the authors also considered the role and possible impact other two tumour suppressor genes, *STK11* and *KEAP1*. In this constellation, they did not significantly alter the response of NSCLC patients to ICIs. As gene function depends on context and co-occuring mutations, any potential influence of these genes in NSCLC is not ruled out.

## Biology: Why are oncogene driven tumours poorly responsive to immunotherapy?

### *Role of TMB*

Lung cancer in never or minimal smokers is generally associated with a low TMB, which results in a lack of immunogenic neo-antigens, and thus a non-inflamed ("excluded") microenvironment [13,75]. This is a possible explanation for the more favourable outcomes observed in the *KRAS, BRAF* non-V600E, and even *MET* exon14 altered NSCLC patients, as these oncogenes are more frequently observed in smokers. These findings are in line with other studies reporting low TMB in *EGFR, ALK, ROS1* [76,77], or *RET*-driven lung cancers, unlike in *KRAS* or *BRAF* where TMB could be higher [76]. NSCLC harbouring EGFR mutations are often associated with low TMB; however, recent data have highlighted that high TMB could have a potential negative prognostic role in *EGFR* mutant NSCLC treated with *EGFR* TKIs [66]. Furthermore, a recent publication by Hastings et al showed that *EGFR* p.L858R and G719 (exon 21 and 18) tumours have higher TMB compared to *EGFR* dels19 tumours, in line with slightly worse outcomes with ICIs in patients harbouring *EGFR* dels19 mutant NSCLC compared to those with wild-type *EGFR* [78].

However, TMB is dynamic biomarker that is influenced by chemotherapy or radiotherapy [79]. These could impact and alter the tumour microenvironment, leading to immunogenic cell death with neoantigen release and local and systemic T cell expansion. The change in the microenvironment along with DNA alterations, with concomitant increases of TMB, could explain the sensitivity to ICIs seen in some never-smokers with NSCLC. It is likely that these changes, combined with DNA alterations (and therefore increased TMB), explain the benefit observed in never-smokers. TMB analysis may, therefore, be a useful biomarker in this population (Fig. 2)

### *Role of PD-L1*

PD-L1 level expression is not a reliable and robust predictor of response to ICIs, even when very elevated, in patients with oncogene addicted NSCLC. Four main mechanisms may explain this finding: (1) alterations of genes, including *EGFR*, *ALK* fusions, *KRAS*, *MYC*, *PTEN*, and p53; (2) high levels of exogenous inflammatory cytokines, such as

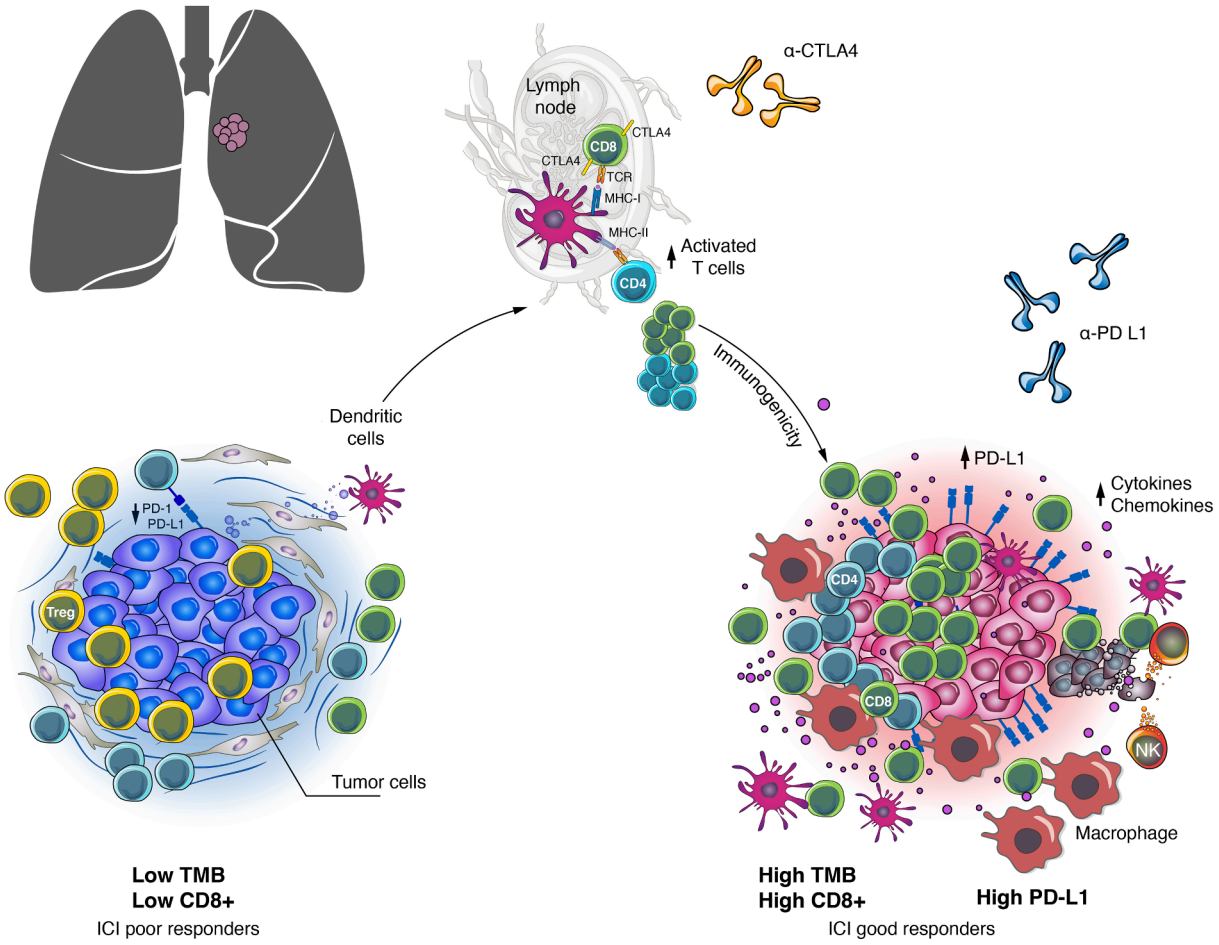


**Fig. 2.** Cold tumours (left) have an immune-poor microenvironment, rich in regulatory T cells but poor in activated T cells. These are associated with low tumour mutation burden and PD-L1 expression. Hot tumours (right) have an immune-rich microenvironment with activated T cells. These are associated with high TMB and PD-L1 expression and respond better to checkpoint inhibitors [93]. TMB: tumour mutation burden; ICI: immune checkpoint inhibitors; PD-L1: program death ligand 1.

interferon-γ; (3) *PD-L1* amplification [80] e due to a constitutional activation of the *STAT3/JAK1* pathway that induces PD-L1 up-regulation in tumours [81] and [4] disruption of the 3 ′-untranslated region of the *PD-L1* gene. Furthermore, in such tumours, there is rarely a strong immune cell infiltration, which is essential to stimulate an immune-response [82]. There have been reports investigating the relationship between PD-L1 and oncogene-driven NSCLC, in particular *EGFR*, *ALK* and *KRAS* that we have summarized in Table 2.

## Tumour microenvironment and tumour infiltrating lymphocytes

The tumour microenvironment (TME) plays a crucial role in immunogenicity, in particular of oncogene-driven lung cancer. The interaction between cancer and immune cells may result in a proliferation of regulatory T cells, downplaying and downregulating tumour infiltrating lymphocytes and major histocompatibility complex [83,84]. Furthermore, the density and diversity of tumour infiltrating immune cells could be related to prognosis and prediction of treatment efficacy. Two major subsets of tumours have been identified so far. They are characterized by the presence/absence of gene expression profile modulating the T-cell–inflamed tumour microenvironment. The T-cell–inflamed subset of tumours, also called “hot tumours”, contains T-cell transcripts, chemokines that mediate effector T-cell recruitment, macrophage activation, and a type I interferon (IFN) transcriptional profile. These tumours are characterised by high infiltration of $CD8^{+}$ T cells, macrophages, some B cells and plasma cells [59]. This inflammatory signalling results in the attraction of various immune cellular populations, including tumour-associated macrophages (TAMs), tumour-reactive lymphocytes, myeloid-derived suppressor cells (MDSCs), tumour-associated neutrophils and mast cells. These interact with tumour cells to ultimately shape a highly immune suppressive TME, with diminished tumour cytotoxic and enhanced tumour-promoting manifestations [85-88]. MDSCs are immune suppressive myeloid cells fostering tumour progression in many different ways, most of which result in the inhibition of activation of tumour-reactive T cells and of natural killer (NK) cell cytotoxicity [87].

A baseline T cell–inflamed TME seems to correlate quite well with responsiveness to ICIs and adoptive cell therapy [89]. On the contrary “not inflamed” or “cold tumours”, have low immune cell infiltration and have been described to be immunologically ignorant. They are characterised by low TMB and low expression of antigen presentation machinery markers such as major histocompatibility complex class I (MHC I). Notably, it has been documented that oncogene activation down-regulates expression of MHC I at the cell surface, thus impairing recognition by CD8 + T cells and promoting immune evasion [90,91]. Oncogene-addicted lung cancers mostly exhibit a phenotype resembling cold tumours, with striking features of T cell absence or exclusion within the TME and poor response to ICIs.

## Conclusion

Taking into consideration the currently available body of literature,

**Table 1**
Oncogenic Drivers and Response to Immunotherapy.

| Biomarker | FDA approved drugs with sensitivity | Response rate to ICI | Reference |
|---|---|---|---|
| ALK rearrangement | Crizotninb<br>Ceritinib<br>Alectinib<br>Lorlatinib<br>Brigatinib | 0–20% | Garassino et al[92]<br>Mazieres et al[93]<br>Gainor et al[94]<br>Bylick et al [95] |
| ROS1 fusion | Crizotinib, Ceretinib,<br>Lorlatinib<br>Repotrectinib | 17% | Mazieres et al [93] |
| BRAF mutation | Vemurafenib,<br>Dabrafenib + Trametinib | 25–33% | Dudnik et al[96]<br>Mazieres et al[97]<br>Guisier et al[98] |
| NRG1 | Afatinib | 0% | Duruisseaux et al [99] |
| NTRK | Larotrectinib<br>Entrectinib | NA | NA |
| MET | Crizotinib<br>Capmatinib<br>Tepotinib<br>Savolitinib | 17–35.7% | Sabari et al[39]<br>Mazieres et al[100]<br>Guisier et al[101] |
| HER2 | Trastuzumab-deruxtecan | 7.4–27.3% | Lai [95]et al<br>Buonocore et al [102]<br>Guisier et al [103]<br>Mazieres J, Drilon A, Lusque A, et al[101] |
| KRAS | Sotorasib adagrasib | 57% | Mok et al [104] |
| RET | Selpercatinib<br>pralsetinib | 6–37.5% | Guisier et al [95]<br>Mazieres et al [93]<br>Hegde et al[104]<br>Offin et al[105] |

**Table 2**
Programmed death-ligand 1 (PD-L1) expression according to status of oncogenic alterations.

| Reference | Years publication | Antibody Company | Cutoff | Oncogene | Sample size | PD-L1 pos | OR [95% CI |
|---|---|---|---|---|---|---|---|
| Azuma et al[66] | 2014 | Lifespan Biosciences | Median value | EGFR | 57 | NA | 25.4 (2.9–47.9) |
| Takada et al[106] | 2016 | SP142 | >1% | EGFR | 112 | 18% vs 36& | NA |
| Chen et al[107] | 2017 | E1L3N | NA | KRAS | 19 | H-score (median = 60) | NA |
| | 2016 | 5H1 | >1% | KRAS | 55 | 42%/ | 2.5 (1.2–5.6) |
| Scheel et al[108] | | | | EGFR | 56 | 71% | NA |
| | | | | ALK | 10 | 60% | NA |
| | 2015 | Ab58810 | >5% | KRAS | 29 | 52% | NA |
| D'Incecco et al[109] | | | | EGFR | 97 | 44% | NA |
| | | | | ALK | 3 | 67% | NA |
| | 2014 | PDL1CD274 | >5% | BRAF | 7 | 57% | NA |
| Yang et al [110] | | | | EGFR | 228 | 56% | NA |
| | | | | ALK | 23 | 78% | NA |
| | | | | KRAS | 25 | 64% | NA |
| Koh et al[111] | 2015 | E1L3N | ≥10% | EGFR | 54 | 9% | 0.24 (0.05–1.06) |
| | | | | ALK | 4 | 25% | 0.22 (0.00–14.77) |
| | | | | KRAS | 108 | 46% | 1.67 (0.64–4.34) |
| Huynh et al [112] | 2016 | E1L3N | ≥5% | EGFR | 908 | 37% | 0.74 (0.52–1.06) |
| | | | | ALK | 57 | 40% | 1.02 (0.75–1.38) |
| | | | | KRAS | 365 | 32% | 1.26 (1.06–1.50) |
| Lee et al[113] | 2019 | 22C3 | >1% | ROS1 | 19 | 85% | NA |
| | | | | EGFR | 106 | 34% | NA |
| | | | | ALK | 7 | 14% | NA |
| Sabari et al[114] | 2019 | E1L3N | >1% | METex14 | 111 | 63% | NA |

Abbreviation: OR, odds ratio; 95% CI, 95% confidential interval; IHC, immunohistochemistry; NA, not available; NS, not significant ($p < 0.05$).

it is important to highlight that all oncogene-driven tumours are not equal and certainly not a homogenous group. It is tempting to try to group all of these drivers as a single entity, but neither patient nor tumour characteristics are uniform, both within groups of alterations like *KRAS*, *MET* or *BRAF* and between oncogenic drivers. As precision medicine gains ground, this important heterogeneity will require further research and analysis. Perhaps the tumour micro-environment and immunogenicity will be a key to better understanding the biology of each cancer and personalising the therapeutic approach. Today, in NSCLC patients with the exception of *KRAS* mutations likely related to smoking status, the established oncogenic drivers appear less sensitive to ICIs than unselected tumours (Table 1). Given the impressive results from selective TKIs and the risk of enhanced toxicity from administering certain TKIs after ICIs, we favour the approach of front-line TKIs, when available. When this is not an option, we would recommend a chemo-immunotherapy combination rather than ICIs alone irrespective of the PD-L1 expression, given the generally poor performance of the latter in oncogene-driven NSCLC. Combinations of targeted therapy and ICI, available in the context of clinical trials, may be more appealing than ICI monotherapy, though data are currently unavailable. Any future trial of

ICIs in NSCLC should consider oncogenic drivers beyond *EGFR* and *ALK*, to help real-life clinical decision making.

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