THERAPEUTIC ADVANCES in
Medical Oncology

Review

Efficacy of immunotherapy in oncogene-driven non-small-cell lung cancer

Ther Adv Med Oncol

2023, Vol. 15: 1–20

DOI: 10.1177/17588359231161409

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***Abstract*:** For advanced metastatic non-small-lung cancer, the landscape of actionable driver alterations is rapidly growing, with nine targetable oncogenes and seven approvals within the last 5 years. This accelerated drug development has expanded the reach of targeted therapies, and it may soon be that a majority of patients with lung adenocarcinoma will be eligible for a targeted therapy during their treatment course. With these emerging therapeutic options, it is important to understand the existing data on immune checkpoint inhibitors (ICIs), along with their efficacy and safety for each oncogene-driven lung cancer, to best guide the selection and sequencing of various therapeutic options. This article reviews the clinical data on ICIs for each of the driver oncogene defined lung cancer subtypes, including efficacy, both for ICI as monotherapy or in combination with chemotherapy or radiation; toxicities from ICI/targeted therapy in combination or in sequence; and potential strategies to enhance ICI efficacy in oncogene-driven non-small-cell lung cancers.

Keywords: immunotherapy, lung cancer, precision oncology, oncogene

Received: 9 October 2022; revised manuscript accepted: 13 February 2023.

Introduction

Classical *EGFR* mutations (exon 19 deletion or *L858R* point mutation) were identified in 2004 as the first targetable oncogenic driver in non-small-cell lung cancer (NSCLC).[1–3] Since then, a growing number of tyrosine kinase inhibitors (TKIs) have received regulatory approval and transformed the NSCLC treatment landscape by offering high response rates and generally good tolerability in a growing list of driver oncogene-selected patients. However, long-term survival is hindered by the almost universal acquisition of resistance. In contrast, anti-programmed death ligand-1 (PD-L1) immune checkpoint inhibitors (ICIs), which were first approved in 2015, have overall modest response rates, but have demonstrated the unique potential to induce long-term durable responses in a subset of patients, especially those with high PD-L1 expression.[4,5] Interestingly, analyses of early ICI trials demonstrated low efficacy in patients with targetable epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) alterations, and consequently, most subsequent trials excluded patients with these and sometimes other actionable alterations. These exclusions have helped reinforce a management paradigm that divides patients into 'driver-positive' and 'driver-negative' subgroups, with the management of 'driver-positive' patients focused, at least initially, on the application of targeted therapies, and 'driver-negative' patients on the use of ICIs with or without chemotherapy.

However, after nearly two decades of targeted therapy development, nine actionable oncogene drivers have been established in NSCLC, each with its own set of approved targeted therapies. With this proliferation of therapeutic options, the phenotype of 'driver-positive' patients has expanded to include tumors with differential sensitivity to ICIs. Understanding the efficacy and toxicity of ICIs in these patient populations is integral to determining how to optimally deploy ICIs in sequence and in combination with the growing list of other systemic therapies, and a better understanding of the biology underlying oncogenic drivers and ICI resistance may help guide rational drug design that allows more patients with oncogenic drivers to benefit from long-term anti-tumor immune responses.

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In this review, we summarize the clinical data on ICIs as monotherapy or in combination with chemotherapy for each of the targetable oncogenic drivers in NSCLC (Table 1 and Figure 1), the known toxicity risks, and discuss potential strategies to enhance benefits in the future.

Clinical efficacy of immunotherapy in NSCLC with oncogene drivers

Epidermal growth factor receptor classical mutations

Classical mutations (exon 19 deletion or exon 21 L858R mutation) in EGFR were the first identified actionable oncogenic driver in NSCLC in 2004,[6] and EGFR-mutated NSCLC remains the best studied oncogene due to high prevalence (~20% of lung adenocarcinoma). Despite early preclinical data suggesting that EGFR mutations upregulated PD-L1 expression,[7–10] and PD-1 blockade improved mouse survival,[11] numerous subgroup analyses from early ICI monotherapy trials demonstrated decreased efficacy in patients with EGFR mutations.[12,13]

In the phase II/III KEYNOTE-010 trial, while pembrolizumab monotherapy showed improved overall survival (OS) compared with docetaxel among previously treated patients with PD-L1 $\geqslant$ 1% [12.7 *versus* 8.5 months; hazard ratio (HR): 0.61; 95% confidence interval (CI): 0.49–0.75; $p < 0.0001$)], subgroup analysis showed no OS improvement in the EGFR-mutant population [HR 0.88 (0.45–1.70)].[4] Similarly, the phase I CheckMate 012 trial demonstrated low efficacy for nivolumab monotherapy as first-line treatment of advanced NSCLC among EGFR-mutant patients, with an overall response rate (ORR) of 23% (14% among patients with no PD-L1 expression *versus* 28% among patients with PD-L1 $\geqslant$ 1%), median progression-free survival (mPFS) of 1.8 months (*versus* 6.6 months among EGFR-WT), and median OS (mOS) of 18.8 months.[14] In the phase III OAK trial, atezolizumab demonstrated a significant improvement in OS with atezolizumab *versus* docetaxel in previously treated NSCLC [mOS 13.8 *versus* 9.6 (HR: 0.73; 95% CI: 0.62–0.87; $p = 0.0003$)]. However, in subgroup analyses, patients with EGFR mutation demonstrated no significant difference in OS whether they were treated with atezolizumab or docetaxel.[15] Similar findings were shown in the phase II BIRCH trial evaluating atezolizumab in the first-, second-, and third-line settings, where atezolizumab had activity in both EGFR-mutant and EGFR-WT tumors, atezolizumab was less efficacious by mOS in the EGFR-mutant group.[16] Finally, the phase II ATLANTIC trial evaluated durvalumab in patients with advanced NSCLC that progressed on at least two prior regimens. While EGFR-mutant NSCLC with PD-L1 $>$ 25% demonstrated improved ORR (12.2%; 95% CI 5.7–21.8%) than PD-L1 $<$ 25% (3.6%, 95% CI: 0.1–18.3%), benefit was very limited, with mPFS of 1.9 months in both groups.[17]

Several meta-analyses confirmed these individual subgroup analyses. A meta-analysis of ICI as second-line therapy in EGFR-mutant NSCLC showed no improved OS compared to docetaxel.[18,19] Patients with EGFR wild-type (WT) non-squamous NSCLC demonstrated a significantly higher ORR to nivolumab than those with EGFR-mutant tumors (19.6% *versus* 8.8%; $p = 0.007$).[20] An independent meta-analysis confirmed that EGFR-mutant NSCLC did not associate with improved OS from anti-PD-1/L1 therapy compared to chemotherapy (HR: 1.11; 95% CI: 0.80–1.53; $p = 0.54$), while the EGFR-WT subgroup demonstrated improved OS (HR: 0.73; 95% CI: 0.61–0.87; $p = 0.001$).[21] One retrospective analysis even showed that the presence of EGFR mutations was associated with a reduced OS when treated with anti-PD-1 nivolumab ($p = 0.02$).[12]

One initial hypothesis was that ICI activity in patients with EGFR mutant may be better in patients without prior TKI exposure. This hypothesis arose from retrospective analysis of the phase I study KEYNOTE-001, where 4 TKI-naïve patients with EGFR-mutant NSCLC had an ORR of 50%, mPFS of 157.5 days, and mOS of 559 days, whereas the 26 TKI-pretreated patients had an ORR of 4%, mPFS of 56 days, and mOS of 120 days.[12] However, this hypothesis was evaluated in a phase II trial (NCT02879994) of pembrolizumab in TKI-naïve patients with EGFR mutations, which was stopped after 11 of 25 planned patients for futility; despite PD-L1 expression $\geqslant$50% in 73% of patients, only one had an objective response, and on re-analysis it was found that an *EGFR* mutation in this patient was reported in error. In addition, two patients subsequently treated with EGFR TKI died, one from pneumonitis, raising concerns about increased toxicity from ICI preceding TKI.[13]

Table 1. Clinical outcomes of ICIs in oncogene-driven NSCLC.

Oncogene	Study name	Phase	Sample (*n*)	Treatment	Line	ORR	mPFS	mOS
EGFR	Monotherapy							
	KEYNOTE 001	I	30	Pembrolizumab	1	TKI naïve: 50% Pretreated: 4%	TKI naïve: 157.5 d Pretreated: 56 d	TKI naïve: 559 d Pretreated: 120 d
	NCT02879994	II	11	Pembrolizumab	1	0%	N/A	N/A
	KEYNOTE 010	II/III	86	Pembrolizumab *versus* docetaxel	2+	N/A	HR: 1.79 (0.94–3.42)	HR 0.88 (0.45–1.70)
	CheckMate 012	I	7	Nivolumab	1	14%	1.8 mo	18.8 mo
	CheckMate 057	III	82	Nivolumab *versus* docetaxel	2+	11%	HR: 1.46 (0.90–2.37)	HR: 1.18 (0.69–2.00)
	POPLAR	II	19	Atezolizumab *versus* docetaxel	2+	N/A	N/A	HR: 0.99 (0.29–3.40)
	OAK	III	85	Atezolizumab *versus* docetaxel	2+	5%	N/A	HR: 1.24 (0.71–2.18)
	BIRCH	II	45	Atezolizumab	1–3	1st line: 23% 2nd line: 0% 3+ line: 7%	1st line: 5.5 mo 2nd line: 1.3 mo 3+ line: 1.4 mo	1st line: 20.1 mo 2nd line: 9.8 mo 3+ line: 7.4 mo
	ATLANTIC	II	102	Durvalumab	3+	PD-L1 > 25%: 12.2% PD-L1 < 25%: 3.6%	PD-L1 > 25%: 1.9 mo PD-L1 < 25%: 1.9 mo	PD-L1 > 25%: 13.3 mo PD-L1 < 25%: 9.9 mo
	CheckMate 012	I	6	Nivolumab + chemo	1	17%	4.8 mo	20.5 mo
	Combination therapies							
	CheckMate 012	I	8	Nivolumab + ipilimumab	1	50%	N/A	N/A
	KEYNOTE 021	I/II	10	Pembrolizumab + ipilimumab	2+	10%	N/A	N/A
	IMpower 150	III	124	ABCP *versus* ACP *versus* BCP	2+	ABCP: 71% ACP: 36% BCP: 42%	ABCP: 10.2 mo ACP: 6.9 mo BCP: 6.9 mo	ABCP: NE ACP: 21.4 mo BCP: 18.7 mo
	ORIENT-031	III	444	Sintilimab + anti-VEGF + chemo (SIC) *versus* Chemo	2+	SIC: 44% Chemo: 25%	SIC: 6.9 mo Chemo: 4.3 mo	N/A
	IMMUNOTARGET	Retro	125	Anti-PD-(L)1	1+	12.2%	2.1 mo	10 mo
HER2	Guisier *et al.*	Retro	23	Anti-PD-(L)1	1+	27.3%	2.2 mo	20.4 mo
	Lai *et al.*	Retro	26	Anti-PD-(L)1	1+	12%	1.9 mo	10.4 mo
	IMMUNOTARGET	Retro	29	Anti-PD-(L)1	1+	7.4%	2.5 mo	20.3 mo
ALK	Monotherapy							
	IMMUNOTARGET	Retro	19	Anti-PD-(L)1	1+	0%	2.5 mo	17.0 mo

(Continued)

Table 1. (Continued)

Oncogene	Study name	Phase	Sample (*n*)	Treatment	Line	ORR	mPFS	mOS
	Bylicki *et al.*	Retro	8	Anti-PD-(L)1	2+	25%	2.4 mo	19.2 mo
	Combination therapy							
	CheckMate 370	I/II	13	Nivolumab + crizotinib	1	38%	N/A	N/A
	JAVELIN Lung 101	Ib	40	Avelumab + crizotinib (A + C) *versus* avelumab + lorlatinib (A + L)	2+	A + C: 16.7% A + L: 46.4%	N/A	N/A
	NCT02393625	I	36	Nivolumab + ceritinib	1+	Nivo 3 mg/kg: 83%/63% (TKI naïve/ treated) Nivo 300 mg: 70%/33%	N/A	N/A
	NCT02013219	Ib	21	Atezolizumab + alectinib	1	81%	21.7 mo	N/A
RET	Guisier *et al.*	Retro	9	Anti-PD-(L)1	2+	37.5%	7.6 mo	N/A
	IMMUNOTARGET	Retro	16	Anti-PD-(L)1	1+	6.3%	2.1 mo	21.3 mo
MET	Guisier *et al.*	Retro	30	Anti-PD-(L)1	2+	35.7%	4.9 mo	13.4 mo
	Sabari *et al.*	Retro	24	Anti-PD-(L)1 + Anti-CTLA-4	1+	17%	1.9 mo	N/A
	IMMUNOTARGET	Retro	23	Anti-PD-(L)1	1+	15.6%	METex14: 4.7 mo	METex14: 25.0 mo
ROS1	Bylicki *et al.*	Retro	1	Anti-PD-(L)1	2+	N/A	1.4 mo	2.8 mo
	IMMUNOTARGET	Retro	7	Anti-PD-(L)1	1+	16.7%		
BRAF V600E	Zhang *et al.*	Retro	6	Anti-PD-(L)1	1+	N/A	N/A	5.0 mo
	Dudnik *et al.*	Retro	21	Anti-PD-(L)1	1+	25%	3.7 mo	NR
	Negrao *et al.*	Retro	37	Anti-PD-(L)1	1+	N/A	9.8 mo	20.8 mo
	IMMUNOTARGET	Retro	17	Anti-PD-(L)1	1+	24.3%	1.8 mo	8.2 mo
KRAS G12C	KEYNOTE 042	Retro	29	Pembrolizumab	1	56.7%	12.0 mo	28.0 mo
	KEYNOTE 189	Retro	37	Pembrolizumab + chemo	1	50.0%	11.0 mo	18.0 mo
	Negrao *et al.*	Retro	30	Anti-PD-(L)1	1+	N/A	2.7 mo	N/A
	IMMUNOTARGET	Retro	100	Anti-PD-(L)1	1+	26.0%	5.5 mo	15.6 mo
KRAS	Huang *et al.*	Meta	121	Anti-PD-(L)1 *versus* chemo	1+	N/A	N/A	HR: 0.60 (0.39–0.93)

ABCP, atezolizumab + bevacizumab + chemotherapy; ACP, Atezo + chemotherapy; BCP, bevacizumab + chemotherapy; d, days; ICIs, immune checkpoint inhibitors; HR, hazard ratio; mo, months; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small-cell lung cancer; ORR, overall response rate; PD-L1, programmed death ligand-1; TKI, tyrosine kinase inhibitor.

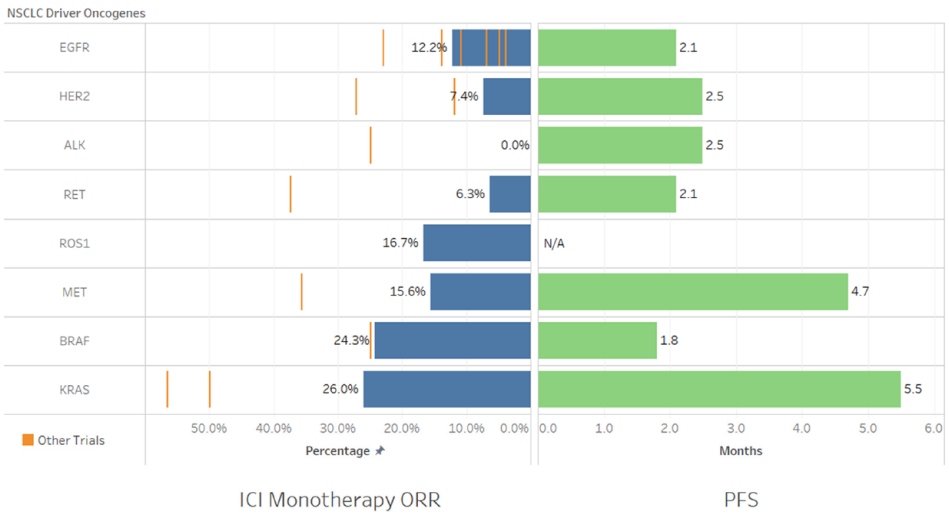

Figure 1. ICI monotherapy ORR and mPFS in NSCLC by driver oncogenes.
*Bars reflect overall ORR (blue) and mPFS (green) demonstrated in retrospective IMMUNOTARGET study. **Vertical orange lines depict ORRs shown in other individual ICI monotherapy trials.
ICIs, immune checkpoint inhibitors; mPFS, median progression-free survival; NSCLC, non-small-cell lung cancer; ORR, overall response rate.

Combination chemoimmunotherapies for EGFR classical mutations. The benefit of adding of ICI to chemotherapy in EGFR-mutant NSCLC is also unclear. In the phase I CheckMate 012 trial evaluating nivolumab in combination with chemotherapy, EGFR mutation status was associated with shorter mPFS [4.8 (95% CI: 0.9–6.8) months *versus* 7.4 (95% CI: 0.1–28.9) months] and OS [20.5 (9.4–35.0) *versus* 24.5 (6.2–35.1) months] compared to EGFR-WT tumors.[22,23] Recently, two retrospective analyses compared combination chemoimmunotherapy to chemotherapy without ICI in TKI-resistant EGFR-mutant NSCLC patients, and both showed no significant from adding ICI in this setting. In one study, the PFS was 5.3 months (chemo-ICI) *versus* 4.8 months (chemotherapy, $p = 0.8$)[24] and in the other, 5.2 *versus* 5.0 months ($p = 0.13$).[25]

Conversely, the addition of chemotherapy with a VEGF inhibitor has shown more potential. In the phase III IMpower 150 trial, the addition of atezolizumab to bevacizumab and chemotherapy (ABCP) as first-line treatment of non-squamous NSCLC demonstrated an OS benefit across all patients, including the EGFR-mutant subgroup. In the dedicated subgroup analysis for patients with *EGFR*-mutations (124 with EGFR mutations, 91 with sensitizing mutations), OS and PFS were improved with ABCP *versus* BCP (OS HR: 0.31 [0.23–0.75]; PFS HR: 0.41 [0.23–0.75]). ORR was 73.5% among those receiving ABCP, compared to 40.9% among those receiving bevacizumab and chemotherapy (BCP). Furthermore, mPFS was 10.2 months in the ABCP group, compared to 7.1 months in the BCP group.[26]

The phase III ORIENT-31 trial evaluated anti-PD1 sintilimab in combination with chemotherapy, with or without the VEGF-inhibitor IBI305 *versus* chemotherapy alone in patients with locally advanced or metastatic NSCLC and EGFR-mutant disease that progressed on EGFR TKI. Significantly longer mPFS of 6.9 months was observed in the group receiving sintilimab plus IBI305 plus chemotherapy, *versus* 4.3 months in those receiving chemotherapy alone [HR 0.46 (95% CI 0.34–0.64), $p < 0.0001$],[27] though inferences regarding the specific benefit attributable to ICI are limited by the use of chemotherapy rather than chemotherapy plus VEGF as the control arm. More data are needed to determine whether VEGF inhibitors truly modulate ICI sensitivity in *EGFR*-mutated tumors.

EGFR exon 20 insertion mutation

EGFR exon 20 insertion (EGFRex20) mutations make up 2–3% of all NSCLC and are associated with poor prognosis due to their resistance to classical EGFR TKIs, with response rates to erlotinib, gefitinib, and afatinib ranging from 3% to 8%. Of note, structurally similar exon 20 insertion mutations are also found in HER2 and make up 90% of HER2 mutations.[28] To date, the FDA has approved two drugs, amivantamab and mobocertinib, for the treatment of EGFRex20-mutated NSCLC,[29,30] and poziotinib has also shown efficacy.[31] While not always explicitly excluded from clinical trials, little data exist on the efficacy of ICIs in EGFRex20-mutant NSCLC. However, a retrospective study did demonstrate improved ORR (71% *versus* 35.7%, $p = 0.14$) and PFS (256 *versus* 50 days, $p = 0.003$) in ICI-treated patients with uncommon EGFR mutations, including exon 18 G719X and exon 20 insertion *versus* common EGFR mutations.[32] Further larger studies would be needed to elucidate the role of ICI in EGFRex20-mutant NSCLC, and whether that truly differs from classical EGFR-mutant NSCLC.

HER2 mutations

HER2 mutations occur in about 3% of lung cancers, and trastuzumab–deruxtecan was recently approved as a targeted therapy for HER2-mutant NSCLC based on results from the DESTINY-Lung02 trial.[33] HER2 (ERBB2) and EGFR (ERBB1) are receptors within the same family of receptor tyrosine kinases and are mutated in similar patient populations (female never smokers),[34] suggesting that these subtypes of NSCLC may also share comparably low ICI response rates.[28] A retrospective study that evaluated nivolumab and pembrolizumab in 23 patients with HER2-mutated NSCLC revealed an ORR of 27.3%, mPFS of 2.2 months (95% CI: 1.7–15.2), and mOS of 20.4 months (95% CI: 9.3–NR). In this study, PFS and OS among HER2-mutated NSCLC treated with ICI were shorter than those with other oncogene drivers, such as BRAF, MET, and RET.[35] PD-L1 status of most study participants was unknown. Another retrospective study showed worse outcomes among 26 HER2-mutated NSCLC patients treated with ICI than non-driver NSCLC, with ORR 12% (95% CI: 3–30%), mPFS 1.9 months (95% CI: 1.5–4.0), and mOS 10.4 months (95% CI: 5.9–NR).[36] PD-L1 expression was also low, with PD-L1 expression $<1\%$ in 77% of the patients analyzed. The retrospective IMMUNOTARGET study included 29 patients with HER2-mutated NSCLC and showed a mPFS of 2.5 months (95% CI: 1.8–3.5). PFS among this population was found to correlate with smoking (3.4 months for smokers *versus* 2.0 months for non-smokers, $p = 0.04$).[21]

Anaplastic lymphoma kinase rearrangement

NSCLC with ALK-fusion rearrangements were evaluated with EGFR alterations in early ICI clinical trials, with comparably low efficacy rates.[21,37] A large retrospective study showed 0% response in 19 patients with ALK-fusion NSCLC treated with single agent ICI. Progressive disease was seen in 68% of the patients, and mPFS was 2.5 months (95% CI: 1.5–3.7).[21] Another retrospective study showed an ORR of 25%, mPFS of 2.4 months (95% CI: 2.1–NR), and mOS of 19.2 months (13.2–NR) among 8 ICI-treated patients with ALK-fusion NSCLC who were previously treated with chemotherapy or targeted therapy.[38]

ALK TKIs such as crizotinib, ceritinib, and alectinib have been established as first-line treatments for ALK-fusion NSCLC, and the addition of immunotherapy to those have been explored. Adding nivolumab to crizotinib in the first-line treatment of ALK-fusion NSCLC was evaluated in phase I/II study CheckMate 370; however, the trials were discontinued due to severe grade $\geqslant 3$ hepatic toxicities among 38% of study participants, two of whom subsequently died. Among the 13 patients, partial response was seen in 38%,[39] which is lower than with crizotinib alone; while efficacy was likely blunted by the observed toxicities, there was little evidence for additional benefit from including ICIs.

Other combinations showed more tolerable toxicity profiles but little convincing evidence of additive or synergistic benefit. The phase Ib JAVELIN Lung 101 trial assessed avelumab in combination with lorlatinib in ALK-fusion NSCLC patients who progressed after chemotherapy, yielding an ORR of 46.4% (95% CI, 27.5–66.1),[40] comparable to lorlatinib alone. Nivolumab in combination with ceritinib was shown to be effective in a phase I dose escalation study (NCT02393625), with an ORR of 63% (95% CI: 25–92%) among ALK TKI-treated patients and ORR 83% (95% CI: 36–100%) among ALK TKI-naïve patients.[41] Alectinib has demonstrated both systemic and

CNS efficacy in ALK-fusion NSCLC, and a phase Ib study evaluated the addition of atezolizumab to alectinib in treatment-naïve patients, including those with untreated asymptomatic brain metastases. This combination demonstrated an ORR of 81% (95% CI: 58.1–94.6), mPFS of 21.7 months (95% CI: 10.3–21.7), and mDoR of 20.3 months (95% CI: 11.5–20.3), with 62% of patients experiencing grade 3 adverse events (AEs).[42] However, it is unclear how much efficacy is due to the addition of ICI rather than arising from the TKI alone, and toxicity rates were higher.

In the IMpower150 trial, improved survival was observed for patients receiving atezolizumab plus bevacizumab and chemotherapy (ABCP) including 28 patients with ALK translocations. Among patients with EGFR mutations or ALK fusion, PFS was 9.7 months in the ABCP group, compared to 6.1 months in the BCP group [HR 0.59 (95% CI: 0.37–0.94)].[26]

RET, ROS1, and NTRK rearrangement

There are scant data assessing the response to immunotherapy among NSCLC patients harboring rare translocations, such as RET, ROS1, or NTRK. A retrospective study evaluated nine patients with RET-translocated NSCLC treated with nivolumab or pembrolizumab in the second line and beyond, and found an ORR of 37.5% and mPFS of 7.6 months (95% CI: 2.3–NR).[43] Another retrospective study by Mazieres *et al.* showed an ORR of 25% and mPFS of 2.1 months (95% CI: 1.3–4.7) among 16 patients with RET-rearranged NSCLC who received single-agent anti-PD1/PD-L1 therapy.[21] For ROS1-rearranged lung cancer patients, one retrospective, multicenter study included only one patient with ROS1-translocated NSCLC treated with ICI that progressed on targeted treatment and chemotherapy. A PFS of 1.4 months and an OS of 2.8 months were observed.[38]

MET exon 14 skipping mutation

MET TKIs have demonstrated durable responses in patients with advanced MET exon 14-altered (METex14) NSCLC and achieved their first regulatory approval in 2020. In contrast to the other driver alterations discussed above, METex14 can occur in patients with smoking history and a subset of METex14 tumors have moderate to high PD-L1 expression. Despite this, a study by Sabari *et al.* showed an ORR of 17% (95% CI 6-36%) and mPFS of 1.9 months (95% CI: 1.7–2.7) in patients with advanced METex14 NSCLC treated with single-agent anti-PD-1/PD-L1 therapy or combination anti-PD-1 and anti-CTLA-4 therapy. No association was found between PD-L1 expression and tumor mutational burden (TMB; $p = 0.0069$), and survival outcomes did not improve among those with high PD-L1 ($\geq$50%) or high-TMB tumors.[44] This relatively low response was further validated by two separate retrospective analyses. One study included 30 patients with MET-mutated metastatic NSCLC treated with single-agent nivolumab or pembrolizumab and showed an ORR of 36%, a mPFS of 4.9 months (2.0–11.4) and a mOS of 13.4 months (9.4–NR). It is worth noting that at least 37% of patients in this study had PD-L1 expression >50%, and that ICI was used in the first- and second-line setting for most participants in this study.[35] In IMMUNOTARGET analysis, the METex14 subgroup ($n = 23$) had an ORR of 15.6% and a PFS of 4.7 months.[21] Taken together, these data suggest that METex14 tumors had some more clinical benefit than EGFR/HER2-mutant or ALK/ROS1/RET-fusion lung cancers, but still overall diminished response to ICI therapies compared to WT patients.

BRAF V600E mutation

Like METex14 alterations, BRAF alterations can occur in different patient populations than the classical EGFR, HER2, and fusions, and BRAF-directed therapies are approved in NSCLC only after first-line systemic chemoimmunotherapy. To elucidate the role of ICIs in BRAF-mutated NSLC, Zhang *et al.* conducted a study evaluating survival outcomes among patients with WT *versus* mutant-BRAF NSCLC treated with ICI. Patients with WT BRAF were shown to have higher PD-L1 expression compared with those with BRAF-mutated NSCLC. While ICI demonstrated no survival difference between patient with WT BRAF *versus* BRAF-mutated NSCLC (OS of 11 *versus* 10 months; $p = 0.334$), subgroup analyses revealed a survival benefit among patients with BRAF V600E compared with the non-V600E group (OS of 14 *versus* 5 months, $p = 0.017$). Mutant-BRAF NSCLC was also associated with high TMB compared with WT BRAF ($p = 0.009$).[45]

Another retrospective study confirmed the findings of higher TMB and PD-L1 expression among

patients with BRAF-mutant NSCLC. Median PFS in those with BRAF V600E *versus* BRAF non-V600E mutations treated with ICIs were comparable [3.7 months (95% CI: 1.6–6.6) *versus* 4.1 months (95% CI: 0.1–19.6)], respectively.[46] However, this study did not include WT BRAF NSCLC treated with ICIs as a control group. Another retrospective analysis also found the longest PFS and OS among NSCLC with BRAF mutation compared with other driver oncogenes (such as EGFR, HER2, KRAS). PFS and OS were numerically improved in BRAF V600E *versus* non-V600E but did not reach statistical difference (PFS 9.8 *versus* 5.4 months; OS 20.8 *versus* 14.9 months).[47]

KRAS G12C mutation

KRAS mutations are the most common oncogenic driver alteration in lung adenocarcinoma in western populations, and until the recent advent of direct KRAS G12C inhibitors,[48,49] patients with *KRAS*-mutant NSCLC were treated with standard ICIs and/or chemotherapy. Even with the recent accelerated approval of sotorasib and adagrasib, the first-line treatment remains ICIs with or without platinum doublet chemotherapy. Like *BRAF* alterations, *KRAS* mutations, and in particular transversion KRAS mutations (e.g. KRAS G12C and G12V), frequently occur in patients with smoke exposure,[50–52] and oncogenic RAS signaling has been implicated in increased PD-L1 expression, increased CD8+ T cell infiltration, and higher TMB, all associated with an increased likelihood of benefit to ICIs,[53,54] though the association with increased PD-L1 expression is conflicting.[55,56]

Concordant with these molecular features, and in contrast to the other driver mutants discussed thus far, clinical trial data have generally demonstrated that patients with *KRAS* mutations benefit from ICI as much or more than WT patients.[57] A planned subgroup analysis of patients treated with second- or later-line nivolumab on CheckMate 057 demonstrated a non-significant trend toward improved outcomes in patients with KRAS mutations.[58] A retrospective analysis of first-line pembrolizumab *versus* chemotherapy in KEYNOTE-042 similarly demonstrated improved outcomes in KRAS-mutant NSCLC, with improved ORR, PFS, and OS from pembrolizumab *versus* chemotherapy in KRAS-mutant patients that was not seen in the WT patients [ORR: KRAS-mutant 56.7% (95% CI: 37.4–74.5) *versus* WT 29.1% (95% CI: 21.4–37.9); PFS: KRAS-mutant 12 *versus* 6 months; HR: 0.51 (95% CI: 0.29–0.87) *versus* WT 6 *versus* 6 months; HR: 1.00 (95% CI: 0.75–1.34); KRAS-mutant 28 *versus* 11 months; HR 0.42; 95% CI: 0.22–0.81 *versus* WT 15 *versus* 12 months; HR: 0.86; 95% CI: 0.63–1.18].[59] A meta-analysis of five randomized trials demonstrated that patients with KRAS mutations benefitted from ICIs compared to chemotherapy, with a pooled HR of 0.60 (95% CI: 0.39–0.93, $p = 0.02$), while no survival benefit was seen in the KRAS-WT subgroup.[60]

Retrospective real-world data have not as consistently shown improved outcomes in KRAS-mutant patients relative to WT, but outcomes have been at least comparable. Analysis of patients treated with second-line nivolumab through the Italian Expanded Access Program ($n = 530$) did not demonstrate differential benefit in KRAS mutant *versus* WT patients (ORR 20% *versus* 17%, $p = 0.39$; PFS 4 *versus* 3 months, $p = 0.50$; OS 11.2 *versus* 10 months, $0 = 0.80$).[61] A retrospective cohort of 282 patients from a single center in France treated with ICIs across lines showed no significant differences in ORR, OS, or PFS in patients with KRAS mutations *versus* WT, nor were there any differences between KRAS-mutant subtypes.[62] The authors did observe, however, that response rates were more consistently linked to high PD-L1 expression (⩾50%) in the KRAS-mutated patients compared to others. Conversely, a retrospective analysis of patients with PD-L1 > 50% from the Flatiron database ($n = 573$ KRAS-mutant, $n = 554$ KRAS-WT) demonstrated improved outcomes in KRAS-mutant patients compared to WT in patients treated with monotherapy (mOS 21.1 *versus* 13.6 months, $p = 0.03$) but not among those treated with chemoimmunotherapy (KRAS-mutant *versus* KRAS-WT, mOS 20.0 *versus* 19.3, $p = 0.93$).[63] Though not statistically significant, patients with KRAS alterations benefitted from either ICI or chemoimmunotherapy, whereas those without KRAS alterations trended toward benefit from combination therapy over ICI monotherapy.

Other analyses demonstrate comparable outcomes in KRAS-mutant *versus* WT patient treated with combination chemoimmunotherapy. A retrospective analysis of KEYNOTE-189 trial evaluating pembrolizumab *versus* placebo in combination with chemotherapy in non-squamous NSCLC did not find any differential

benefit with the addition of ICI to chemotherapy in patients with KRAS mutations compared to those without; notably, patients with both KRAS mutant and WT tumors appeared to benefit from combination chemoimmunotherapy compared to chemotherapy alone, though the OS benefit in KRAS mutant tumors did not reach statistical significance (KRAS-WT HR 0.55, 95%: CI 0.37–0.81; KRAS-mutant HR 0.79, 95% CI: 0.45–1.38).[64] A pooled analysis from the FDA of 12 registrational clinical trials of ICI monotherapy or chemoimmunotherapy ($n = 1430$, 39% KRAS-mutated, 61% WT) demonstrated similar outcomes in patients with and without KRAS mutations, both when treated with ICI monotherapy or with ICI + chemotherapy.[65] Both KRAS-mutant and KRAS-WT patients had higher ORR and median OS when treated with chemo plus ICI *versus* ICI alone.

Recent data have also evaluated the safety and efficacy of combining KRAS inhibitors with ICI. CodeBreak 100/101 evaluated the combination of sotorasib with pembrolizumab or atezlizumab and demonstrated a higher incidence of grade 3–4 AEs, specifically liver enzyme elevations, which occurred in 43% of patients. Response rates were 29% which is comparable to or lower than monotherapy.[66] In contract, adagrasib combined with pembrolizumab demonstrated fewer safety events, with only grade 3 increases in liver enzymes occurring in 9% of patients. ORR was 49% in KRYSTAL-7 (26 of 53) and 57% (4 of 7) in the KRYSTAL-1 phase Ib cohort.[67]

Taken together, these data suggest that patients with driver alterations in EGFR, HER2, and fusion alterations (ALK, ROS1, RET, NTRK) rarely derive benefit from ICIs even when PD-L1 expression is high. Patients with MET and BRAF alterations have higher rates of efficacy that are nonetheless decreased compared to the WT population, which may correspond with increased tobacco and other immunogenic mutagen exposure in this patient population. Conversely, the overall population of patients with KRAS mutations appear to have a likelihood of benefit comparable to the driver negative population, and putative biomarkers such as high PD-L1 expression, high TMB, and smoking history appear to be more predictive in the KRAS population than with other driver oncogenes. There does appear to be more heterogeneity of ICI outcome in KRAS-mutant lung cancers, which may reflect distinct biologies within *KRAS*-altered NSCLC. Accumulating data have demonstrated that *KRAS* mutant NSCLC can be divided into biologically distinct subgroups defined by co-mutations in TP53 (KP), LKB1/STK11 and KEAP1 (KL), and CDKN2A/B (KC), with distinct biology and clinical outcomes.[68–70] *STK11* co-mutations may promote a cold tumor microenvironment with increased T-cell suppressive neutrophils and markers of T-cell exhaustion,[70–72] and KEAP1 may associate with decreased sensitivity to both chemotherapy and anti-PD1 therapy. Concordantly, increasing data have also demonstrated worse ICI outcomes in patients with KRAS and STK11 co-mutations, including worse ORR (KRAS/STK11 7.4% *versus* KRAS-mutant/STK11-WT 31.9%, $p < 0.001$), PFS and OS (PFS: 1.8 *versus* 2.7 months; HR: 1.87; 95% CI: 1.32–2.66; $p < 0.001$; OS: 6.4 *versus* 16.0 months; HR: 1.99; 95% CI: 1.29–3.06; $p = 0.0015$).[73] Analysis of patients treated with chemotherapy and immunotherapy also demonstrated worse ORR in STK11-mutated patients (mPFS 4.8 *versus* 7.2 months, HR: 1.58, 95% CI: 1.1–2.0; $p = 0.0063$) and shorter OS (mOS 10.6 *versus* 16.7 months, HR: 1.58, 95% CI: 1.09–2.27; $p = 0.0083$), with no benefit from the addition of pembrolizumab to chemotherapy.[74] Analyses in larger, multi-center retrospective cohorts also demonstrated worse clinical outcomes to ICI in patients with either STK11 and KEAP1 mutations, but this decrement was more specific to patients with KRAS co-mutations.[75]

Conversely, the presence of *TP53* co-mutations may increase the likelihood of ICI benefit. KRAS/TP53 co-mutated tumors have higher PD-L1 expression[76,77] and higher TMB,[70,71] possibly independent of the KRAS mutation, and small clinical case series have demonstrated improved ICI outcomes in KRAS/TP53 co-mutated tumors.[78,79] Indeed, one small series demonstrated that, while patients with KRAS/STK11 co-mutations had poor outcomes as expected, patients with KRAS/STK11/TP53 co-mutations had improved outcomes (PFS 2.4 months *versus* 13 months; OS 7.1 months *versus* 22 months).[80]

Taken together, the association between KRAS mutations and ICI outcomes is complex, likely shaped by diverse associations with PD-L1 expression, tumor immune reprogramming, and smoking, along with independent biologic and prognostic effects from other co-mutations. This diversity may undergird the mixed clinical results, and more work will need to be done to disentangle the effects of these different alterations on tumor biology and ICI efficacy. However, most

evidence suggests that patients with KRAS-mutated patients may benefit from ICIs, and KRAS-directed TKIs remain approved only in the second-line setting after a trial of immunotherapy with or without chemotherapy.

ICI after radiotherapy for oncogene-driven NSCLC

The role of adjuvant ICI following radiation therapy (RT) in oncogene-driven NSCLC is limited. While the PACIFIC trial has been practice-changing for the management of unresectable stage III NSCLC with the addition of durvalumab following chemoradiation, the survival benefit did not extend to the *EGFR*-mutant NSCLC subgroup. Among a post-hoc subgroup analysis of 35 patients with *EGFR*-mutant NSCLC from the PACIFIC trial, median PFS with adjuvant durvalumab did not differ from placebo (11.2 *versus* 10.9 months, respectively; HR: 0.91), nor did OS (46.8 *versus* 43.0 months; HR 1.02).[81] Similarly, consolidation durvalumab after chemoradiation has not shown to be efficacious in *HER2*-mutant stage III NSCLC in a small retrospective analysis, with shorter disease-free survival among patients with *HER2*/*EGFR* mutations *versus* WT (7.5 months *versus* NR, $p = 0.04$).[82] An institutional analysis at MD Anderson also showed significantly shorter PFS after chemoradiation and consolidative durvalumab among patients with oncogene-driven stage III unresectable NSCLC compared to those without driver mutations [mPFS 8.4 *versus* 40.1 months (HR: 2.75; 95% CI: 1.64–4.62)]. Specifically, *KRAS*-mutant NSCLC was associated with worse PFS (HR: 5.79; 95% CI: 2.69–12.47).[83] Due to the limited sample size and stage of disease analyzed, the benefit of ICI following RT in the oncogene-driven population remains unclear to date.

Toxicity

While ICIs offer antineoplastic benefits in NSCLC, they also come with various immune-related AEs (irAEs) which can limit their use in certain patients. Most irAEs are mild and self-limiting; however, severe cases can occur and can be life threatening. IrAEs include colitis, pancreatitis, hepatotoxicity, inflammatory arthritis, dermatitis or rash, pyrexia, endocrine toxicities such as thyroid and pituitary dysfunction, and pulmonary toxicities including pneumonitis and interstitial lung disease (ILD).[84] While some irAEs such as diarrhea and rash can be proactively managed, more serious, higher grade irAEs such as colitis, pneumonitis, and hepatotoxicity may prompt treatment discontinuation. These irAEs of ICIs often overlap with the AEs of TKIs and other targeted therapies commonly used in NSCLC.

Pulmonary toxicity

The combination of TKIs with ICIs has shown high rates of pulmonary toxicities, especially ILD/pneumonitis, in particular with EGFR and ALK inhibitor combinations. The phase Ib TATTON trial that evaluated osimertinib combined with durvalumab in 23 patients with EGFR-mutant NSCLC demonstrated a 22% rate of ILD, and recruitment to the phase III CAURAL trial was suspended. Osimertinib was discontinued in 26% of patients due to AEs, and 39% discontinued durvalumab due to AEs. The most common AEs were rash (48%), vomiting (43%), and diarrhea (39%), with 48% having grade 3 and above AE.[85] In addition, one patient had grade 3 neutropenia and one with grade 2 abnormal liver enzymes. A retrospective study evaluating the use of nivolumab with EGFR-TKIs found a higher rate of interstitial pneumonitis (25.7%, 95% CI: 16.0–37.6) than with EGFR-TKI monotherapy (4.59%; 95% CI: 4.06–5.16).[86]

Even sequential use of ICI followed by osimertinib demonstrated high risk of ILD/pneumonitis. A study by Schoenfeld *et al.* assessed severe irAEs among patients receiving sequential PD-(L)1 blockade followed by osimertinib, most of which were grade 3 pneumonitis (66.7%). Among 41 patients treated with ICI followed by osimertinib, 15% developed irAEs, especially in those who began osimertinib within 3 months of prior ICI (24%). This was less pronounced in those who began osimertinib within 3–12 months of prior ICI (13%) and within >12 months of ICI (0%). Hence, timing of therapy is a strong determinant of irAE risk. No severe irAEs were observed among patients receiving ICI followed by afatinib or erlotinib.[87] A mechanistic study showed osimertinib led to severe lung injury more frequently than gefitinib due to increased proinflammatory cytokines,[88] suggesting this association may be particularly pronounced with osimertinib.

Newer antibody-based therapies, such as amivantamab and trastuzumab deruxtecan, carry independent risks of ILD. The DESTINY-Lung01 trial reports a 26% rate of ILD/ pneumonitis with

trastuzumab deruxtecan 6.4 mg/kg every 3 weeks dosing. However, a pooled analysis that evaluated trastuzumab deruxtecan in 1150 heavily pretreated patients with lung and breast cancer demonstrated a 15.4% rate of ILD, with 2.2% grade 5 irAE from ILD.[33] Thus, the most recent DESTINY-Lung02 trial investigating the 5.4 mg/kg dosing required no current history of ILD, suspected ILD or pneumonectomy in eligible participants. In the phase I CHRYSALIS trial evaluating amivantamab in EGFRex20 mutated NSCLC, ILD including pneumonitis was observed in 4% of patients.[30] Thus, certain new targeted therapies should be used with caution in lung cancer patients with ILD or suspected ILD, and the optimal and safest sequencing of these drugs with respect to ICIs will need to be evaluated. Currently, while trastuzumab deruxtecan is approved in the second-line setting after standard first-line systemic therapy, many providers will hold first-line ICI due low efficacy rates and the risk of developing pneumonitis and thereby preventing second-line use of trastuzumab deruxtecan.

Hepatotoxicity

Hepatotoxicity is common, occurring in 16% of patients receiving ICIs and is often asymptomatic. Other than treating with steroids, society guidelines recommend holding ICI in grade 2 immune-mediated hepatotoxicity (IMH) and permanently discontinuing ICI in grade 3 and above IMH.[89]

Crizotinib after ICI has been associated with increased hepatotoxicity in patients with ALK-fusion NSCLC. Among 11 patients treated with ICI followed by crizotinib, 45.5% developed grade 3 or 4 increase in alanine transaminase (ALT) level and 36.4% experienced grade 3 or 4 increase in aspartate transaminase (AST) level, though toxicity was reversible.[90] In contrast, only 8.1% and 3.4% of those treated with crizotinib alone experienced grade 3 or 4 increase in ALT and AST, respectively ($p < 0.0001$). Similarly, 5 of 13 (38%) patients with ALK-fusion NSCLC treated with nivolumab plus crizotinib in the phase I/II CheckMate 370 trial developed grade 3 or higher hepatic toxicities that led to the discontinuation of therapy. Hepatotoxicity was thought to have contributed to the death of two patients.[39] These toxicities were not as pronounced with other ALK inhibitors.

The concurrent use of durvalumab and gefitinib in a phase I study (NCT02088112) led to grade 3–4 elevated liver enzymes in 35% of patients, resulting in drug discontinuation. The combination led to greater toxicity than each individual agent without significant improvement in PFS.[91] Another phase Ib study evaluated atezolizumab plus erlotinib in patients with NSCLC. While the ORR was promising at 75% (95% CI: 51–91%), grade 3–4 AEs occurred in 39% of patients, with the most common being pyrexia (18%) and elevated ALT (18%).[92]

The phase I/II KEYNOTE 021 study evaluated the use of pembrolizumab in combination with erlotinib or gefitinib as first-line treatment for EGFR-mutant NSCLC. Among seven patients treated with pembrolizumab plus gefitinib, 71.4% had grade 3–4 liver toxicity, deeming this combination unfeasible. While pembrolizumab plus erlotinib demonstrated a manageable safety profile, with rash (50%), diarrhea (33.3%), and hypothyroidism (33.3%) being the most common AEs, its ORR of 41.7% is worse than historical controls with single-agent erlotinib.[93]

Recently, a phase Ib trial evaluating the combination of sotorasib with pembrolizumab or atezolizumab in advanced KRAS G12C-mutated NSCLC observed grade 3–4 hepatotoxicity in 43% of patients, significantly higher than previously observed with monotherapy.[66]

Taken together, these data suggest higher incidence of irAEs in the context of targeted therapy given with ICIs. Notably, in many cases, these toxicities seem more pronounced with certain drugs, suggesting an interaction between ICI and the drug-specific mechanisms of toxicities that would allow different combinations to be explored. However, despite this specificity, the incidence of higher grade toxicities on the whole appears to be higher, without any evidence to-date of improved outcomes from combination rather than sequential therapy. More data will be necessary to identify safe combination approaches that enhance clinical outcomes.

Mechanisms for low response rates and possible strategies to improve benefit

Taken together, the data suggest that patients with driver alterations in EGFR, HER2, and the fusion alterations (ALK, ROS1, RET, and others) do not receive comparable benefit from ICIs as do patients without these driver alterations, and even those alterations that can occur in smokers,

specifically METex14 and BRAF, may have a lower rates of response and PFS. Understanding the mechanisms of low antitumor immunity and identifying strategies to overcome this phenotype has thus become an urgent unmet clinical need. Here we discuss some of the hypotheses to-date for low ICI efficacy in these specific drivers, and the therapeutic strategies that have been trialed.

Differential PD-L1 expression and outcome association

The association between driver alterations and PD-L1 expression is heterogeneous. Focusing specifically on EGFR mutations, a pooled analysis of 15 clinical trials along with analyses of the TCGA and a cohort from the Guangdong Lung Cancer Institute demonstrated decreased PD-L1 expression in EGFR-mutated tumors,[37,94,95] while many other studies have demonstrated no association between EGFR mutation status and PD-L1,[96] or an association between EGFR mutations and high PD-L1.[11,97–99] Another meta-analysis by Lan *et al.* concluded that PD-L1 expression was lower in EGFR-mutated NSCLC than in EGFR-WT NSCLC (OR: 0.64; 95% CI: 0.45–0.91; $p=0.014$), but did show higher PD-L1 levels in KRAS mutant lung cancers (OR: 1.45; 95% CI: 1.18–1.80; $p=0.001$).[100] Schoenfeld *et al.* also found that KRAS-mutated NSCLC, along with TP53-mutation, correlated the most strongly with high PD-L1 expression, while STK11 and EGFR alterations were associated with low PD-L1 expression. Notably, PD-L1 expression was found to vary by the organ from which tissue was sampled, which may confound the use of PD-L1 as a predictor of ICI response.[95] Other driver mutations are less well studied; in one series, RET-fusion tumors were found to have decreased PD-L1 expression (PD-L1 < 50% in 81% of tumors) and decreased TMB, and PD-L1 did not associate with response.[101]

Biologically, it may be that EGFR-mutated tumors are distinct from other tumors that are typically associated with smoking. A retrospective study suggested that low rates of CD8+ tumor infiltrating lymphocytes and concurrent PD-L1 expression within the tumor microenvironment may explain the low ORRs of EGFR-mutant NSCLC to PD-1/L1 inhibitors.[37] In addition, the predictive role of PD-L1 expression among NSCLC with EGFR mutation was unclear. In a study of patients with PD-L1 expression >50%, those with EGFR-mutant NSCLC were found to have significantly shorter OS than those with EGFR-WT tumor treated with pembrolizumab (mOS 6.5 *versus* 15.7 months). Among those with EGFR mutations, OS did not significantly differ based on PD-L1 expression.[4] While another retrospective study indicated that PD-L1 expression was associated with a significantly longer PFS among patients with EGFR-mutated NSCLC treated with ICI monotherapy, compared to those with negative PD-L1 expression (2.8 *versus* 1.7 months, $p=0.01$),[21] it may be that PD-L1 is not as tightly linked to outcome as it is in patients without oncogenic driver alterations.

Conversely, smoking may be associated with response even in EGFR mutant tumors. In a study of non-squamous NSCLC patients treated with nivolumab, former and current smokers with demonstrated an ORR of 21.5% compared to 9.2% in never-smokers ($p=0.0001$). Among never-smokers, those with EGFR-WT NSCLC demonstrated an ORR of 11% *versus* 1.9% among EGFR-mutant subgroup ($p=0.04$), though median OS and 12-month PFS were not significantly different. However, among former and current smokers, ORR, DCR, PFS, and OS were not significantly different between those with EGFR-mutant *versus* WT tumors.[58]

Tumor mutational burden

While the association between driver alterations and PD-L1 is heterogeneous, the link between driver mutation status and TMB has been more conclusively established,[102–105] with markedly lower TMBs in patients with EGFR, HER2, and fusion alterations compared to those with KRAS mutations or no detectable driver. One hypothesis for low rates of response in these tumors, therefore, is that these tumors are less immunogenic due to lower neoantigen loads. It is also the case that many oncogenic driver alterations are known to be more prevalent in patients with minimal or no smoking exposure, and smoking is associated with both a higher TMB and with a higher likelihood of benefit to ICI.[103,106,107] Whether the association between TMB and outcome reflects neoantigen load, or whether smoking or other mutagenic processes themselves are important in generating an antitumor response, has not been fully established.

Cold tumor microenvironment

Concordant with the hypothesis that driver-mutated tumors are less immunogenic, histologic analyses have suggested that these tumors associate with less inflamed tumor immune microenvironments. EGFR-mutated tumors, for example, in addition to associating with likely lower PD-L1, were also associated with decreased CD8+ TIL infiltrate,[37,94] as was a small series of ALK-positive specimens.[37] A retrospective analysis of surgically resected NSCLC specimens demonstrated an immunologically inert phenotype in EGFR-mutant lung cancers, with decreased cytotoxic T-cell infiltrate, low T-cell receptor clonality, and increased CD73/adenosine pathway signaling,[102] with a similar though underpowered immunoprofile in tumors harboring other driver alterations. Increased immune suppression through CD73/adenosine signaling was also concordantly observed in multiple EGFR-mutant NSCLC cell lines.[108] EGFR alterations may have other immune effects as well,[109] including effects on the activity of regulatory T cells (Tregs),[110,111] and increased activation of myeloid-derived suppressor cells after EGFR TKI therapy.[112]

Another distinct mechanism of immune suppression implicated in both EGFR and ALK-altered tumors is dysregulation of the Hippo pathway, which acts through the YAP protein and has crosstalk both with EGFR and ALK signaling.[113,114] In addition to its known role in cancer progression, drug resistance, and metastasis,[115] YAP may also inhibit antitumor immunity through negative regulation of the innate immune response,[116] other tumor-associated immune cells,[116–118] and regulation of PD-L1 protein expression.

Therapeutic strategies

Given the apparent primary resistance of many driver-mutated tumors to ICIs, strategies to enhance antitumor immunity in these tumors remains an important unmet clinical need, not least because targeted therapies do not regularly provide the long-term durable treatment responses that can be seen with immune-based therapies. To date, most efforts have relied on combining ICIs with other therapies. While there is ample theoretical evidence that chemotherapy, RT, or targeted therapies can enhance antitumoral immunity,[119–122] as discussed above there are little data definitively demonstrating that this actually occurs, and in fact simulation experiments suggest that the improved ICI + chemotherapy response rates are largely due to non-overlapping treatment sensitivities.[123] The enhanced efficacy of chemotherapy + ICIs in driver-mutated patients is also difficult to assess because EGFR/ALK-altered patients were excluded from many of these later ICI trials. The PACIFIC trial evaluated the benefits of durvalumab given after definitive concurrent chemoradiation and demonstrated no benefit to durvalumab over placebo in EGFR-mutated patients, both in planned subgroup analyses and in subsequent real-world retrospective datasets.[83,124–126] Other trials of combination chemotherapy with immunotherapy that include driver-mutated patients are ongoing (CHECKMATE 722, NCT02864251; KEYNOTE-789, NCT03515837).

The most convincing benefit occurred in the combination of chemotherapy with atezolizumab and bevacizumab (ABCP) *versus* chemotherapy + bevacizumab (BCP) in the IMpower150 trial, even in patients with EGFR and ALK alterations.[127] Specific evaluation of the role of bevacizumab in this combination was not done, but the benefit observed in this trial compared to comparable negative data in other trials that included patients with EGFR or ALK alterations treated with ICIs suggests that the VEGF inhibitor may have a differential therapeutic benefit, consistent with preclinical data demonstrating immunomodulatory effects from VEGF inhibition.[128–130] Other combination strategies, such as anti-PD-(L)1 combined with CTLA-4 inhibitors, have not been evaluated specifically in EGFR/driver-mutated NSCLC, and other rational combinations, including IL-10 receptor agonists, YAP inhibitors, and an anti-CD73 compound, remain under early-phase investigation.[109]

Conclusion

The development of targeted therapies and immunotherapies has revolutionized the treatment landscape for NSCLC. It is increasingly important to understand when and how to use targeted therapy, immunotherapy, chemotherapy, and RT alone or in combination, as each driver has its distinct pattern of response to each treatment categories. EGFR classical and exon 20 mutations, HER2 mutations, and ALK/ROS1/RET/NTRK-fusion lung cancers have overall low response rate and short PFS with ICI, either as monotherapy or given with chemotherapy.

METex14 skipping and BRAF-mutant lung cancer have relatively increased clinical benefit, but efficacy that is still less than the general population of NSCLC patients. Patients with KRAS-mutated lung cancer can have excellent responses to ICIs, but the clinical picture is heterogeneous, likely due in part to the effects of KRAS co-mutations on outcome. Efforts to combine ICIs with targeted therapies have been hampered by higher rates of toxicity without evidence of enhanced benefit, though investigation of novel agents and combinations will be important. Future research and clinical investigation are still urgently needed to bring immunotherapy's long-term benefit to different oncogene-driver lung cancer subgroups.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Author contribution(s)
Natalie I. Vokes: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

Kelsey Pan: Conceptualization; Data curation; Investigation; Methodology; Visualization; Writing – original draft; Writing – review & editing.

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Acknowledgements
We thank Drs. Jianjun Zhang and John V. Heymach for helpful discussion.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: NIV is supported by The Mark Foundation Damon Runyon Physician Scientist Award, Conquer Cancer Young Investigatory, and SITC Genentech Women in Cancer Immunotherapy Fellowship. XL is supported by Damon Runyon Cancer Research Foundation and V Foundation for Cancer Research.

Competing interests
XL receives consulting/advisory fees from AstraZeneca, EMD Serono (Merck KGaA), Spectrum Pharmaceutics, Novartis, Eli Lilly, Boehringer Ingelheim, Hengrui Therapeutics, Janssen, Blueprint Medicines, Sensei Biotherapeutics, Daiichi Sankyo, Bicara, Regeneron, ArriVent, Abion, Pinetree therapeutics, and Abbvie. XL receives research funding to the institution from Eli Lilly, EMD Serono, Regeneron, Janssen, Boehringer Ingelheim, ArriVent, and Teligene.

NIV receives consulting/advisory feeds from Regeneron, Sanofi, Eli Lilly, OncoCyte, and research funding from Mirati.

Availability of data and materials
Not applicable.

References

1. Pao W, Miller V, Zakowski M, *et al*. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci* 2004; 101: 13306–13311.
2. Lynch TJ, Bell DW, Sordella R, *et al*. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non–small-cell lung cancer to gefitinib. *N Engl J Med* 2004; 350: 2129–2139.
3. Paez JG, Jänne PA, Lee JC, *et al*. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* 2004; 304: 1497–1500.
4. Herbst RS, Baas P, Kim D-W, *et al*. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. *Lancet* 2016; 387: 1540–1550.
5. Reck M, Rodríguez-Abreu D, Robinson AG, *et al*. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *N Engl J Med* 2016; 375: 1823–1833.
6. Gazdar AF. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. *Oncogene* 2009; 28: S24–S31.

7. Chen N, Fang W, Zhan J, *et al*. Upregulation of PD-L1 by EGFR activation mediates the immune escape in EGFR-driven NSCLC: implication for optional immune targeted therapy for NSCLC patients with EGFR mutation. *J Thorac Oncol* 2015; 10: 910–923.
8. Lin K, Cheng J, Yang T, *et al*. EGFR-TKI down-regulates PD-L1 in EGFR mutant NSCLC through inhibiting NF-κB. *Biochem Biophys Res Commun* 2015; 463: 95–101.
9. Shostak K and Chariot A. EGFR and NF-κB: partners in cancer. *Trends Mol Med* 2015; 21: 385–393.
10. Zhang N, Zeng Y, Du W, *et al*. The EGFR pathway is involved in the regulation of PD-L1 expression via the IL-6/JAK/STAT3 signaling pathway in EGFR-mutated non-small cell lung cancer. *Int J Oncol* 2016; 49: 1360–1368.
11. Akbay EA, Koyama S, Carretero J, *et al*. Activation of the PD-1 pathway contributes to immune escape in EGFR-driven lung tumors. *Cancer Discov* 2013; 3: 1355–1363.
12. Garon EB, Rizvi NA, Hui R, *et al*. Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer. *N Engl J Med* 2015; 372: 2018–2028.
13. Lisberg A, Cummings A, Goldman JW, *et al*. A phase II study of pembrolizumab in EGFR-mutant, PD-L1+, tyrosine kinase inhibitor naïve patients with advanced NSCLC. *J Thorac Oncol* 2018; 13: 1138–1145.
14. Gettinger S, Rizvi NA, Chow LQ, *et al*. Nivolumab monotherapy for first-line treatment of advanced non–small-cell lung cancer. *J Clin Oncol* 2016; 34: 2980–2987.
15. Rittmeyer A, Barlesi F, Waterkamp D, *et al*. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet* 2017; 389: 255–265.
16. Peters S, Gettinger S, Johnson ML, *et al*. Phase II trial of atezolizumab as first-line or subsequent therapy for patients with programmed death-ligand 1–selected advanced non–small-cell lung cancer (BIRCH). *J Clin Oncol* 2017; 35: 2781–2789.
17. Garassino MC, Cho B-C, Kim J-H, *et al*. Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. *Lancet Oncol* 2018; 19: 521–536.
18. Lee CK, Man J, Lord S, *et al*. Checkpoint inhibitors in metastatic EGFR- mutated non–small cell lung cancer—a meta-analysis. *J Thorac Oncol* 2017; 12: 403–407.
19. Lee CK, Man J, Lord S, *et al*. Clinical and molecular characteristics associated with survival among patients treated with checkpoint inhibitors for advanced non–small cell lung carcinoma. *JAMA Oncol* 2018; 4: 210.
20. Garassino MC, Gelibter AJ, Grossi F, *et al*. Italian nivolumab expanded access program in nonsquamous non–small cell lung cancer patients: results in never-smokers and EGFR-mutant patients. *J Thorac Oncol* 2018; 13: 1146–1155.
21. Mazieres J, Drilon A, Lusque A, *et al*. Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry. *Ann Oncol* 2019; 30: 1321–1328.
22. Hellmann MD, Rizvi NA, Goldman JW, *et al*. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. *Lancet Oncol* 2017; 18: 31–41.
23. Rizvi NA, Hellmann MD, Brahmer JR, *et al*. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non–small-cell lung cancer. *J Clin Oncol* 2016; 34: 2969–2979.
24. Hong L, Lewis WE, Nilsson M, *et al*. Limited benefit from the addition of immunotherapy to chemotherapy in TKI-refractory EGFR-mutant lung adenocarcinoma. *Cancers* 2022; 14: 3473.
25. White MN, Piper-Vallillo AJ, Gardner RM, *et al*. Chemotherapy plus immunotherapy versus chemotherapy plus bevacizumab versus chemotherapy alone in EGFR-mutant NSCLC after progression on osimertinib. *Clin Lung Cancer* 2022; 23: e210–e221.
26. Reck M, Mok T, Socinski MA, *et al*. 1293P IMpower150: updated efficacy analysis in patients with EGFR mutations. *Ann Oncol* 2020; 31: S837–S838.
27. Lu S, Wu L, Jian H, *et al*. Sintilimab plus bevacizumab biosimilar IBI305 and chemotherapy for patients with EGFR-mutated non-squamous non-small-cell lung cancer who progressed on EGFR tyrosine-kinase inhibitor therapy (ORIENT-31): first interim results from a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2022; 23: 1167–1179.
28. Vyse S and Huang PH. Targeting EGFR exon 20 insertion mutations in non-small cell lung cancer. *Signal Transduct Target Ther* 2019; 4: 5.

29. Zhou C, Ramalingam SS, Kim TM, *et al.* Treatment outcomes and safety of mobocertinib in platinum-pretreated patients with ***EGFR*** exon 20 insertion–positive metastatic non–small cell lung cancer. *JAMA Oncol* 2021; 7: e214761.

30. Park K, Haura EB, Leighl NB, *et al.* Amivantamab in EGFR exon 20 insertion-mutated non-small-cell lung cancer progressing on platinum chemotherapy: initial results from the chrysalis phase I study. *J Clin Oncol* 2021; 39: 3391–3402.

31. Le X, Cornelissen R, Garassino M, *et al.* Poziotinib in non–small-cell lung cancer harboring HER2 exon 20 insertion mutations after prior therapies: ZENITH20-2 trial. *J Clin Oncol* 2022; 40: 710–718.

32. Yamada T, Hirai S, Katayama Y, *et al.* Retrospective efficacy analysis of immune checkpoint inhibitors in patients with EGFR-mutated non-small cell lung cancer. *Cancer Med* 2019; 8: 1521–1529.

33. Li BT, Garrigós L, Gion M, *et al.* Trastuzumab deruxtecan in ***HER2*** -mutant non–small-cell lung cancer. *N Engl J Med* 2022; 386: 241–251.

34. Le X, Cornelissen R, Garassino M, *et al.* Poziotinib in non-small-cell lung cancer harboring HER2 Exon 20 insertion mutations after prior therapies: ZENITH20-2 trial. *J Clin Oncol* 2022; 40: 710–718.

35. Guisier F, Dubos-Arvis C, Viñas F, *et al.* Efficacy and safety of anti–PD-1 immunotherapy in patients with advanced NSCLC with BRAF, HER2, or MET mutations or RET translocation: GFPC 01-2018. *J Thorac Oncol* 2020; 15: 628–636.

36. Lai W-CV, Feldman DL, Buonocore DJ, *et al.* PD-L1 expression, tumor mutation burden and response to immune checkpoint blockade in patients with *HER2* -mutant lung cancers. *J Clin Oncol* 2018; 36: 9060–9060.

37. Gainor JF, Shaw AT, Sequist LV, *et al.* EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non–small cell lung cancer: a retrospective analysis. *Clin Cancer Res* 2016; 22: 4585–4593.

38. Bylicki O, Guisier F, Monnet I, *et al.* Efficacy and safety of programmed cell-death-protein-1 and its ligand inhibitors in pretreated patients with epidermal growth-factor receptor-mutated or anaplastic lymphoma kinase-translocated lung adenocarcinoma. *Medicine* 2020; 99: e18726.

39. Spigel DR, Reynolds C, Waterhouse D, *et al.* Phase 1/2 study of the safety and tolerability of nivolumab plus crizotinib for the first-line treatment of anaplastic lymphoma kinase translocation — positive advanced non–small cell lung cancer (CheckMate 370). *J Thorac Oncol* 2018; 13: 682–688.

40. Shaw AT, Lee S-H, Ramalingam SS, *et al.* Avelumab (anti–PD-L1) in combination with crizotinib or lorlatinib in patients with previously treated advanced NSCLC: phase Ib results from JAVELIN lung 101. *J Clin Oncol* 2018; 36: 9008–9008.

41. Felip E, De Braud FG, Maur M, *et al.* Ceritinib plus nivolumab (NIVO) in patients (pts) with anaplastic lymphoma kinase positive (ALK+) advanced non-small cell lung cancer (NSCLC). *J Clin Oncol* 2017; 35: 2502–2502.

42. Kim D-W, Gadgeel SM, Gettinger SN, *et al.* Safety and clinical activity results from a phase Ib study of alectinib plus atezolizumab in *ALK*+ advanced NSCLC (aNSCLC). *J Clin Oncol* 2018; 36: 9009–9009.

43. Seegobin K, Majeed U, Wiest N, *et al.* Immunotherapy in non-small cell lung cancer with actionable mutations other than EGFR. *Front Oncol* 2021; 11: 750657.

44. Sabari JK, Leonardi GC, Shu CA, *et al.* PD-L1 expression, tumor mutational burden, and response to immunotherapy in patients with MET exon 14 altered lung cancers. *Ann Oncol* 2018; 29: 2085–2091.

45. Zhang C, Zhang C, Lin J, *et al.* Patients with BRAF-mutant NSCLC may not benefit from immune checkpoint inhibitors: a population-based study. *JTO Clin Res Rep* 2020; 1: 100006.

46. Dudnik E, Peled N, Nechushtan H, *et al.* BRAF mutant lung cancer: programmed death ligand 1 expression, tumor mutational burden, microsatellite instability status, and response to immune check-point inhibitors. *J Thorac Oncol* 2018; 13: 1128–1137.

47. Negrao MV, Soulidis F, Montesion M, *et al.* Oncogene-specific differences in tumor mutational burden, PD-L1 expression, and outcomes from immunotherapy in non-small cell lung cancer. *J Immunother Cancer* 2021; 9: e002891.

48. Skoulidis F, Riely GJ, Gadgeel SM, *et al.* Sotorasib for lung cancers with KRAS p.G12C mutation. *N Engl J Med* 2021; 384: 2371–2381.

49. Jänne PA, Riely GJ, Gadgeel SM, *et al.* Adagrasib in non–small-cell lung cancer harboring a KRAS G12C mutation. *N Engl J Med* 2022; 387: 120–131.

50. Ricciuti B, Alessi JV, Elkrief A, *et al.* Dissecting the clinicopathologic, genomic, and

immunophenotypic correlates of KRASG12D-mutated non-small-cell lung cancer. *Ann Oncol* 2022; 33: 1029–1040.

51. Riely GJ, Kris MG, Rosenbaum D, *et al*. Frequency and distinctive spectrum of *KRAS* mutations in never smokers with lung adenocarcinoma. *Clin Cancer Res* 2008; 14: 5731–5734.
52. El Osta B, Behera M, Kim S, *et al*. Characteristics and outcomes of patients with metastatic KRAS-mutant lung adenocarcinomas: the lung cancer mutation consortium experience. *J Thorac Oncol* 2019; 14: 876–889.
53. Liu C, Zheng S, Jin R, *et al*. The superior efficacy of anti-PD-1/PD-L1 immunotherapy in KRAS-mutant non-small cell lung cancer that correlates with an inflammatory phenotype and increased immunogenicity. *Cancer Lett* 2020; 470: 95–105.
54. Holmes M, Mahar A, Lum T, *et al*. Real-world programmed death-ligand 1 prevalence rates in non-small cell lung cancer: correlation with clinicopathological features and tumour mutation status. *J Clin Pathol* 2021; 74: 123–128.
55. Zhang M, Li G, Wang Y, *et al*. PD-L1 expression in lung cancer and its correlation with driver mutations: a meta-analysis. *Sci Rep* 2017; 7: 10255.
56. Petrelli F, Maltese M, Tomasello G, *et al*. Clinical and molecular predictors of PD-L1 expression in non–small-cell lung cancer: systematic review and meta-analysis. *Clin Lung Cancer* 2018; 19: 315–322.
57. Davis AP, Cooper WA, Boyer M, *et al*. Efficacy of immunotherapy in ***KRAS*** -mutant non-small-cell lung cancer with comutations. *Immunotherapy* 2021; 13: 941–952.
58. Borghaei H, Paz-Ares L, Horn L, *et al*. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. *N Engl J Med* 2015; 373: 1627–1639.
59. Herbst RS, Lopes G, Kowalski DM, *et al*. LBA4 association of KRAS mutational status with response to pembrolizumab monotherapy given as first-line therapy for PD-L1-positive advanced non-squamous NSCLC in Keynote-042. *Ann Oncol* 2019; 30: xi63–xi64.
60. Huang Q, Zhang H, Hai J, *et al*. Impact of PD-L1 expression, driver mutations and clinical characteristics on survival after anti-PD-1/PD-L1 immunotherapy versus chemotherapy in non-small-cell lung cancer: a meta-analysis of randomized trials. *Oncoimmunology* 2018; 7: e1396403.
61. Passiglia F, Cappuzzo F, Alabiso O, *et al*. Efficacy of nivolumab in pre-treated non-small-cell lung cancer patients harbouring KRAS mutations. *Br J Cancer* 2019; 120: 57–62.
62. Jeanson A, Tomasini P, Souquet-Bressand M, *et al*. Efficacy of immune checkpoint inhibitors in KRAS-mutant non-small cell lung cancer (NSCLC). *J Thorac Oncol* 2019; 14: 1095–1101.
63. Sun L, Hsu M, Cohen RB, *et al*. Association between KRAS variant status and outcomes with first-line immune checkpoint inhibitor–based therapy in patients with advanced non–small-cell lung cancer. *JAMA Oncol* 2021; 7: 937.
64. Gadgeel S, Rodriguez-Abreu D, Felip E, *et al*. KRAS mutational status and efficacy in KEYNOTE-189: pembrolizumab (pembro) plus chemotherapy (chemo) vs placebo plus chemo as first-line therapy for metastatic non-squamous NSCLC. *Ann Oncol* 2019; 30: xi64–xi65.
65. Nakajima EC, Ren Y, Joseph Vallejo J, *et al*. Outcomes of first-line immune checkpoint inhibitors with or without chemotherapy according to KRAS mutational status and PD-L1 expression in patients with advanced NSCLC: FDA pooled analysis. *J Clin Oncol* 2022; 40: 9001–9001.
66. Li BT, Falchook GS, Durm GA, et al. OA03.06 CodeBreaK 100/101: first report of safety/efficacy of Sotorasib in combination with Pembrolizumab or Atezolizumab in advanced KRAS p.G12C NSCLC. *J Thorac Oncol* 2022; 17: S10–S11.
67. Jänne PA, Smit EF, de Marinis F, *et al*. LBA4 - preliminary safety and efficacy of adagrasib with pembrolizumab in treatment-naïve patients with advanced non-small cell lung cancer (NSCLC) harboring a KRASG12C mutation. *Immun-Oncol Technol* 2022; 16: 100360–100361.
68. Arbour KC, Jordan E, Ryan Kim H, *et al*. Effects of co-occurring genomic alterations on outcomes in patients with *KRAS* -mutant non–small cell lung cancer. *Clin Cancer Res* 2018; 24: 334–340.
69. Scheffler M, Ihle MA, Hein R, *et al*. K-ras Mutation subtypes in NSCLC and associated co-occuring mutations in other oncogenic pathways. *J Thorac Oncol* 2019; 14: 606–616.
70. Skoulidis F, Byers LA, Diao L, *et al*. Co-occurring genomic alterations define major subsets of *KRAS* -mutant lung adenocarcinoma with distinct biology, immune profiles, and therapeutic vulnerabilities. *Cancer Discov* 2015; 5: 860–877.
71. Biton J, Mansuet-Lupo A, Nicolas P, *et al*. TP53, STK11, and EGFR mutations predict tumor immune profile and the response to anti–PD-1 in

lung adenocarcinoma. *Clin Cancer Res* 2018; 24: 5710–5723.

72. Koyama S, Akbay EA, Yvonne YL, *et al.* STK11/LKB1 deficiency promotes neutrophil recruitment and proinflammatory cytokine production to suppress T-cell activity in the lung tumor microenvironment. *Cancer Res* 2016; 76: 999–1008.
73. Skoulidis F, Goldberg ME, Greenawalt DM, *et al.* STK11/LKB1 mutations and PD-1 inhibitor resistance in *KRAS* -mutant lung adenocarcinoma. *Cancer Discov* 2018; 8: 822–835.
74. Skoulidis F, Arbour KC, Hellmann MD, *et al.* Association of STK11/LKB1 genomic alterations with lack of benefit from the addition of pembrolizumab to platinum doublet chemotherapy in non-squamous non-small cell lung cancer. *J Clin Oncol* 2019; 37: 102–102.
75. Ricciuti B, Arbour KC, Lin JJ, *et al.* Diminished efficacy of programmed death-(Ligand)1 inhibition in STK11- and KEAP1-mutant lung adenocarcinoma is affected by KRAS mutation status. *J Thorac Oncol* 2022; 17: 399–410.
76. Aredo JV, Padda SK, Kunder CA, *et al.* Impact of KRAS mutation subtype and concurrent pathogenic mutations on non-small cell lung cancer outcomes. *Lung Cancer* 2019; 133: 144–150.
77. Dong Z-Y, Zhong WZ, Zhang XC, *et al.* Potential predictive value of TP53 and KRAS mutation status for response to PD-1 blockade immunotherapy in lung adenocarcinoma. *Clin Cancer Res* 2017; 23: 3012–3024.
78. Skoulidis F, Yasir E, Papadimitrakopoulou V, *et al.* MA04.07 impact of major co-mutations on the immune contexture and response of KRAS-mutant lung adenocarcinoma to immunotherapy. *J Thorac Oncol* 2017; 12: S361–S362.
79. Dong Z-Y and Wu Y-L. What is the significance of TP53 and KRAS mutation for immunotherapy in non-small cell lung cancer? *Transl Cancer Res* 2017; 6: S1115–S1117.
80. Bange E, Marmarelis ME, Hwang W-T, *et al.* Impact of KRAS and TP53 co-mutations on outcomes after first-line systemic therapy among patients with *STK11* -mutated advanced non–small-cell lung cancer. *JCO Precis Oncol* 2019; 3: 1–11.
81. Naidoo J, Antonia SJ, Wu Y-L, *et al.* Durvalumab (durva) after chemoradiotherapy (CRT) in unresectable, stage III, EGFR mutation-positive (EGFRm) NSCLC: a post hoc subgroup analysis from PACIFIC. *J Clin Oncol* 2022; 40: 8541–8541.
82. Hellyer JA, Aredo JV, Das M, *et al.* Role of consolidation durvalumab in patients with EGFR- and HER2-mutant unresectable stage III NSCLC. *J Thorac Oncol* 2021; 16: 868–872.
83. Liu Y, Zhang Z, Rinsurongkawong W, *et al.* Association of driver oncogene variations with outcomes in patients with locally advanced non–small cell lung cancer treated with chemoradiation and consolidative durvalumab. *JAMA Netw Open* 2022; 5: e2215589.
84. Hussaini S, Chehade R, Boldt RG, *et al.* Association between immune-related side effects and efficacy and benefit of immune checkpoint inhibitors – a systematic review and meta-analysis. *Cancer Treat Rev* 2021; 92: 102134.
85. Oxnard GR, Yang JC-H, Yu H, *et al.* TATTON: a multi-arm, phase Ib trial of osimertinib combined with selumetinib, savolitinib, or durvalumab in EGFR-mutant lung cancer. *Ann Oncol* 2020; 31: 507–516.
86. Oshima Y, Tanimoto T, Yuji K, *et al.* EGFR–TKI-associated interstitial pneumonitis in nivolumab-treated patients with non–small cell lung cancer. *JAMA Oncol* 2018; 4: 1112.
87. Schoenfeld AJ, Arbour KC, Rizvi H, *et al.* Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib. *Ann Oncol* 2019; 30: 839–844.
88. Ohmori T, Yamaoka T, Ando K, *et al.* Molecular and clinical features of EGFR-TKI-associated lung injury. *Int J Mol Sci* 2021; 22: 792.
89. Peeraphatdit TB, Wang J, Odenwald MA, *et al.* Hepatotoxicity from immune checkpoint inhibitors: a systematic review and management recommendation. *Hepatology* 2020; 72: 315–329.
90. Lin JJ, Chin E, Yeap BY, *et al.* Increased hepatotoxicity associated with sequential immune checkpoint inhibitor and crizotinib therapy in patients with non–small cell lung cancer. *J Thorac Oncol* 2019; 14: 135–140.
91. Creelan BC, Yeh TC, Kim S-W, *et al.* A phase 1 study of gefitinib combined with durvalumab in EGFR TKI-naive patients with EGFR mutation-positive locally advanced/metastatic non-small-cell lung cancer. *Br J Cancer* 2021; 124: 383–390.
92. Ma BBY, Rudin CM, Cervantes A, *et al.* 441O preliminary safety and clinical activity of erlotinib plus atezolizumab from a phase Ib study in advanced NSCLC. *Ann Oncol* 2016; 27: ix141.

93. Gubens MA, Sequist LV, Stevenson JP, *et al.* Pembrolizumab in combination with ipilimumab as second-line or later therapy for advanced non–small-cell lung cancer: KEYNOTE-021 cohorts D and H. *Lung Cancer* 2019; 130: 59–66.

94. Dong Z-Y, Zhang J-T, Liu S-Y, *et al.* EGFR mutation correlates with uninflamed phenotype and weak immunogenicity, causing impaired response to PD-1 blockade in non-small cell lung cancer. *Oncoimmunology* 2017; 6: e1356145.

95. Schoenfeld AJ, Rizvi H, Bandlamudi C, *et al.* Clinical and molecular correlates of PD-L1 expression in patients with lung adenocarcinomas. *Ann Oncol* 2020; 31: 599–608.

96. Koh J, Go H, Keam B, *et al.* Clinicopathologic analysis of programmed cell death-1 and programmed cell death-ligand 1 and 2 expressions in pulmonary adenocarcinoma: comparison with histology and driver oncogenic alteration status. *Mod Pathol* 2015; 28: 1154–1166.

97. D'Incecco A, Andreozzi M, Ludovini V, *et al.* PD-1 and PD-L1 expression in molecularly selected non-small-cell lung cancer patients. *Br J Cancer* 2015; 112: 95–102.

98. Azuma K, Ota K, Kawahara A, *et al.* Association of PD-L1 overexpression with activating EGFR mutations in surgically resected nonsmall-cell lung cancer. *Ann Oncol* 2014; 25: 1935–1940.

99. Tang Y, Fang W, Zhang Y, *et al.* The association between PD-L1 and EGFR status and the prognostic value of PD-L1 in advanced non-small cell lung cancer patients treated with EGFR-TKIs. *Oncotarget* 2015; 6: 14209–14219.

100. Lan B, Ma C, Zhang C, *et al.* Association between PD-L1 expression and driver gene status in non-small-cell lung cancer: a meta-analysis. *Oncotarget* 2018; 9: 7684–7699.

101. Offin M, Guo R, Wu SL, *et al.* Immunophenotype and response to immunotherapy of *RET* -rearranged lung cancers. *JCO Precis Oncol* 2019; 3: PO.18.00386.

102. Le X, Negrão M, Reuben A, *et al.* Characterization of the immune landscape of EGFR-mutant NSCLC identifies CD73/adenosine pathway as a potential therapeutic target. *J Thorac Oncol* 2021; 16: 583–600.

103. Vokes NI, Liu D, Ricciuti B, *et al.* Harmonization of tumor mutational burden quantification and association with response to immune checkpoint blockade in non–small-cell lung cancer. *JCO Precis Oncol* 2019; 3: PO.19.00171.

104. Offin M, Rizvi H, Tenet M, *et al.* Tumor mutation burden and efficacy of EGFR-tyrosine kinase inhibitors in patients with *EGFR* -mutant lung cancers. *Clin Cancer Res* 2019; 25: 1063–1069.

105. Rizvi H, Sanchez-Vega F, La K, *et al.* Molecular determinants of response to anti–programmed cell death (PD)-1 and anti–programmed death-ligand 1 (PD-L1) blockade in patients with non–small-cell lung cancer profiled with targeted next-generation sequencing. *J Clin Oncol* 2018; 36: 633–641.

106. Mo J, Hu X, Gu L, *et al.* Smokers or non-smokers: who benefits more from immune checkpoint inhibitors in treatment of malignancies? An up-to-date meta-analysis. *World J Surg Oncol* 2020; 18: 15.

107. Wang X, Ricciuti B, Alessi JV, *et al.* Smoking history as a potential predictor of immune checkpoint inhibitor efficacy in metastatic non-small cell lung cancer. *J Natl Cancer Inst* 2021; 113: 1761–1769.

108. Streicher K, Higgs BW, Wu S, *et al.* Increased CD73 and reduced IFNG signature expression in relation to response rates to anti-PD-1(L1) therapies in EGFR-mutant NSCLC. *J Clin Oncol* 2017; 35: 11505–11505.

109. To KKW, Fong W and Cho WCS. Immunotherapy in treating EGFR-mutant lung cancer: current challenges and new strategies. *Front Oncol* 2021; 11: 635007.

110. Wang S, Zhang Y, Wang Y, *et al.* Amphiregulin confers regulatory T cell suppressive function and tumor invasion via the EGFR/GSK-3β/Foxp3 axis. *J Biol Chem* 2016; 291: 21085–21095.

111. Mascia F, Schloemann DT, Christophe C, *et al.* Cell autonomous or systemic EGFR blockade alters the immune-environment in squamous cell carcinomas. *Int J Cancer* 2016; 139: 2593–2597.

112. Jia Y, Li X, Jiang T, *et al.* EGFR-targeted therapy alters the tumor microenvironment in EGFR-driven lung tumors: implications for combination therapies. *Int J Cancer* 2019; 145: 1432–1444.

113. McGowan M, Kleinberg L, Halvorsen AR, *et al.* NSCLC depend upon YAP expression and nuclear localization after acquiring resistance to EGFR inhibitors. *Genes Cancer* 2017; 8: 497–504.

114. Nouri K, Azad T, Lightbody E, *et al.* A kinome-wide screen using a NanoLuc LATS

luminescent biosensor identifies ALK as a novel regulator of the hippo pathway in tumorigenesis and immune evasion. *FASEB J* 2019; 33: 12487–12499.

115. Lo Sardo F, Strano S and Blandino G. YAP and TAZ in lung cancer: oncogenic role and clinical targeting. *Cancers* 2018; 10: 137.

116. Wang G, Lu X, Dey P, *et al.* Targeting YAP-dependent MDSC infiltration impairs tumor progression. *Cancer Discov* 2016; 6: 80–95.

117. Murakami S, Shahbazian D, Surana R, *et al.* Yes-associated protein mediates immune reprogramming in pancreatic ductal adenocarcinoma. *Oncogene* 2017; 36: 1232–1244.

118. Ni X, Tao J, Barbi J, *et al.* YAP is essential for Treg-mediated suppression of antitumor immunity. *Cancer Discov* 2018; 8: 1026–1043.

119. Ahmed A and Tait SWG. Targeting immunogenic cell death in cancer. *Mol Oncol* 2020; 14: 2994–3006.

120. Fucikova J, Kepp O, Kasikova L, *et al.* Detection of immunogenic cell death and its relevance for cancer therapy. *Cell Death Dis* 2020; 11: 1013.

121. Wang Y-J, Fletcher R, Yu J, *et al.* Immunogenic effects of chemotherapy-induced tumor cell death. *Genes Dis* 2018; 5: 194–203.

122. Pfirschke C, Engblom C, Rickelt S, *et al.* Immunogenic chemotherapy sensitizes tumors to checkpoint blockade therapy. *Immunity* 2016; 44: 343–354.

123. Palmer AC, Izar B, Hwangbo H, *et al.* Predictable clinical benefits without evidence of synergy in trials of combination therapies with immune-checkpoint inhibitors. *Clin Cancer Res* 2022; 28: 368–377.

124. Spigel DR, Faivre-Finn C, Gray JE, *et al.* Five-year survival outcomes from the PACIFIC trial: durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. *J Clin Oncol* 2022; 40: 1301–1311.

125. Faivre-Finn C, Vicente D, Kurata T, *et al.* Four-year survival with durvalumab after chemoradiotherapy in stage III NSCLC—an update from the PACIFIC trial. *J Thorac Oncol* 2021; 16: 860–867.

126. Aredo J V, Mambetsariev I, Hellyer JA, *et al.* Durvalumab for stage III EGFR-mutated NSCLC after definitive chemoradiotherapy. *J Thorac Oncol* 2021; 16: 1030–1041.

127. Socinski MA, Jotte RM, Cappuzzo F, *et al.* Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med* 2018; 378: 2288–2301.

128. Kim JM and Chen DS. Immune escape to PD-L1/PD-1 blockade: seven steps to success (or failure). *Ann Oncol* 2016; 27: 1492–1504.

129. Voron T, Colussi O, Marcheteau E, *et al.* VEGF-A modulates expression of inhibitory checkpoints on CD8+ T cells in tumors. *J Exp Med* 2015; 212: 139–148.

130. Hegde PS, Wallin JJ and Mancao C. Predictive markers of anti-VEGF and emerging role of angiogenesis inhibitors as immunotherapeutics. *Semin Cancer Biol* 2018; 52: 117–124.