Immunotherapy in oncogene addicted non-small cell lung cancer

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: The use of immune checkpoint inhibitors (ICIs) targeting the programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) has led to notable changes in treatment strategies for patients with advanced non-small cell lung cancer (NSCLC) and now forms a part of standard of care treatment in patients with advanced disease. However, most patients do not respond to ICI monotherapy, which may be explained by significant variations in efficacy according to different immune and molecular profiles in tumours. Improved response rates have been observed in smokers and are associated with tumors that have high mutation loads, with a higher tendency to form neoantigens. This premise itself defies the eventual significance of ICIs for oncogene-driven NSCLC, which in general are more common in never smokers and potentially have reduced capacity for neoantigen formation. Furthermore, pivotal trials investigating ICIs in advanced NSCLC have usually excluded patients with oncogenic drivers, hence the outcome of these agents in this population is poorly characterized. In this article, we aim to review the most current evidence, encompassing clinical and preclinical data focused on a wide range of oncogene-addicted NSCLCs.

Keywords: Oncogene; immunotherapy; lung cancer; tyrosine kinase inhibitors (TKIs)

doi: 10.21037/tlcr-20-772
View this article at: http://dx.doi.org/10.21037/tlcr-20-772

Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide and non-small cell lung cancer (NSCLC) accounts for almost 85% of all lung cancer cases (1). In the last decade the identification of various oncogenes (see Figure 1), development of targeted therapies and more recently immunotherapies have refined and indeed transformed therapeutic algorithms for NSCLC. Genotype-directed treatments targeting oncogene-addicted NSCLC, including EGFR (5-8) and BRAF V600E mutations (9) or ALK (10-12), ROS1 (13) and RET (14) oncogenic rearrangements, have demonstrated high response rates and prolonged survival resulting in their adoption as front line therapies. By contrast, immunotherapies when used as single agents are ineffective in the majority of patients, although offer long term benefits in some patient subgroups—particularly when used in combinations with chemotherapy.

While the efficacy of targeted therapies is contingent on the target being detectable within the tumour, predictive markers for immunotherapy are less reliable. Several studies have indicated that PD-L1 expression, tumour-infiltrating lymphocytes (TILs), tumour mutational burden (TMB), neoantigens and DNA mismatch repair (MMR) deficiency may serve as potential predictive biomarkers for immune checkpoint inhibitor (ICI) effectiveness. The main biomarker that has emerged as clinically useful is tumour cell PD-L1 expression as assessed by immunohistochemistry.
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Figure 1 Single oncogenic drivers in metastatic lung adenocarcinoma. Oncogenic driver alterations in advanced NSCLC (including treatment-naive patients and patients who had previously received anticancer therapies). Data adapted from Skoulidis et al. (2), based on next-generation sequencing of predefined panels from patients treated at the Memorial Sloan Kettering Cancer Center [n=860; MSK-IMPACT panel (Jordan et al. (3)) and samples referred to Foundation Medicine [n=4,402; FoundationOne panel (Frampton et al.) (4)] (n=5,262 patients with advanced/metastatic NSCLC in total). The increased prevalence of EGFR mutations in the metastatic dataset may partially reflect referral bias.

However, even in patients with high expression of PD-L1, about 50% of patients do not respond to single agent ICI and some patients negative for PD-L1 experience strong and durable responses. Such diversity of response cannot be purely explained by tumour heterogeneity suggesting that other factors, either within the tumour, the host, or both must be at play. Oncogene addicted tumours collectively represent a broad set of tumours and the role of immunotherapy from existing trials may not be broadly generalizable. Phase three data in this setting for oncogene addicted tumours is unfortunately limited, given that many trials excluded these patients, and when included they represent small subsets depending on the type of oncogenic driver.

In this article, we review the clinical data available regarding outcome of oncogene addicted NSCLC patients treated with ICIs and the primary preclinical evidence concerning immunologic characteristics in oncogene-driven NSCLC, which seems to be critical in unravelling the potential benefit of these agents in this specific patient population.

Epidermal growth factor receptor (EGFR) mutations

Current practice and the limitations of TKIs

Actionable EGFR mutations vary in their incidence from 15% up to 65% of lung adenocarcinomas with the higher incidence occurring in East Asian populations (15) and are associated with improved response rates to tyrosine kinase inhibitor (TKI) therapy (16). Most treatment algorithms mandate initial testing for EGFR to guide first line therapy given the efficacy and low toxicity of TKIs compared to chemotherapy (17-23). Inevitably, however, resistance to TKIs develops and chemotherapy is currently the main subsequent treatment employed after failure of TKI options.

Rationale for immunotherapy

The interest in immunotherapy was supported by preclinical studies demonstrating that PD-L1 expression by EGFR-mutant tumours increased as a mechanism of immune evasion (24) and that PD-L1 overexpression by
tumour cells occurred through the ERK1/2-c-jun pathway by activating mutant EGFR (25). Discordant treatment effects have however been seen in vitro with erlotinib reducing PD-L1 expression in one study (26) and gefitinib increasing PD-L1 in serial biopsies in a clinical setting (27). To add to a lack of consistency, Gainor and colleagues found in their retrospective analysis that PD-L1 expression was low prior to TKI exposure (16%) and at acquired resistance (29%) (28). Similarly, Offin and colleagues reported TMB increased with resistance, but that the overall levels were still low (29). Whilst the presence of an actionable EGFR mutation is associated with increased TKI response rates there is a lack of a robust marker for immunotherapy agents (30) and PD-L1 and TMB may not be informative in this context.

Further evidence from a retrospective series has also suggested EGFR TKI resistance results in increased TMB which has supported the current practice of sequencing TKIs prior to immunotherapy (29). The lack of benefit from immunotherapy has been hypothesised to be due to several factors. Pre-clinical studies suggest a “cold” and more immunosuppressive tumour microenvironment with reduced tumour infiltrating lymphocytes and T cell infiltration exists in EGFR-mutant lung cancers (31,32) as well as CD73 overexpression with associated reduced interferon gamma signature and increased adenosine production which has been associated with a more resistant immunophenotype (33,34). EGFR mutated tumours also have a mutational signature with decreased production of neoantigens and less clonal expansion (30,35). This represents an important clinical finding as high TMB correlates with improved progression free survival (PFS), objective response rate (ORR) and duration of response to immunotherapy (27). Although TMB increases with subsequent therapies, it is more likely that the neoantigen increase and neoepitopes that are generated are polyclonal and therefore less immunogenic.

**Single agent immunotherapy**

Patients with EGFR mutations performed poorly in initial phase three studies comparing immunotherapy to docetaxel (36-38). In the CheckMate 057, Keynote 010, OAK and POPLAR studies, cohorts with EGFR mutations were 82, 86, 85 and 18 patients respectively. A small subset of the total trial population, but with universally poorer outcomes. This finding was supported in a retrospective review and a metanalysis which yielded poor response rates and lack of overall survival (OS) benefit (HR 1.11; 95% CI, 0.80–1.53) when compared to chemotherapy (28,39).

In a small initial study, Lisberg et al. assessed the role of pembrolizumab as first line treatment prior to EGFR TKI and reported no objective responses in 10 patients even within a PD-L1 enriched cohort (PD-L1 ≥50%) of seven patients. The study was discontinued due to futility (40,41).

**Combination approaches**

**TKI + immunotherapy**

In order to improve response rates to immunotherapy numerous early phase studies have employed combination approaches with TKIs, however several safety concerns have been flagged by this approach and few trials have progressed beyond phase one. Yang and colleagues looked at standard dosing erlotinib or gefitinib in combination with pembrolizumab every two weeks in EGFR-mutant patients enrolled in cohorts E and F of KEYNOTE-021. Enrolment in the gefitinib cohort was however suspended after 71.4% (5/7) of patients developed grade three or four aspartate aminotransferase (AST)/alanine aminotransferase (ALT) elevations deeming the combination not feasible. The erlotinib cohort (n=12) however was deemed feasible with no grade four toxicities (42). Despite being more tolerable than the gefitinib combination the ORR was 41.7% which is lower than what historical controls have demonstrated with erlotinib in the first line setting (30). An early phase trial by Creelan et al. also demonstrated significant toxicity of gefitinib in combination with durvalumab (43). A further phase one study evaluating erlotinib with nivolumab in a cohort of 20 patients demonstrated a similar adverse event profile and low ORR of 15% (44). Further safety signals were raised in the TATTON trial where the combination of osimertinib and durvalumab in a TKI naïve population saw a 38% rate of interstitial lung disease (45). A planned phase III study by Yang et al. (CAUREL study) with a similar osimertinib and durvalumab arm had recruitment terminated early secondary to these findings limiting comparisons between the two groups (46). In contrast to the aforementioned studies a phase I study evaluating the combination of atezolizumab and erlotinib yielded a response rate of 75% (n=20) and more manageable safety profile (47).

Overall these early studies (see Table 1) demonstrated that combination TKI plus immunotherapy approaches were...
not associated with any consistent benefit but potentially increased toxicities in EGFR-mutant NSCLC.

Chemotherapy + immunotherapy

Although several combination chemotherapy plus immunotherapy studies excluded EGFR-mutant tumours, the IMPOWER150 study was an exception after the protocol was amended to include patients who had failed prior TKIs. The trial enrolled 1,202 patients overall with equal randomisation to one of three arms: atezolizumab/carboplatin/paclitaxel (arm A), atezolizumab/carboplatin/paclitaxel/bevacizumab (arm B) and carboplatin/paclitaxel/bevacizumab (arm C).

The exploratory analysis included 124 patients with EGFR mutation positive tumours [approximately 10% of in the intention-to-treat (ITT) population] of which 91 had sensitising mutations and 78 had progressed on prior TKIs. Forty-five, 34 and 45 patients were allocated to arms A, B and C respectively. There was a trend towards median OS improvement in arm B (NE) versus arm C (18.7 months) with a HR of 0.61 (95% CI, 0.29–1.28) as well as in median PFS (10.2 vs. 6.9 months; HR 0.61; 95% CI, 0.36–1.03). The ORR was 36%, 71% and 42% in groups A, B and C respectively.

Table 1 Early phase studies for immunotherapy in EGFR mutated lung cancers

<table>
<thead>
<tr>
<th>Author, phase</th>
<th>Intervention</th>
<th>N = number of participants</th>
<th>Response rates %</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yang et al. [2019], phase I/II</td>
<td>TKI: erlotinib; gefitinib arm closed due to toxicity; ICI: Pembrolizumab</td>
<td>12</td>
<td>41.7</td>
<td>No G4 events; G3 AE 33%; ALT increased G1/2 25%; AST increased G1/2 25%; gefitinib arm closed due to G3/4 hepatotoxicity in 71.4% patients</td>
</tr>
<tr>
<td>Creelan et al. [2019], phase I</td>
<td>TKI: Gefitinib; ICI: Durvalumab</td>
<td>56</td>
<td>63</td>
<td>70%; Combination therapy was associated with high discontinuation rate due to hepatotoxicity (&gt;50%)</td>
</tr>
<tr>
<td>Gettinger et al. [2018], phase I</td>
<td>TKI: Erlotinib; ICI: Durvalumab</td>
<td>20</td>
<td>15</td>
<td>G3 events - 25% [5]</td>
</tr>
<tr>
<td>Ahn et al. [2016], TATTON, Phase Ib</td>
<td>TKI: Osimertinib; ICI: Durvalumab</td>
<td>44</td>
<td>38</td>
<td>38% interstitial lung disease like events</td>
</tr>
<tr>
<td>Rudin et al. [2018], Phase Ib</td>
<td>TKI: Erlotinib; ICI: Atezolizumab</td>
<td>28</td>
<td>75</td>
<td>G3 AE in 43%</td>
</tr>
</tbody>
</table>

TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; G3, grade 3; G4, grade 4; AE, adverse event.
relationship. The absence of a survival benefit in the ACP group supports this therapeutic pathway but it needs to be further explored.

The approach of combining chemotherapy with immunotherapy will also be looked at in an additional up and coming phase three trial, Keynote-789, where pembrolizumab is added to platinum doublet chemotherapy post failure on first line TKI and in the ABC-Lung phase two study investigating the combination of atezolizumab and bevacizumab with chemotherapy.

Immunotherapy combinations
While PDL-1 and CTLA4 represent two independent pathways that can be targeted by immune checkpoint inhibition and targeting them in combination has been shown to have synergistic responses, the major lung studies investigating this, Checkmate-227 and MYSTIC, excluded EGFR mutant patients (52). The Illuminate and Checkmate-772 studies will investigate durvalumab/tremelimumab and nivolumab/ipilimumab respectively in this context.

Summary
For EGFR-mutant tumours it is clear that single agent immunotherapy and TKI combinations with immunotherapy do not offer any benefit for the majority of patients. Combination strategies are the most promising approach, however, the only prospective data comes from an underpowered subset analysis suggesting chemotherapy plus bevacizumab and atezolizumab was superior to chemotherapy and bevacizumab alone. Results from further clinical trials specifically powered to address this question are eagerly awaited.

Anaplastic lymphoma kinase (ALK) rearrangements

Current practice and the limitations of TKIs

ALK gene fusions are present in 3–7% of lung adenocarcinomas and serve as an important oncogene (53). Crizotinib was quickly identified as an effective agent in targeting ALK rearranged tumours in the PROFILE 1007 study (10) with the registrational PROFILE 1014 study demonstrating a superior response rate (74% vs. 45%) as well as PFS (10.9 vs. 7.0 months) for crizotinib over chemotherapy (54). As with EGFR-mutant tumours resistance inevitably develops and further approved therapies such as ceritinib and alectinib have been developed with success in extending the median time to progression with a recent update in the ALEX study confirming median PFS times of 34.8 months with alectinib compared with 10.9 months with crizotinib (11).

Similarly to EGFR mutant NSCLC, the role of immunotherapy in ALK rearranged lung cancers initially suggested potential benefit.

Combination approaches

TKI + immunotherapy
An early phase study by Spigel et al. looking at the combination of nivolumab plus crizotinib as a first line treatment in ALK rearranged patients was notable for 38% (n=5) developing severe hepatotoxicity which resulted in closure of the cohort (55). After the interim safety review two patients developed severe hepatotoxicity and died. Of those who were evaluable five patients (38%) had partial response, two (15%) had stable disease and three (23%) progressed (56). The phase Ib JAVELIN 101 trial had an ALK positive cohort treated with avelumab and lorlatinib in combination after progression on initial ALK TKI (57). In contrast to the study performed by Spigel et al. there were no dose limiting toxicities with an ORR 46.4% (55,57). The combination of alectinib and atezolizumab has also been evaluated (58). ORR was 81% and duration of response 21.7 months which is still below that of the reported duration of response to single agent alectinib in ALEX (11). Felip and colleagues have also looked at the combination of nivolumab and ceritinib in 36 ALK rearranged patients where 25% experienced at least a grade three elevation in ALT and 22% in GGT (59). A safety signal resulted in a protocol amendment resulting in sequential therapy. Recently, the ATLANTIC trial also reported on a cohort of 15 patients (out of a total 111) with ALK rearrangements who received third line or later durvalumab; none of whom had an objective response (60).

Table 2 summarises the main results from these early phase studies.

Chemotherapy + immunotherapy
As with EGFR-mutant lung cancer there are numerous theories as to why ALK rearranged tumours have had disappointing responses to immune checkpoint blockade but the underlying reasons remain unclear. The lack of a smoking phenotype and low TMB have been proposed. It is for these reasons in addition to a lack of safety signals that
Table 2 Early phase studies for immunotherapy in ALK rearranged lung cancers

<table>
<thead>
<tr>
<th>Author, phase</th>
<th>Intervention</th>
<th>N = number of participants</th>
<th>Response rates %</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spigel et al. [2018], Phase I/II</td>
<td>TKI: Crizotinib, ICI: Nivolumab</td>
<td>13</td>
<td>38</td>
<td>38% developed severe hepatoxicity leading to discontinuation of this combination; 2 patients died from their hepatoxicity</td>
</tr>
<tr>
<td>Shaw et al. [2018], JAVELIN 101</td>
<td>TKI: Lorlatinib; ICI: Avelumab</td>
<td>28</td>
<td>46.4</td>
<td>54%; high triglycerides 14.3%; GGT increase 10.7%</td>
</tr>
<tr>
<td>Kim et al. [2018]</td>
<td>TKI: Alectinib; ICI: Atezolizumab</td>
<td>21</td>
<td>81</td>
<td>G3 62%; Rash/ALT rise/Pneumonitis</td>
</tr>
<tr>
<td>Felip et al. [2020], Phase I b</td>
<td>TKI: Ceritinib, ICI: Nivolumab</td>
<td>36</td>
<td>First line 450 mg: 83; 300 mg: 60; Second line 450 mg: 50; 300 mg: 25</td>
<td>ALT rise 25%; GGT rise 22%; Amylase 14%</td>
</tr>
</tbody>
</table>

TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; G3, grade 3; G4, grade 4.

have made it difficult for combination immunotherapy and TKI approaches to proceed beyond the early phase setting.

The IMPOWER150 study, post protocol amendment, also allowed ALK positive patients to be recruited. The addition of atezolizumab to the combination of bevacizumab, carboplatin and paclitaxel improved PFS and OS in the ITT population. However, these cohorts only included 13 ALK positive patients in the quadruplet cohort and 21 in the control. The data for EGFR and ALK were combined as discussed above, making it difficult to interpret the specific benefit in the ALK population although it remains an FDA approved treatment option for both populations.

Summary

For ALK rearranged NSCLC little benefit has been seen with immunotherapy and TKI combinations. Chemotherapy and immunotherapy combinations represent a promising approach however application of clinical trials is often limited by the exclusion of these patients or small cohorts, as was the case for IMPOWER150.

KRAS mutations

KRAS is the most common proto-oncogene associated with NSCLC in western populations. It has a heterogeneous distribution according to ethnic origin; having been described in 26.1% of lung adenocarcinomas and 6.4% of squamous cell carcinomas in Western countries and in 11.2% and 1.8% of lung cancer cases in Asia respectively (2,61,62). Traditionally it has been associated with smoking (63) and considered a poor prognostic biomarker (64); however, current data indicates a limited effect on OS in patients with early-stage NSCLC (65). The most frequent oncogenic KRAS mutations in NSCLC are missense substitutions occurring at codons 12 and 13: G12C (40%), G12V (20%), and G12D (20%) (66).

KRAS-mutant NSCLC: not a single disease

Growing preclinical and clinical evidence suggests that KRAS-mutant NSCLC might not be a unique entity, and translational studies have unravelled some of the main determinants of this biological diversity. Perhaps this heterogeneity is related to the unfavourable outcomes seen when targeting this pathway in the past. Only recently, a type-specific G12C KRAS inhibitor has shown for the first time some clinically meaningful efficacy for patients with KRAS-mutant NSCLC (67).

Unlike other oncogene-driven lung cancers, KRAS-mutant lung tumours frequently appear with other major genetic co-mutations. Skoulidis et al. identified three robust expression based clusters in such malignancies: ‘KL’ subgroup, with STK11 and KEAP co-mutations, ‘KP’ subgroup, with TP53 co-mutations, and ‘KC’ subgroup, with CDKN2A/B inactivation plus low thyroid transcription factor-1 (TTF-1) (68). ‘KC’ tumours showed enrichment of gene expression signatures reflecting both upper and lower gastrointestinal neoplastic processes and wild-type TP53.
transcriptional activity. ‘KP’ subgroup was characterised by active inflammation with high levels of PD-L1 expression. ‘KL’ tumours were mostly immune inert tumours, with moderate T-cell inflammation and weak PD-L1 expression. Furthermore, co-occurring STK11 and KEAP1 mutations with KRAS appeared to be associated with worse OS (68,69). Hence, the presence of major co-occurring genetic events might also predict distinct therapeutic vulnerabilities in addition to their prognostic significance.

Rationale for immunotherapy

There is preclinical rationale supporting immunotherapy use in KRAS-mutant NSCLC. PD-L1 expression appears to be intrinsically rather than adaptively elevated, via activation of downstream KRAS signalling pathways (70,71). Besides its relation with KRAS-mutant NSCLC, tobacco smoke induces PD-L1 expression and renders the exposed cells able to evade the immune system and promote lung carcinogenesis (72), and smoking-associated lung cancers have a high mutational burden and abundant T-cell infiltration (73). Huynh et al. described up to 50% of KRAS-mutant NSCLC with some PD-L1 expression which was correlated both with smoking history and high T-cell infiltration (74). Nevertheless, it is important to consider the previously mentioned heterogeneity. KRAS-mutant NSCLCs display different immune profiles and could consequently have varying levels of sensitivity to immunotherapy (68). In the case of KRAS-TP53 co-mutated tumours, a higher mutational burden and genomic instability could explain, at least partially, the T-cell-inflamed microenvironment and the adaptive immune-resistant phenotype (68,75). KRAS-STK11 co-mutant subgroups have been associated with high hypoxia-inducible factor 1 (HIF1α), which leads to impaired T-cell function (76). In a retrospective pooled analysis, including three independent subgroups (n=174) and a subset of patients with KRAS-mutant lung adenocarcinomas (n=44) all treated with ICIs, patients with KRAS-STK11 co-mutations demonstrated a significantly lower ORR, PFS and OS than patients with KRAS-TP53 tumours (77); furthermore, STK11 was associated with resistance to PD-1 blockade in PD-L1 positive NSCLC, regardless of KRAS mutational status (77). This data suggests that despite ICIs being one of the most promising biological therapies for KRAS-mutant NSCLC, they do not benefit all patients equally. A potential means of predicting immuno-resistance in these patients may involve consideration of the heterogeneity of KRAS-mutant tumours, particularly the presence of significant co-mutations.

Clinical evidence

The current clinical evidence to support treatment in NSCLC based solely on a KRAS mutation is confounding. In an extensive retrospective registry in NSCLC with common driver mutations treated with ICIs, almost half of patients had KRAS mutations (N=271 of 551), with an overall cohort best response of 19%, and median PFS of 2.8 months (mainly driven by the large KRAS-subgroup) (78) (Table 3). When using prospective data, in an unplanned subgroup analysis of trials comparing ICIs such as nivolumab or atezolizumab with chemotherapy in second-line treatment for NSCLC, it was suggested that KRAS mutations were more sensitive to ICIs compared with wild-type and that ICIs as second or third-line therapy in KRAS-mutant NSCLC improved OS (36,38,79). For instance, in the CheckMate-057 trial, KRAS-mutant subsets (n=62) were among the molecular subgroups to achieve the most significant OS benefits with nivolumab (HR 0.52; 95% CI, 0.29–0.95) (36). A meta-analysis (80) including these trials investigated the predictive role of KRAS-mutations in 519 patients with previously treated NSCLC, resulting in a greater benefit in the KRAS-mutant subgroup (HR, 0.65; 95% CI, 0.44–0.97; P=0.03). Individually, these studies were not powered to address this question, and KRAS-mutation status was known only in a small fraction of cases, undermining the clinical validity of this finding. Furthermore, using prospective ‘real-world’ observational patient data, two studies have concluded that KRAS mutation status did not confer significant differences in ORR, PFS and OS (81,82). A summary of these studies can be found in Table 3. In Figure 2 we also provide an example of a patient with metastatic NSCLC who had a KRAS G12C mutation and TP53 co-mutation with complete response post three cycles of immunotherapy.

Summary

Immunotherapy is one of the most promising new therapies in KRAS-mutant NSCLC, but recent data suggests variable efficacy of immunotherapy according to the presence of other co-mutations. The targetability of KRAS G12C mutation also adds further complexity when considering which patients are most likely to benefit from
targeted therapies compared to ICIs. Given the biological heterogeneity of KRAS-mutant NSCLC, treatment will likely need to be individualized and may require combinations of treatment, many of which are currently under investigation.

**BRAF mutations**

BRAF mutations result in persistent activation of downstream cell signalling through the MAPK pathway and lead to unchecked cell growth and proliferation (83). The most common variant responsible for this process is a BRAF point mutation V600E and has been described with variable frequency in melanoma, colorectal cancer, papillary thyroid cancer, among others malignancies (84). BRAF mutations are uncommon in NSCLC, occurring in 1–5% of cases (85-88). Large clinicopathologic studies show some variability relating to the specific clinical characteristics associated with BRAF mutations (85-88). Overall, studies suggest slightly increased frequency in females. Smoking and its link with BRAF status has varied among studies, however in Caucasians with a positive smoking history there is also an association with sarcomatoid histology and both non-V600E and V600E BRAF mutations (85-87). Across all studies, the main consistent finding was poor ORR, PFS and disease-free survival (DFS) in patients

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Retrospective studies of ICIs in KRAS and BRAF mutant NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KRAS-mutant</strong></td>
<td></td>
</tr>
<tr>
<td>Mazieres et al. [2019], Global</td>
<td>Various ICIs (94% Nivolumab)</td>
</tr>
<tr>
<td></td>
<td>G12C =100</td>
</tr>
<tr>
<td></td>
<td>Non-G12C/D =171</td>
</tr>
<tr>
<td>Passiglia et al. [2019], Italy</td>
<td>Nivolumab</td>
</tr>
<tr>
<td>Jeanson et al. [2019], France</td>
<td>Various ICIs (88% Nivolumab)</td>
</tr>
<tr>
<td></td>
<td>G12C =69</td>
</tr>
<tr>
<td></td>
<td>Non-G12C/D =93</td>
</tr>
<tr>
<td><strong>BRAF-mutant</strong></td>
<td></td>
</tr>
<tr>
<td>Guisier et al. [2020], France</td>
<td>Nivolumab (N=35); Pembrolizumab (N=8); Others (N=1)</td>
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<tr>
<td></td>
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<tr>
<td>Dudnik et al. [2018], Israel</td>
<td>Nivolumab (N=11); Pembrolizumab (N=10); Atezolizumab (N=1)</td>
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<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Offin et al. [2019], USA</td>
<td>Various ICIs: Nivolumab (N=30); Pembrolizumab (N=7); Nivolumab/Ipilimumab (N=6); Atezolizumab (N=3)</td>
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<td></td>
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ICI, immune checkpoint inhibitor.
Figure 2 A 72 years old male, heavy smoker (40 pack-years). Metastatic non-small cell lung cancer: PDL1 90%, KRAS G12C mutation and TP53 co-mutation. Commenced on pembrolizumab 200 mg 3-weekly. Positron emission tomography (PET): (A) baseline PET prior starting therapy shows primary tumour on the upper right lobe and extensive hepatic, retroperitoneal and right kidney metastases. (B) PET CT after three cycles of pembrolizumab showing almost complete metabolic response. (C) PET CT after 36 months of starting pembrolizumab which shows an ongoing complete response.

with a BRAF V600E mutation treated with chemotherapy when compared with non-V600E mutants (86-88).

Current practice and the limitations of TKIs

Like melanoma, BRAF V600E NSCLC has emerged as an important target for drug therapy with BRAF inhibitors (89). Since resistance invariably develops with BRAF inhibition alone, via the development of bypass pathways such as redirection of cell signalling via MEK 1/2 kinases, adding a MEK inhibitor improved clinical outcomes in both melanoma and NSCLC (89).

The data supporting the use of a BRAF inhibitor with or without MEK inhibition in BRAF positive NSCLC has been adopted from a small number of positive phase two studies. In a phase two, multi-cohort, non-randomized, open-label study, 78 previously treated BRAF V600 mutation-positive NSCLC patients received dabrafenib; responses were observed in 33%, the median PFS was 5.5 months (95% CI, 3.4–7.3) and median OS 12.7 months (95% CI, 7.3–16.9) (90). A second cohort of the same study evaluated the combination of dabrafenib/trametinib with an ORR of 63% and median PFS of 9.7 months when compared to single-agent dabrafenib (91). The median OS was also 12.7 months in the dabrafenib monotherapy cohort versus 18.2 months in the dabrafenib/trametinib cohort (91). Vemurafenib was tested in another multi-tumour phase two study where responses were seen in 42%, the median PFS was 7.3 months (95% CI, 3.5–10.8) and median OS had not been reached (92).

Immunotherapy in BRAF-mutant NSCLC

Evidence to support immunotherapy in BRAF mutated NSCLC comes only from retrospective evidence. A retrospective review included 39 BRAF-mutated NSCLC patients, stratified by PD-L1 status, TMB and
microsatellite instability (MSI), but not all patients were tested for each of these markers. Twenty-two received an ICI: 57% of the V600E group and 55% of the non-V600E group. ORR was 25% and 33% and median PFS 3.7 and 4.1 months respectively. PD-L1 status and BRAF mutation type did not alter the outcome, and the study suggested that BRAF-mutated NSCLC was more likely to have high expression of PD-L1; a point to interpret with caution given the low number of cases (27,93).

Another retrospective study addressing the efficacy of ICIs in Japanese patients with oncogenic driver mutations, reported only five cases with a BRAF mutated NSCLC, with no responses observed (94). The most substantial report comes from a recent publication by Guisier et al. of a retrospective review from several centres in France. They detected 44 patients with BRAF mutations receiving ICIs (V600: 26, non-V600: 18). The ORR, median PFS, OS, and 12-month OS for BRAF V600E and BRAF non-V600E were 26% and 35%, 5.3 and 4.9, 22 and 12 months, 53% and 44% respectively (95). Less than half of the patients had a PD-L1 status assessment and thus no conclusions were drawn. A brief summary of these reports is available in Table 3.

**Summary**

Overall based on the current literature it seems that, in contrast to other oncogene addicted NSCLCs, ICIs seem to have some activity in those with a BRAF mutation. This activity is similar to that observed in patients with pretreated unselected NSCLC in randomised controlled trials or observational studies and seems to be irrespective of PD-L1 status or BRAF mutation type. However, BRAF mutations can occur in heavy smokers and also in non-smokers and it is likely that the best responses are driven by the smoking phenotype although current data are limited.

**Other oncogene addicted tumours**

**c-ROS oncogene 1 (ROS1) rearrangements/Human epidermal growth factor receptor 2 (HER2)/RET/MET**

Since discovery in 2007 ROS1 rearrangements have become another important target in NSCLC and are identified in 1–2% of patients (96). The recently published Immunotarget trial (78) was a retrospective study evaluating single agent immune checkpoint inhibition in advanced NSCLC across numerous oncogenic alterations. They reviewed 551 patients and evaluated their molecular alterations: KRAS (n=271), EGFR (n=125), BRAF (n=43), MET (n=36), HER2 (n=29), ALK (n=23), RET (n=16), ROS1 (n=7) and multiple drivers (n=1). They then evaluated clinicopathologic characteristics and outcomes for immune checkpoint blockade. In the overall cohort the best response with immunotherapy was 19% with a median PFS of 2.8 months. Most of this benefit appeared to be driven by the KRAS cohort. For the rarer oncogenic addicted tumours, which expectedly had small numbers, this study represents the limited data evaluating ICI use in this setting. For HER2-mutant tumours a median PFS of 2.5 months (95% CI, 1.8–3.5) was noted and 2.1 months (95% CI, 1.3–4.7) for RET rearranged NSCLC. Only seven patients had ROS1 rearrangements and a median PFS was not reported.

Findings for tumours with MET alterations [median PFS 3.4 months (95% CI, 1.7–6.2)] were in keeping with a study by Sabari et al. (97) which demonstrated only a modest benefit to immune checkpoint inhibition with an ORR of 17% and median PFS 1.9 months (95% CI, 1.7–2.7) in a cohort of 24 patients who had received prior chemotherapy. Sabari and colleagues also evaluated PD-L1 expression in their study but found no correlation to treatment response. TMB was also found to be low in these patients. These response rates sit well below the reported 32% ORR and 7.3 months median PFS seen with crizotinib in the PROFILE 1001 study (98) and newer TKIs such as capmatinib, tepotinib and savolitinib are also reporting high responses for this population (99-101).

Overall response rates appear to be very modest to immunotherapy in these rarer oncogene addicted tumours with most benefit being derived by the KRAS cohort. The approach for the rare patients with multiple alterations such as additional TP53 or PIK3Ca mutations is uncertain and requires further research (102). Pursuing other systemic therapies or TKIs for these tumours is recommended and ongoing trials are required to review whether combination approaches (such as the addition of immunotherapy to chemotherapy) may improve outcomes for these patients.

**Conclusions**

Oncogene addicted tumours while heterogeneous, collectively account for over 40% of non-squamous NSCLCs. It is important to note that most single agent and combination immunotherapy trials that have been reported to date excluded specific oncogene addicted
NSCLCs such as ALK and EGFR; however, it is likely that other oncogene driven tumours were not tested for but included in the non-smoker subsets. Trials that focused on these tumours have largely been negative. However, of key importance is that the use of chemotherapy in combination with immunotherapy may provide benefits to this approach not seen with single agent ICIs.

Whilst it is clear for most non-smoking related oncogene addicted tumours that immunotherapy should only be used in combination, the actual data underpinning this approach remains limited. It is more likely that these tumours develop immunoevasion abilities through mechanisms which PD-1/CTLA4 blockade does not abrogate. It is clear that a better understanding of these pathways is needed in order to develop robust markers and targets for therapies so that the immunotherapy benefits seen in some smoking associated NSCLC can also be realised in this patient group.

Best evidence to date supports the use of TKI therapy prior to immunotherapy or chemotherapy in oncogene addicted tumours and clinical trials should always be considered for this population of patients. Combination approaches with chemotherapy and immunotherapy in EGFR positive or ALK rearranged tumours post TKI exhaustion appears to be most promising as suggested by the IMpower150 data. The role of biopsy in progressing disease has largely been limited to the identification of T790M in EGFR mutant disease as a method of accessing osimertinib, however, in the era of precision medicine with the ongoing development and evolution of targeted therapies and as we develop a greater understanding of the mechanisms of resistance to TKI therapy this is may very well change in the future.

**Acknowledgments**

**Funding:** None.

**Footnote**

**Peer Review File:** Available at [http://dx.doi.org/10.21037/tlcr-20-772](http://dx.doi.org/10.21037/tlcr-20-772)

**Provenance and Peer Review:** This article was commissioned by the Guest Editor (Daniel Steinfort) for the series “Lung Cancer & The Immune System” published in *Translational Lung Cancer Research*. The article was sent for external peer review organized by the Guest Editor and the editorial office.

**Conflicts of Interest:** All authors have completed the ICMJE uniform disclosure form (available at [http://dx.doi.org/10.21037/tlcr-20-772](http://dx.doi.org/10.21037/tlcr-20-772)). The series “Lung Cancer & The Immune System” was commissioned by the editorial office without any funding or sponsorship. JL reports grants and personal fees from MSD (Merck) Roche, Boheringer Ingelheim, Pfizer, Astra Zeneca, BMS and personal fees from Sanofi, Tecnofarma, Elly-Lilly. BS reports Advisory Boards/Honoraria AstraZeneca, Roche/Genentech, Pfizer, Novartis, Merck Shape Dohme, Bristol Myers Squibb, Specialized Therapeutics, Loxo Oncology, Amgen. TJ reports Honoraria: AZ, BMS, Roche, Pfizer, Novartis, Specialised Therapeutics, Amgen, MSD, Merck, Takeda. The authors have no other conflicts of interest to declare.

**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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