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REVIEW

Non-small-cell lung cancer: how to manage *BRAF*-mutated disease

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Abstract

BRAF mutations are reported in about 3–5% of non-small-cell lung cancer (NSCLC), almost exclusively in adenocarcinoma histology, and are classified into three different classes. The segmentation of *BRAF* mutations into V600 (class 1) and non-V600 (classes 2 and 3) relies on their biological characteristics and is of interest for predicting the therapeutic benefit of targeted therapies and immunotherapy. Given the relative rarity of this molecular subset of disease, evidence supporting treatment choices is limited. This review aims to offer a comprehensive update about available therapeutic options for patients with NSCLC harbouring *BRAF* mutations to guide the physician in the choice of treatment strategies. We collected the most relevant available data, from single-arm phase II studies and retrospective analyses conducted in advanced NSCLC, regarding the efficacy of BRAF and MEK inhibitors in both V600 and non-V600 *BRAF* mutations. We included case reports and smaller experiences that could provide information on specific alterations. With respect to immunotherapy, we reviewed retrospective evidence on immune-checkpoint inhibitors in this molecular subset, whereas data about chemo-immunotherapy in this molecular subgroup are lacking. Moreover, we included the available, though limited, retrospective evidence of immunotherapy as consolidation after chemo-radiation for unresectable stage III *BRAF*-mutant NSCLC, and an overview of ongoing clinical trials in the peri-operative setting that could open new perspectives in the future.

Keywords: BRAF, dabrafenib, immune-checkpoint inhibitors, NSCLC, trametinib.

Citation

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Introduction

Treatment options in non-small-cell lung cancer (NSCLC) have recently evolved to include immunotherapy and targeted agents for a variety of oncogene-addicted entities in the first-line setting.[1] *BRAF* mutations define a precise molecular entity of NSCLC (accounting for 3–5% of cases) that can benefit from both molecular and immunotherapy agents. This consideration, almost unique in the setting of oncogene-driven cancers, paradoxically challenges the definition of a precise treatment algorithm for this subset of patients. The heterogeneity of *BRAF* mutations and their different response to molecular agents provides an additional caveat for clinical decision-making. In the present review, we report the evidence sustaining the pragmatic management of *BRAF*-mutant NSCLC, moving from molecular diagnosis to the treatment of advanced disease. In addition, the introduction of novel treatment strategies incorporating targeted agents and immunotherapy in the early and locally advanced setting of NSCLC sustains their evaluation for patients with *BRAF*-mutant NSCLC.

Review

Distribution of *BRAF* mutation classes in NSCLC

BRAF mutations are reported across many types of cancers, including melanoma, colorectal cancer, thyroid cancer and NSCLC.[2,3] BRAF is a serine/threonine protein kinase belonging

to the RAF kinase family, together with the other isoforms ARAF and CRAF. Upon activation by RAS, these proteins play a pivotal role in cell growth, proliferation, migration and survival by the activation of the MAPK–ERK pathway. ERK translocates into the nucleus and activates transcription factors, resulting in enhanced expression of genes involved in many oncogenic cellular processes. Oncogenic mutations in components of this pathway result in constitutive activation of the MAPK–ERK cascade and oncogenic transformation.[4] RAF isoforms share three conserved regions, including the RAS-binding domain (C1), catalytic kinase domain (C3) and the regulatory domain between them (C2).

BRAF mutations are classified into three classes according to their dimerization status, their kinase activity, and RAS dependence for activation.[4] Class 1 mutations are characterized by RAS-independent, high BRAF kinase activity in a monomeric status. This class contains mutations of codon 600 on exon 15, including the most common V600E point mutation that is found in 90% of *BRAF*-mutated tumours. Other V600 mutations are less frequent and include V600D/K/R/M.[4] Overall, V600 mutations represent one-third of *BRAF* mutations detected in NSCLC.[3]

Class 2 and 3 mutations are reported in Table 1. Class 2 mutations (such as K601, L597, G469 and G464) are located in exons 11 (e.g. codon G464 and G469) and 15 (e.g. codon L597 and K601), and result in RAS-independent homodimers with high/intermediate kinase activity.[4] Class 3 mutants (e.g. G466, D594, G596 and N581) have low or absent kinase activity, and transmit signalling through RAS-dependent dimerization with CRAF or wild-type *BRAF*.[5] In addition, other missense mutations of unknown significance have been identified.

In the largest dataset reported to date, comprehensive genomic profiling with next-generation sequencing (NGS) was performed on samples from 114,662 patients with different solid tumours, including 18,944 patients with NSCLC. Amongst them, *BRAF* mutations were identified in 4% of cases (*n*=772) and were equally distributed amongst the three subgroups (30.7%, 34.2% and 30.7% in class 1, 2 and 3, respectively), with 4.4% of other pathogenic mutations.[3] In another cohort (*n*=236), class 1 mutations seemed more frequent than the others (45% for class 1, 32% and 23% for class 2 and 3, respectively).[6] The prognostic significance of the different mutation classes is still unclear.[7–10]

Clinicopathological features

Overall, *BRAF* mutations are present in 3–5% of NSCLC, almost exclusively in adenocarcinoma histology,[7,10] though mutations in squamous cell carcinoma have been described.[6,7] The aggressive micropapillary architecture has been associated with V600E, whilst a mucinous pattern is common in non-V600 mutations.[7]

Differently from other oncogene-addicted diseases (but similar to *KRAS*-mutant NSCLC), the majority of patients with *BRAF*-mutated disease are current or former smokers.[11] Smoking habits appear to be more common in class 2 and 3,[6] whilst patients harbouring V600 mutations are more likely to be never smokers.[7,9]

Table 1. Class 2 and class 3 *BRAF* mutations.

BRAF class	Mutation	
2	L597V/S/R/Q/P/K	L525R
	K601E/N	L485W/F
	A598V/T599insV	V600_K601del
	T599I/dup/ V600insT	V600_K601D/E/N
	G464V/E	V600_K602delinsDT
	N486_P490del	V600_ W604delinsDQTDG
	G469V/S/R/L/A/ T170delinsAK	
3	D594N/G/F	F595L
	G466E/V/A	T470R
	N581S/T/I	Q524L
	G596V/R	
	G469E	
	S467L	

Adapted with the permission from ref.[57]

BRAF mutations are less frequent in people of Chinese origin than in white individuals, occurring only in 0.5–2% of patients of Chinese origin affected by NSCLC.[12,13]

Metastatic spread to the central nervous system appears to be frequent. In a retrospective analysis of 236 patients diagnosed with a *BRAF*-mutated NSCLC, brain metastases were detected at diagnosis in 69 (29%). Class 2 and class 3 mutations were associated with a higher risk of brain metastases at diagnoses, compared with class 1 alterations (p=0.011 *versus* class 2; p=0.007 *versus* class 3).[6]

Molecular diagnostics

After the approval of BRAF and MEK inhibitors (BRAFi and MEKi), *BRAF* mutation testing became part of the fundamental molecular characterization of advanced NSCLC. Any adequately sensitive and specific method is allowed, but the most used to date are DNA sequencing techniques.[14]

BRAF assessment is thus required in stage IIIB–IIIC (when unsuitable for locoregional treatment) and stage IV NSCLC. It should be performed in all adenocarcinomas, in not-otherwise-specified NSCLC and in mixed histology such as adenosquamous NSCLC. For this reason, in squamous histology, *BRAF* status should be evaluated in the case of small tissue samples that cannot rule out the presence of an adenocarcinoma component, and in light or non-smoker patients.

BRAF mutations are detectable by sequencing techniques such as PCR-based Sanger sequencing and NGS. NGS is becoming the preferred technique given the possibility to simultaneously test many molecular alterations. Immunohistochemistry (IHC) for *BRAF* V600E assessment has also been explored. Indeed, a monoclonal antibody specific for *BRAF* V600E mutation in solid tumours (clone VE1) showed promising sensitivity and specificity when compared with molecular testing in NSCLC.[15,16] Subsequently, VE1 IHC has shown 100% concordance with NGS assays and, in samples prospectively tested with IHC, positive results were confirmed by PCR in 83% of cases. Despite its selectivity for V600E mutation precluding the detection of non-V600E variants[17] and its sub-optimal specificity, IHC may serve as a screening tool,[18] integrating IHC assays in current practice to assess PD-L1 status and *ALK* or *ROS1* fusions.

Given the increasing number of biomarkers that need to be tested at the time of diagnosis of advanced NSCLC, use of tissue NGS is increasingly widespread. Compared with a sequential approach, simultaneous testing of different biomarkers has the advantage to potentially identify, with a single test, all druggable alterations and concomitant mutations that may have a prognostic role or may explain resistance to treatments. Additionally, NGS is more efficient in tissue optimization, with favourable cost-effectiveness and a median turnaround time shorter than the sequential approach.[19–21]

Currently, one of the main advantages of NGS is its applicability to cell-free circulating tumour DNA (cfDNA) by liquid biopsy. The first experience of the detection of *BRAF* mutations in NSCLC DNA was led by Guibert et al., who demonstrated that digital droplet PCR applied on cfDNA has good specificity and higher sensitivity than DNA extracted from circulating tumour cells.[22] Subsequently, other experiences reported that NGS on cfDNA (Guardant Health assay) is able to detect V600 and non-V600 alterations in samples from patients with advanced NSCLC.[23,24] Recently, a prospective collection of tissue and matched blood samples obtained from patients with advanced NSCLC reported 85% positive percentage agreement between tissue DNA assay and cfDNA (Guardant Health) for the detection of *BRAF* V600E mutation.[25] Clinical trials, such as the ongoing, randomized, real-life LIBELULE study (NCT03721120),[26] aim to evaluate the feasibility of liquid biopsy in patients with suspicious metastatic NSCLC and whether the analysis of cfDNA may decrease time-to-appropriate treatment initiation and improve patient outcomes.

Even if the assessment of *BRAF* status in cfDNA is not yet established as an alternative to tumour tissue analysis,[27,28] plasma NGS testing may integrate routine diagnosis of advanced NSCLC[29] and its application may be considered when an insufficient quantity or quality of DNA from tissue biopsy preclude molecular assessment. The recent FDA approval of Guardant Health[30] and FoundationOne[31] liquid biopsy assays sustain the validity of this strategy in the field of molecular diagnostics.

Treatment of advanced disease

Evidence on BRAFi and MEKi and on immune-checkpoint inhibitors (ICIs) in patients with *BRAF*-mutant NSCLC deserves a detailed approach, as they represent the main therapeutic options together with chemotherapy. As discussed below, the definition of a treatment algorithm for *BRAF*-mutated NSCLC is challenging because indications of targeted agents or (chemo-) immunotherapy are not as clear as for other oncogene-driven diseases.

Target therapy: BRAFi/MEKi

Because BRAFi, alone or in combination with MEKi, has improved response and survival outcomes of patients with *BRAF* V600 melanoma,[32–36] these strategies have been translated into treatment of NSCLC. In particular, vemurafenib and dabrafenib as monotherapies or dabrafenib-trametinib combination therapy have been investigated in phase II and retrospective studies (Table 2).

Dabrafenib and trametinib

Dabrafenib (BRAFi) monotherapy (150 mg twice daily) and its combination with trametinib (MEKi, 2 mg once daily) have been studied in advanced NSCLC harbouring *BRAF* V600E in a phase II multicentric trial (NCT01336634). The study included three cohorts: cohort A investigated the role of dabrafenib as monotherapy, and cohorts B and C enrolled patients treated with dabrafenib-trametinib as subsequent or frontline treatment options, respectively. Patients were enrolled sequentially in the three cohorts and primary outcome was overall response rate (ORR).[37–39]

Cohort A enrolled 84 patients, of whom six were treatment naive. ORR was 33% in pre-treated patients and 4/6 treatment-naive patients achieved a partial response (PR).[37] Combination of BRAFi-MEKi showed better response outcomes than BRAFi alone. Indeed, 63% of 57 patients enrolled in cohort B and 64% of 36 previously untreated patients in cohort C achieved a response. Moreover, when cohorts B and C were compared, combination therapy seemed to achieve longer duration of response (9.0 *versus* 15.2 months, respectively) and progression-free survival (PFS) (median 8.6 *versus* 14.6 months, respectively) in treatment-naive compared with pre-treated patients.[38,39] At the 5-year update of the study, 4-year and 5-year survival rates were higher in treatment-naive than in pre-treated patients (34% and 22% *versus* 26% and 19%).[40]

Survival outcomes achieved by patients treated in this phase II study have been retrospectively compared to those of patients harbouring *BRAF* mutations (V600 and non-V600) obtained from the Flatiron Health database, who had been treated with platinum-based chemotherapy (PBC) alone or in combination with ICIs or ICI monotherapy in real-world settings. Compared with PBC as first-line treatment, dabrafenib-trametinib showed longer overall survival (OS) (median 17.3 *versus* 9.7 months, p=0.01) and lower risk of death (hazard ratio (HR) 0.51, 95% CI

Table 2. Main studies of target therapies in advanced *BRAF*^{V600} NSCLC.

Study	Type	Drugs	Patients (*n*)	ORR (%)	DCR (%)	Median PFS, months (95% CI)	Median OS, months (95% CI)
NCT01336634-A[37]	Phase II	Dabrafenib	84	33	56	5.5 (2.8–7.3)	15.4 (7.3–NR)
NCT01336634-B[a,38]	Phase II	Dabrafenib + trametinib	57	68	81	10.2 (6.9–16.7)	18.2 (14.3–28.6)
NCT01336634-C[b,39]	Phase II	Dabrafenib + trametinib	36	64	75	10.8 (7.0–14.5)	17.3 (12.3–402)
NCI-MATCH (sub-protocol H)[42]	Phase II	Dabrafenib + trametinib	5	40	100	NA	NA
Auliac et al.[48]	Retrospective	Dabrafenib + trametinib	40	NA	NA	17.5 (7.1–23.0)	25.5 (16.6–NR)
EURAF cohort[49]	Retrospective	Dabrafenib	3	33	33	NA	NA
VE-BASKET (NSCLC cohort)[46]	Phase II	Vemurafenib	62	37.5[b] 37.0[a]	79	12.9[b] (4.0–NR) 6.1[a] (5.1–8.3)	NR[b] (6.0–NR) 15.4[a] (8.2–22.8)
AcSé (NSCLC cohort)[47]	Phase II	Vemurafenib	101	45	NA	5.3 (3.8–6.8)	10.0 (6.8–15.7)
EURAF cohort[49]	Retrospective	Vemurafenib	24[c]	54	96	NA	NA
EURAF cohort[49]	Retrospective	Sorafenib	1	100	100	NA	NA

[a]Previously treated patients; [b]Untreated patients; [c]V600E only.
DCR, disease control rate; NA, not available; NR, not reached; NSCLC, non-small-cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

0.29–0.92; p=0.03) in the weighted analysis. However, the same survival benefits were not seen in the comparison with first-line PBC plus ICI (p=0.13 for death risk reduction, median OS 17.3 *versus* 18.0 months). However, >90% of patients treated with PBC plus ICI started treatment between 2018 and 2019, thus follow-up for this group was immature at the data cut-off (June 2019). As in the phase II trial, PD-L1 status was not recorded for patients treated with dabrafenib-trametinib and therefore comparison with first-line pembrolizumab (approved for patients with PD-L1 ≥1% or ≥50% in the USA and Canada) was not feasible. The comparison between dabrafenib-trametinib and single-agent immunotherapy (mainly pembrolizumab or nivolumab) was then performed only for patients treated in second line, with dabrafenib-trametinib not showing statistically significant survival benefit over ICIs.[41]

Moreover, a sub-protocol of The National Cancer Institute Molecular Analysis for Therapy Choice (NCI-MATCH) enrolled patients with solid tumours harbouring *BRAF* V600 to receive dabrafenib-trametinib. Only five patients with lung cancer were treated before FDA approval of the two inhibitors for this indication led to an early exclusion of patients affected by lung cancer from enrolment. However, two and three patients obtained a PR and stable disease, respectively.[42]

The combination of dabrafenib-trametinib is approved by the EMA for the treatment of advanced NSCLC harbouring *BRAF* V600 mutations,[43] whilst FDA approval is restricted to *BRAF* V600E mutation.[44] In both cases, the two drugs can be administered in any treatment line.

Vemurafenib

The first systematic evidence of the activity of BRAF inhibition in *BRAF*-mutated tumours other than melanoma was provided in the phase II basket trial of vemurafenib (960 mg twice daily). Amongst the 19 evaluable patients with NSCLC (all but one with V600E-mutated disease), 8 (42%) achieved PR, with 7.3 months PFS.[45]

Activity, efficacy and safety have been assessed in the larger cohort of VE-BASKET phase II study in which 62 patients with NSCLC were included, of whom only 8 (13%) had not received prior therapies. Even though ORR (primary outcome) was similar between naive and previously treated patients (37%), untreated patients experienced higher disease control rate (DCR) and better outcomes in terms of PFS and OS.[46]

Results from the NSCLC cohort of the AcSé vemurafenib trial confirmed efficacy of vemurafenib in patients with *BRAF* V600-mutated disease but not in non-V600 mutations. In total, 101

pre-treated patients harbouring *BRAF* V600 (97 with V600E mutation) were included and 100 received treatment with vemurafenib; ORR was 44.8%.[47]

As the combination of dabrafenib-trametinib represents the standard of care in *BRAF* V600 disease, vemurafenib monotherapy does not represent the treatment of choice.

Additional retrospective evidence

A retrospective observational study of 40 patients treated with dabrafenib-trametinib for *BRAF* V600E-mutated NSCLC confirmed safety and efficacy of the combination in real-world clinical practice, with a median PFS of 17.5 months and median OS of 25.5 months. Notably, only 9 patients received this treatment as first-line strategy.[48]

Another retrospective observational analysis (the EURAF cohort) of 35 patients (29 *BRAF* V600E and 6 *BRAF* non-V600E) treated with BRAFi monotherapy (vemurafenib, dabrafenib or sorafenib) showed an ORR of 53% and DCR of 85%. With BRAFi, median PFS and median OS were 5.0 and 10.8 months, respectively.[49] In another two-centre retrospective analysis, only 11 (15%) out of 72 patients with *BRAF*-mutated disease identified between 2009 and 2019 were treated with anti-BRAF +/– anti-MEK therapy; ORR was 53%.[8]

Due to the lower prevalence of *BRAF* mutations in population of Chinese origin than in white individuals, safety and efficacy of both chemotherapy and target therapy in patients of Chinese origin is poorly explored. Mu et al.[50] conducted a retrospective analysis on 65 patients harbouring *BRAF* mutations (54 V600E and 11 non-V600E) treated in 22 hospitals in China between 2017 and 2019; 55 out of 65 (85%) patients had advanced disease and, amongst these, 32 received anti-BRAF target therapy (vemurafenib, dabrafenib, or dabrafenib-trametinib), either as first or subsequent line. Sixteen patients harbouring *BRAF* V600E received BRAFi as first line, showing higher ORR than chemotherapy (67% *versus* 25%) and longer PFS, yet without statistical significance (median 9.8 *versus* 5.4 months; p=0.149). No patient harbouring non-V600E mutations received BRAFi +/– MEKi as first-line treatment choice. Two patients with non-V600E mutations received dabrafenib-trametinib after PBC, showing stable disease and PD as best response.[50]

In all the studies and retrospective analyses presented above, the toxicity profile of target therapies was manageable.

New perspectives

A phase II, single-arm trial (NCT03915951) is currently evaluating safety and efficacy of the combination of encorafenib (BRAFi) 450 mg once daily and binimetinib (MEKi) 45 mg twice daily for NSCLCs harbouring *BRAF* V600. The trial is expected to enrol approximately 107 patients, both treatment-naive and previously treated. Primary outcome is independent radiology-reviewed ORR. The advantage of this combination could be both a more manageable safety profile and higher efficacy, because encorafenib shows a longer dissociation half-life from mutant *BRAF* V600E compared with other BRAFi (>30 hours *versus* 2 hours for dabrafenib and 0.5 for vemurafenib).[51]

Activity of targeted therapy against non-V600 BRAF mutations

The sensitivity to specific MAPK pathway inhibitors for cancers with non-V600 *BRAF* mutations is an open field of investigation. There are several pre-clinical reports that support the use of combined BRAFi and MEKi *versus* BRAFi or MEKi monotherapy in a variety of cancers with non-V600 *BRAF* mutations, including NSCLC.[24,52–54] Most retrospective clinical evidence in this field comes from melanoma, because it has historically marked the path for BRAFi/MEKi therapies and because of some similarities in treatment strategies with NSCLC. Approximately 50% of melanoma harbour a *BRAF* mutation that are most commonly V600 mutations (60–80%).[2] Thus, data on safety and efficacy of target therapies used for uncommon *BRAF* mutations are limited in melanoma as well.

Menzer et al. reported the outcomes of patients with melanoma harbouring uncommon *BRAF* V600 (i.e. non-E/K V600) or non-V600 mutations exposed to targeted agents, mainly in the first-line setting.[55] In the non-E/K V600 group (n=58, amongst which n=44 V600R), the administration of BRAFi+MEKi in 36 cases lead to better clinical outcomes (ORR 56%, DCR 83%, median PFS 8 months, median OS 17.3 months) compared with BRAFi alone (ORR 27%, DCR 55%, median PFS 3.7 months, median OS 7.3 months). In the *BRAF* non-V600 population (n=38), outcomes varied remarkably according to mutation type and treatment received. No responses were recorded with monotherapy with BRAFis and, even in the setting of BRAFi+MEKi (or MEKi alone), the clinical outcomes were dismal with median PFS <4 months, except for three $BRAF^{G469}$ cases achieving a median PFS of 9.2 months. Detailed outcomes are reported in the paper for patients positive for *BRAF* L597, K601E, G469, G593 and other mutations; present in one case each.[55]

In a phase II study of trametinib administered to nine patients affected by melanoma with non-V600 *BRAF* mutations or *BRAF* fusions, objective response was obtained in three cases, with median PFS of 7.3 months. Best outcomes were observed in patients with $BRAF^{G469R}$, $BRAF^{L597Q}$ and $BRAF^{T470R}$ mutations.[56] Complexity in the approach to non-V600 *BRAF* mutations is well depicted by G469R and G469E mutations as the different aminoacidic substitutions attribute the mutations to classes 2 and 3, respectively, with the second one not sensitive to MEKi in one patient.

In a recent systematic review and meta-analysis, Dankner et al.[57] reported the outcomes of 238 patients affected by different solid tumours harbouring class 2 and class 3 *BRAF* mutations. Most patients (n=227) were treated with BRAFi/MEKi (alone or in combination), whilst 11 patients received an anti-EGFR agent, in nine cases as monotherapy. The best outcomes (ORR, PFS) were observed in cases harbouring class 2 mutants both in the overall population and when limiting the

analysis to patients with melanoma or NSCLC. MEKi +/– BRAFi were characterized by the highest activity across mutational classes.[57]

The disappointing activity of BRAF inhibition alone against non-V600 *BRAF* mutations was confirmed in the NSCLC cohort of the AcSé trial. Amongst the 17 patients who received treatment with vemurafenib, no response was observed,[45] eliciting a median PFS of 1.8 months. In the EURAF cohort, amongst 6 patients with non-V600 *BRAF* mutations, only one response to BRAF inhibition alone was reported in a patient with *BRAF*^{G569V} mutation. Moreover, no response to vemurafenib was seen in a case report of a patient with *BRAF*^{G469L} advanced NSCLC.[58]

Besides the activity of BRAFi/MEKi, two case reports showed efficacy of sorafenib against *BRAF*^{G469V} and G469R mutations.[59,60] Nevertheless, *BRAF*^{G469} mutants (with the exception of the class 3 G469E, see above) are likely sensitive to combined BRAF/MEK inhibition in both melanoma and NSCLC,[50,61] such that BRAFi/MEKi may be preferred to sorafenib in this setting. Moreover, a complete response lasting over 4 years was reported in a patient with *BRAF*^{Y472C}-mutated NSCLC treated with dasatinib (BCR/ABL and Src family inhibitor) in a clinical trial.[62]

Additional granular data on precise mutations and outcomes to targeted therapies in non-V600-mutant NSCLC are reported in Table 3.[63,64] Clinical trials dedicated to *BRAF* non-V600-mutated tumours (including NSCLC) are ongoing, amongst others, assessing drugs such as encorafenib-binimetinib, ulixertinib (ERK 1/2 inhibitor) or BGB-3245 (BRAFi) in phase I or II trials (NCT03843775, NCT04488003, NCT04249843).[65]

A systematic report of the outcomes of patients with non-V600 *BRAF*-mutant malignancies treated with BRAFi/MEKi would be of interest to support clinical decision based on granular evidence from the literature. As the objective of this review is to provide general guidance for the treatment of *BRAF*-mutant NSCLC, we direct readers to the Appendix 2 of the systematic work provided by Dankner et al. to obtain precise information on the subject.[57]

Expected toxicity of BRAFi and MEKi

Data regarding the safety profile and toxicity management of BRAFi and MEKi in NSCLC are mostly limited to the combination of dabrafenib-trametinib or translated from evidence obtained from melanoma. The toxicity profile of the combination includes pyrexia, increases in blood levels of alanine aminotransferase, aspartate aminotransferase and creatine phosphokinase, nausea, vomiting and fatigue[36,37] (Table 4).

Pyrexia (in the absence of infection) is related specifically to dabrafenib and is the most frequent adverse event (AE) reported with this treatment. Although it is commonly grade 1 (38–39°C) or grade 2 (>39–40°C), it is the most frequent cause of discontinuation due to treatment-related AEs in patients with melanoma.[66]

An analysis of 1076 patients affected by melanoma or NSCLC, treated with dabrafenib-trametinib in phase II and phase III trials, reported that 61% (*n*=660) had pyrexia, with 5.7% of patients experiencing grade 3 or 4 events. The highest incidence of AEs was reported in the first 3 months of treatment. Of note, 67% of patients experiencing pyrexia had recurrent events. The most common management strategy (41.5%) of the AEs was temporary interruption of one or both dabrafenib and trametinib, whereas no action was required in 43.6% of cases.[66]

Gastrointestinal AEs under dabrafenib-trametinib treatment are frequent and mostly consist of nausea and vomiting. Colitis and gastrointestinal perforations are rarely reported but may be severe. For instance, MEKi treatment (cobimetinib, trametinib, binimetinib), with or without accompanying BRAFi, have been correlated with some cases of perforation in small and large intestine.[67] A retrospective analysis of 119 patients treated with MEKi (cobimetinib, trametinib, binimetinib) for unresectable stage III or stage IV melanoma showed 33% of gastrointestinal toxicities of any grade: patients experienced colitis (*n*=3), gastrointestinal perforation grade 4 (*n*=2) and diarrhoea (*n*=1). No fatal outcomes were reported. Amongst the two cases of perforation, the first involved a female patient with a medical history of ulcerative colitis who had received previous treatment with ICI, but reactivation of the inflammatory disease occurred only under vemurafenib-cobimetinib administration.[68]

A case of inflammatory bowel disease during encorafenib 450 mg once daily plus binimetinib 45 mg twice daily in a clinical trial for NSCLC was reported. The radiological finding was confirmed by biopsy, showing mixed inflammatory infiltrate in the lamina propria of caecum with severe eosinophilia. The patient was completely asymptomatic and did not receive any specific treatment but withheld encorafenib-binimetinib. After the complete resolution of radiological findings, the patient resumed oncological treatment at the same dose, with no recurrence of gastrointestinal toxicity.[69]

With regards to cardiovascular toxicity, a retrospective pharmacovigilance study conducted on the VigiBase database and focused on treatment with targeted therapies revealed a higher risk of heart failure with dabrafenib and trametinib compared to other kinase inhibitors used in oncogene-addicted NSCLC. Dabrafenib also had an increased risk of supraventricular tachycardia compared with other NSCLC kinase inhibitors.[70]

MEKi have been correlated with visual disturbances and different ocular toxicities such as retinal vein occlusion, retinal detachment, MEK-associated retinopathy and dry eye. Retinal vein occlusion has been reported to occur in 14% of patients treated with trametinib.[71] Uveitis, conjunctivitis and dry eye are more frequently caused by BRAFi, particularly by vemurafenib.[72]

Table 3. Main evidence on target therapies outcomes in advanced *BRAF*$^{non\text{-}V600}$ NSCLC.

Study	Type	Drug	Pts (*n*)	Mutations	Response	Median PFS, months (95% CI)
AcSé (NSCLC cohort)[47]	Phase II	Vemurafenib (≥first line)	17	3 G466V 3 G469A 3 K601E 3 N581S 2 K601N 1 G466A 1 G469V 1 G569R	No response	1.8 (1.4–2.1)
EURAF cohort[49]	Retrospective	Vemurafenib, Dabrafenib (median third line)	6	1 G466V 1 G469A 1 G469L 1 G596V 1 V600K 1 K601E	1 PR (G596V)[a]	NA
Gautschi et al.[58]	Case report	Vemurafenib (first line)	1	G469L	No response	NR
Dagogo-Jack et al.[61]	Case report	Dabrafenib + trametinib (fourth line)	1	G469A	PR (DoT 6 m)	NR
Citarella et al.[64]	Case report	Dabrafenib + Trametinib (fourth line)	1	G466R	No response	NR
Su et al.[120]	Case report	Dabrafenib + Trametinib (first line)	1	K601E	PR (DoT 9 m)[b]	NR
Turshudzhyan et al.[63]	Case report	Dabrafenib + Trametinib (first line)	1	T599dup	PR (DoT4 m)	NR
Saalfeld et al.[121]	Case report	Trametinib (third line)	1	K601E	PR (DoT 4 m)	NR
Casadei Gardini et al.[59]	Case report	Sorafenib[c] (second line)	1	G469V	PR (DoT 13 m)	NA
Sereno et al.[60]	Case report	Sorafenib (>fourth line)	1	G469R	PR (DoT 6 m)	NA
Sen et al.[62]	Case report	Dasatinib (first line)	1	Y472C	CR (DoT 12 w, DoR 4 y)	NR

[a]G596V PR to vemurafenib; [b]Near total regression; [c]Concomitant hepatocarcinoma.
CR, complete response; DCR, disease control rate; DoR, duration of response; DoT, duration of treatment; NA, not available; NR, not reached; NSCLC, non-small-cell lung cancer; ORR, overall response rate; PFS, progression-free survival; PR, partial response; pts, patients.

Table 4. Safety of target therapies for patients with *BRAF*-mutant NSCLC.

Study	Drug	Most frequent TRAEs	Grade 3–4 TRAEs	Grade 5 TRAEs	TRAE-related discontinuation	TRAE-related interruption	TRAE-related dose reduction
NCT01336634 – A[37]	Dabrafenib	Pyrexia; hyperkeratosis; decreased appetite	39% G3 5 % G4	1%	6%	43%	18%
NCT01336634 – B[38]	Dabrafenib + trametinib	Pyrexia; nausea; vomiting	49% G3+G4	0	12%	61%	35%
NCT01336634 – C[39]	Dabrafenib + trametinib	Pyrexia; nausea; fatigue; peripheral oedema	64% G3 6% G4	3%	22%	75%	39%
Auliac et al.[48]	Dabrafenib + trametinib	NA	NA	NA	18%	20%	30%
VE-BASKET (NSCLC cohort)[46]	Vemurafenib	Nausea; hyperkeratosis; decreased appetite	77% G3+G4	3%	10%	40%	61%
AcSé (NSCLC cohort)[47]	Vemurafenib	Fatigue; decreased appetite; acneiform dermatitis	NA	NA	22%	NA	NA

G, grade; NA, not available; NSCLC, non-small-cell lung cancer; TRAEs, treatment-related adverse events.

Amongst class effects of BRAFi and MEKi, cutaneous toxicities, including rash, dermatitis and cutaneous squamous cell carcinoma, basal cell carcinoma and keratoacanthoma, must be mentioned. Skin toxicities, particularly hyperproliferative disorders, are strongly correlated with BRAFi due to the paradoxical activation of the MAPK signalling pathway in *BRAF* wild-type cells and are, thus, less frequent in treatment combination strategies.[36,73]

MEKi, particularly trametinib, has also been reported to cause interstitial lung disease and pneumonitis in real-world clinical practice. Management of this pathological entity should include discontinuation of trametinib and continuation of dabrafenib. If possible, switching to another combination of BRAFi and MEKi could be considered.[74,75]

Immunotherapy in *BRAF*-mutated NSCLC

Providing a clear overview on the activity and efficacy of ICI in *BRAF*-mutant NSCLC is challenging given the absence of prospective data, the small populations included in retrospective/observational studies, and their fragmentation based on different mutation classes, PD-L1 expression, or tumour mutational burden (TMB).[8,76–80] Moreover, in the majority of studies, outcome data are not separated based on different anti-PD-(L)1 treatments nor on different lines of treatment, even if the majority of patients received ICIs as a second or later treatment line (Table 5). Similarly to *KRAS*-mutated disease, prevalence of smoking habits is higher in patients with *BRAF*-mutated NSCLC compared with those harbouring other oncogene alterations.[7,9] The correlation with tobacco exposure, and the related differences in tumour microenvironment, likely explain the activity of immunotherapy in *BRAF*-mutant disease. Indeed, whilst ICIs have shown limited activity in *EGFR*-mutated or *ALK*-rearranged NSCLC, their benefit in *BRAF*-mutant disease appears more satisfactory, similar to the one observed in wild-type and *KRAS*-mutated NSCLC.[8,81]

Retrospective evidence with single-agent immunotherapy

In the Italian Expanded Access Program (EAP) of second-line nivolumab, 11 patients treated with *BRAF*-mutant NSCLC were enrolled, achieving a median OS of 10.3 months (range 2.1–18.5 months), similar to that reported in the wild-type *BRAF* population (11.2 months, range 9.2–13.2).[82] Additionally, in another small population of 11 *BRAF*-mutated patients treated with immunotherapy, ORR appeared to be similar to *KRAS*-mutated and wild-type NSCLC, and independent from different mutational classes.[8]

Table 5. Main observational studies of immune-checkpoint inhibitors in *BRAF*-mutated non-small cell lung cancer and amongst different mutational classes.

Study	Patients (*n*)	Treated with ICIs (*n*)	Line of treatment	Drugs	ORR	Median PFS, months (95% CI)	Median OS, months (95% CI)
Dudnik et al.[76]	39 21 V600E 18 non-V600E	22 12 V600E 10 non-V600E	First to third	Pembrolizumab Nivolumab Atezolizumab	V600E 25% non-V600E 33% (1 patient not evaluable) *p*=1.0	V600E 3.7 (1.6–6.6) non-V600E 4.1 (0.1–19.6) *p*=0.37	V600E NR non-V600E NR *p*=0.53
Dudnik et al.[77]	18 9 V600E 9 non-V600E	10 5 V600E 5 non-V600E	First (1 patient) to fourth	Pembrolizumab Nivolumab Atezolizumab	V600E 25% non-V600E 20%	V600E 1.5 (1.2–8.3) non-V600E 2.6 (2.0–4.2)	V600E NR (1.2–NR) non-V600E NR (2.3–NR)
Rihawi et al.[82]	11	11	Second	Nivolumab	9%	Not reported	10.3 (2.1–18.5)
Mazieres et al.[79]	43 17 V600E 18 non-V600E 8 unknown	43	First and further	anti-PD-(L)1	V600E and others 24% (9/37 evaluable)	V600E 1.8 (1.0–4.6) non-V600E 4.1 (2.9–9.0) *p*=0.20	V600E 8.2 (11–NR) non-V600E 17.2 (2.7–NR) *p*=0.28
Offin et al.[78]	177 41 V600 136 non-V600	46 36 V600 10 non-V600	Second (median)	Pembrolizumab Nivolumab Atezolizumab Nivolumab + ipilimumab	V600 10% non-V600 22% *p*=0.66	Not reported	Non-V600 2.4
Guisier et al.[80]	44 26 V600 18 non-V600	44	First and further (42 pre-treated patients)	anti-PD-(L)1	V600 26% non-V600 35%	V600 5.3 (2.1–NR) non-V600 4.9 (2.3–NR)	V600 22.5 (8.3–NR) non-V600 12.0 (6.8–NR)
Murciano-Goroff et al.[84]	127 29 class 1 36 class 2 23 class 3 39 VUS	50 13 class 1 37 class 2/3	First and further	Pembrolizumab Nivolumab Atezolizumab Nivolumab + ipilimumab Experimental	Class 1 9% class 2/3 26% *p*=0.25	NA	NA
Wiesweg et al.[8]	72 31 V600E 41 class 2/3	14	Second to fourth	anti-PD-(L)1	29%	2.2 (0.9–NA)	OS inferior in BRAF *versus* BRAF wild type (HR 1.38, *p*=0.048)
Di Federico et al.[87,a]	35 12 class 2 10 class 3 13 undefined	20	Second	Atezolizumab	NA	NA	8.4 (4.6–11.2)

[a]Patients from POPLAR and OAK randomized trials. DoR, duration of response; (m)OS, (median) overall survival; (m)PFS, (median) progression-free survival; NA, not available; NR, not reached; ORR, objective response rate; PD-(L)1, programmed cell death-(ligand)1.

Comparable outcomes were reported in the Immunotarget study, where amongst 43 patients with *BRAF*-mutated disease treated with immunotherapy median OS was 13.6 months, similar to that reported for *KRAS*-mutated disease (13.5 months).[79] Although not significant, OS was shorter in patients with V600E mutation when compared with other *BRAF* mutations (median 8.2 *versus* 17.2 months; p=0.28).[78] Overall, median PFS of patients with *BRAF* mutations and treated with ICIs was numerically similar to those of patients with *KRAS* or *MET* alterations but a trend towards shorter median PFS with immunotherapy in the V600E group compared with non-V600E one (1.8 *versus* 4.1 months; p=0.20) was reported. Of note, in the *BRAF*-mutant subgroup, a difference in median PFS of smoker patients versus never smokers was reported (4.1 *versus* 1.9 months; p=0.03).[80]

In another retrospective study, Negrao et al. included two cohorts of patients with oncogene-addicted NSCLC to evaluate outcomes with single-agent ICIs.[83] In the first cohort, ten patients with *BRAF* mutations were included (the majority receiving ICIs as third or further line of treatment), and these patients experienced the highest ORR (62%) and the longest PFS across all the oncogene subgroups, also significantly longer than for those with *KRAS*-mutated disease (median 7.4 *versus* 2.8 months, HR 0.36, 95% CI 0.14–0.88; p=0.026). Median OS was numerically longer than in those with *KRAS* mutations, though not significant (35.6 *versus* 16.8 months, HR 0.65, 95% CI 0.26–1.63; p=0.363). The second cohort included 37 patients with *BRAF* V600E mutations and 45 patients with *BRAF* non-V600E mutations. The majority received immunotherapy as first or second line of treatment and approximately 60% did not receive subsequent therapies. Even in this case, the *BRAF*-mutant groups experienced the longest PFS and OS amongst other oncogene-addicted subgroups, though not statistically significant. Median PFS was indeed 9.8 months and 5.4 months for patients harbouring V600E and non-V600E mutations, respectively. Median OS was 20.8 months (95% CI 7.9–NA) in *BRAF* V600E and 14.9 months (95% CI 8.87–29.14) in *BRAF* non-V600E groups.

Exploring the predictive role of different mutational classes

In addition to the abovementioned studies performed by Mazieres et al.[79] and Negrao et al.,[83] several other studies explored outcomes of different functional classes of *BRAF* mutations, but evidence remains inconsistent and failed in demonstrating that mutation type may affect immunotherapy outcome.

In a retrospective review of 39 cases of patients treated with anti-PD-(L)1 alone or in combination with anti-CTLA4, ORR and median PFS were, respectively, 25% *versus* 33% (p=1.0) and 3.7 *versus* 4.1 months (p=0.37) for patients harbouring a V600E (n=21) or a non-V600E (n=18) *BRAF* mutation.[75] In an additional cohort of 177 patients (n=127 metastatic), ORR to immunotherapy for V600 (n=29) or non-V600 (n=98) *BRAF* alterations were, respectively, 10% *versus* 22% (p=0.66). Moreover, in the same cohort, no difference in time to immunotherapy discontinuation was found (p=0.26).[78]

In the population described by Guisier et al.,[80] patients harbouring *BRAF* V600 (n=26) and *BRAF* non-V600 (n=18) mutations achieved 5.3 (95% CI 2.1–NR) and 4.9 (95% CI 2.3–NR) months of median PFS, and 22.5 (95% CI 8.3–NR) and 12 (95% CI 6.8–NR) months of median OS, respectively.

Murciano-Goroff et al.[84] reported data from a population of 50 patients with *BRAF*-mutant NSCLC treated with ICIs (13 V600 and 37 non-V600). Whilst considering the higher number of patients with non-V600 mutations, numerically higher ORR was reported in this subgroup (9% amongst V600 *versus* 26% amongst non-V600; p=0.25). Overall, limited benefits with immunotherapy and short duration of treatment (median 1.9 months) were reported, but 9 patients amongst the different classes experienced durable response (≥2 years).

Recently, an analysis of patients (n=35) carrying non-V600 mutations enrolled in the POPLAR and OAK phase II and phase III trials on second-line atezolizumab[85,86] reported shorter OS than that of patients with wild-type *BRAF* (8.4 *versus* 11.5 months; HR 1.70 (95% CI 1.19–2.44); p=0.0033).[87]

PD-L1 expression and TMB in BRAF-mutated NSCLC

In general, in NSCLC harbouring *BRAF* mutations, PD-L1 expression and TMB values seem to be higher than in unselected or *EGFR/ALK*-driven disease.[76,83] Concerning PD-L1 expression, different studies report wide ranges of expression rates, sometimes with conflicting results about PD-L1 expression amongst different mutational classes (Table 6).[76–78,80] Offin et al.[78] described higher TMB in non-V600 (n=136) than in V600 (n=41), with median 10.8 mut/Mb *versus* 4.9 mut/Mb (p<0.0001) (Table 7), reporting that, overall, patients with non-V600 tumours have a higher TMB and lower PD-L1 expression.[78] Similarly, in a cohort of 139 patients with *BRAF*-mutant NSCLC, median TMB was significantly higher in class 3 than in the other classes (p<0.001).[87]

In the population described by Murciano-Goroff et al.,[84] TMB was higher in class 2/3 than in class 1 *BRAF* mutations (p<0.001), and a trend, though not significant (p=0.09), was observed even stratifying by smoking status.

Despite defining the different levels of PD-L1 expression and TMB, these studies failed in finding a correlation between PD-L1 and/or TMB and clinical outcomes in patients treated with immunotherapy, with the limitation of small patient populations (Tables 6 and 7).[76–78]

Taken together, evidence suggests that, in the pre-treated setting, ICIs in patients with *BRAF*-mutated tumours have similar efficacy than in unselected patients but I is not possible to identify subgroups of patients more likely to benefit from immunotherapy. As mentioned above, few studies included patients treated with first-line immunotherapy, with no annotation of the clinical outcomes in isolation from pre-treated patients.[76,77,79,80] Importantly, no evidence is available concerning the outcomes of patients with *BRAF*-mutant NSCLC undergoing chemo-immunotherapy.

Table 6. PD-L1 expression in *BRAF*-mutated NSCLC amongst different mutational class in observational studies.

Study	BRAF mutations	PD-L1 expression		
Dudnik et al.[76]		**PD-L1 <1%**	**PD-L1 1–49%**	**PD-L1 ≥50%**
	V600E	5/19 (26%)	6/19 (32%)	8/19 (42%)
	Non-V600E	4/10 (40%)	1/10 (10%)	5/10 (50%)
Dudnik et al.[77]		**PD-L1 <1%**	**PD-L1 1–49%**	**PD-L1 ≥50%**
	V600E	2/8 (25%)	4/8 (50%)	2/8 (25%)
	Non-V600E	2/5 (40%)	0/5 (0%)	3/5 (60%)
Mazieres et al.[79]	V600 and non-V600	**PD-L1 >1%**	**PD-L1 <50%**	**PD-L1 ≥50%**
		7/10 (70%)	4/10 (44%)	5/10 (56%)
Offin et al.[78]		**PD-L1 0%**	**PD-L1 1–49%**	**PD-L1 ≥50%**
	V600	2/7 (28.5%)	3/7 (43%)	2/7 (28.5%)
	Non-V600	29/49 (59%)	15/49 (31%)	5/49 (10%)
Guisier et al.[80]		**PD-L1 negative**	**PD-L1 positive**	**PD-L1 >50%**
	V600	3/26 (12%)	11/26 (42%)	10/26 (38%)
	Non-V600	2/18 (11%)	5/18 (28%)	2/18 (11%)
Murciano-Goroff et al.[84]		**PD-L1 0%**	**PD-L1 1–49%**	**PD-L1 ≥50%**
	Class 1	3/11 (27.2%)	4/11 (36.4%)	4/11 (36.4%)
	Class 2	11/19 (57.9%)	6/19 (31.6%)	2/19 (10.5%)
	Class 3	8/11 (72.7%)	3/11 (27.3%)	0/11 (0%)

The possibility of combining pan-RAF and BRAFi/MEKi with anti-PD-(L)1 antibodies is under evaluation also in NSCLC (B-FAST trial – NCT03178552).

Incorporating data of targeted agents and immunotherapy into a potential therapeutic algorithm

First-line treatment options in advanced NSCLC have multiplied in recent years.[88–91] Treatment algorithms are based on histology, molecular status and PD-L1 levels, still considering clinical features such as burden of disease, age, comorbidity and performance status. Providing indications in *BRAF*-mutant disease is challenging for three main reasons: (1) heterogeneity of *BRAF* mutations; (2) documented clinical activity and FDA/EMA approval available for patients with *BRAF* V600-mutant NSCLC and (3) immunotherapy has shown profiles of activity in *BRAF*-mutant disease, making its application appealing in the first-line setting, as monotherapy if PD-L1 ≥50% or in combination with chemotherapy regardless of PD-L1 expression levels.

In patients with advanced *BRAF* V600E NSCLC, the combination dabrafenib-trametinib should be offered upfront, as it is the only regimen with satisfying prospective data in this molecular subset of patients.[92] Especially for cases with features suggesting good outcomes achievable with immunotherapy (i.e. high PD-L1, smoking history), first-line treatment options including ICIs should also be considered.

After targeted therapy, immunotherapy alone or combined with chemotherapy, according to PD-L1 expression levels, should be considered. Docetaxel with anti-angiogenic agents or single-agent regimens should be considered for further lines of treatment as for non-oncogene-addicted NSCLC.[93] Given the rarity of these alterations, enrolment in clinical trials should be also encouraged.

Given the absence of systematic studies, current guidelines recommend that diseases harbouring non-V600E *BRAF* mutations should be treated as non-oncogene-addicted NSCLC.[94] Patients with non-V600E *BRAF* mutations should then

Table 7. TMB in *BRAF*-mutated NSCLC and amongst different mutational class in observational studies.

Study	BRAF mutations	TMB			
Dudnik et al.[76]		**≤5 muts/Mb**	**6–19 muts/Mb**	**≥20 muts/Mb**	**Median TMB**
	V600E	4/8 (50%)	2/8 (25%)	2/8 (25%)	5 muts/Mb (range 1–42)
	Non-V600E	0/3 (0%)	3/3 (100%)	0/3 (0%)	11 muts/Mb (range 7–14)
Dudnik et al.[77]		**≤5 muts/Mb**	**6–19 muts/Mb**		**≥20 muts/Mb**
	V600E	4/7 (57%)	1/7 (14%)		2/7 (29%)
	Non-V600E	1/3 (33%)	2/3 (67%)		0/3 (0%)
		Median TMB		*p*<0.0001	
Offin et al.[78]	V600 (*n*=41)	4.9 muts/Mb			
	Non-V600 (*n*=136)	10.8 muts/Mb			
Murciano-Goroff et al.[84]		**Median TMB**		*p*<0.001	
	Class 1 (*n*=29)	4.9 muts/Mb (range 1–19.3)			
	Class 2 (*n*=36)	8.9 muts/Mb (range 0–82.5)			
	Class 3 (*n*=23)	9.8 muts/Mb (range 2–32.5)			
Di Federico et al.[87]		**Median TMB**		*p*<0.001	
	Class 1 (*n*=45)	3.91 muts/Mb			
	Class 2 (*n*=47)	6.73 muts/Mb			
	Class 3 (*n*=46)	10.57 muts/Mb			

Mb, megabase; muts, mutations; TMB, tumour mutational burden.

receive standard first-line regimens according to PD-L1 levels, and chemotherapy with anti-angiogenic agents thereafter,[93,94] and BRAF/MEK inhibition may follow in later lines of treatment. Nevertheless, we deem that physicians facing molecular reports of non-V600 *BRAF* mutations should interrogate the available literature on melanoma and NSCLC (partially reported here) to look for clinical experience with targeted agents in precise molecular alterations and propose these to pre-treated patients.

As a shared consideration involving the management of lung cancer driven by oncogenic alterations, the objective is deriving the longest clinical benefit from targeted agents. In line with this concept, BRAFi/MEKi should be maintained 'beyond progression' in case of slow, asymptomatic disease progression and in the case of oligoprogression, in addition to local treatments.[95]

Locally advanced and early-stage disease

In unresectable stage III NSCLC, the role of consolidation immunotherapy after chemo-radiotherapy is now well established.[96–98] Patients harbouring oncogene-addicted disease (in particular *EGFR*-mutated NSCLC) may not benefit from consolidation immunotherapy.[99,100] Recently, a multicentre international retrospective study involving 323 patients treated with durvalumab after chemo-radiotherapy, including 43 patients with driver genomic alterations, amongst which five harboured *BRAF* mutations,[101] found no significant difference on PFS when comparing patients harbouring oncogene alterations overall with those with wild-type disease (14.9 *versus* 18.0 months, respectively; *p*=1.0). Of note, median PFS for *BRAF*-mutated disease was 3.9 months (95% CI 3.9–NR).[101]

Phase III trials of immunotherapy as adjuvant/neoadjuvant treatment are currently shaping a new management of

early-stage NSCLC.[102–105] No data about patients with *BRAF*-mutated disease are available in this setting, but it is possible to argue that they will represent a small percentage of patients enrolled overall, making it difficult to draw strong conclusions about their outcomes or to differentiate them according to different mutational classes.

In oncogene-addicted NSCLC, target therapies are also moving to the perioperative setting.[106–110] Experience in neoadjuvant treatment of *BRAF* V600E-related malignancies is growing[111–113] but remains limited in NSCLC. Recently, major pathological response to neoadjuvant dabrafenib-trametinib in stage IIIA (cT1cN2M0) lung adenocarcinoma harbouring *BRAF* V600E mutation was reported. Treatment was administered for 2 months before surgery and resumed 1 month post-surgery. During preoperative treatment, patients experienced only pyrexia as a side-effect. Left upper lobectomy and systematic lymphatic dissection were performed without complication and with full recovery few weeks after.[114] Although it is a single experience, it suggests that double BRAF blockade may be a possible treatment option in potentially resectable *BRAF* V600E NSCLC.

NAUTIKA1 (NCT04302025) is an ongoing phase II study of multiple drugs directed towards different molecular alterations in neoadjuvant and adjuvant treatment of resectable stage IB–III NSCLC. In the *BRAF* V600 cohort, patients will receive vemurafenib 960 mg twice daily and cobimetinib 60 mg once daily for 8 weeks as a neoadjuvant strategy and, if not progressed after surgery, they will receive adjuvant chemotherapy followed by 2 years of target therapy.

Given the current evidence and pending the results of ongoing clinical trials, patients with *BRAF*-mutated, early-stage disease should be treated as those with unselected NSCLC.

Conclusions and open questions

To date, *BRAF* testing with sequencing assays is mandatory for the correct diagnosis and treatment of patients with advanced NSCLC as they could benefit from treatment with BRAFi plus MEKi. *BRAF*-mutant NSCLC is more heterogenous than other oncogene-addicted NSCLCs given the divergent response of different mutational classes to BRAF and MEK inhibition. Dabrafenib-trametinib combination is the standard of care for *BRAF* V600 mutations, but resistance invariably occurs and mechanisms behind it are not fully elucidated. Wider molecular evidence about resistance mechanisms is available in melanoma,[115,116] with some initial suggestions in NSCLC.[117,118] New generation BRAFi and combination therapies are under investigation in melanoma[119] and will hopefully be translated to other malignancies, including NSCLC.

On the other hand, patients harbouring *BRAF* mutations may experience improved outcomes when treated with immunotherapy, paradoxically complicating the development of treatment algorithms. Prospective evidence on the outcomes generated by immunotherapy +/– chemotherapy in *BRAF*-mutant disease is eagerly awaited, as this will help guide first-line treatment decisions.

Non-V600 mutations include a heterogeneous group of *BRAF* mutations with various outcomes to targeted agents according to available evidence. First-line treatment should be administered mainly based on PD-L1 status, as for unselected NSCLC. The granular data available of patients with melanoma or NSCLC with precise *BRAF* mutations sustain the administration of BRAFi/MEKi. In the absence of prospective evidence, publication of case reports or series about clinical experience with targeted agents in precise molecular alterations and corresponding patient outcomes should be encouraged. This can increase the knowledge on this subject and may provide further treatment options for selected subgroups of patients.

In the locally advanced and early setting, there remains no indication in *BRAF* testing in these cases, but the introduction of immunotherapy and targeted options will hopefully generate novel treatment options.

Given the relative rarity of *BRAF* mutations in NSCLC, and even more if considering the differential mutational classes and the individual mutants, dedicated evidence on treatment outcomes across disease settings is awaited to address clinical attitudes.

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References

1. Thai AA, Solomon BJ, Sequist LV, et al. Lung cancer. *Lancet*. 2021;398(10299):535–554. https://doi.org/10.1016/S0140-6736(21)00312-3
2. Davies H, Bignell GR, Cox C, et al. Mutations of the BRAF gene in human cancer. *Nature*. 2002;417(6892):949–954. https://doi.org/10.1038/nature00766
3. Owsley J, Stein MK, Porter J, et al. Prevalence of class I-III BRAF mutations among 114,662 cancer patients in a large genomic database. *Exp Biol Med*. 2021;246(1):31–39. https://doi.org/10.1177/1535370220959657
4. Dankner M, Rose AAN, Rajkumar S, et al. Classifying BRAF alterations in cancer: new rational therapeutic strategies for actionable mutations. *Oncogene*. 2018;37(24):3183–3199. https://doi.org/10.1038/s41388-018-0171-x
5. Yao Z, Yaeger R, Rodrik-Outmezguine VS, et al. Tumours with class 3 BRAF mutants are sensitive to the inhibition of activated RAS. *Nature*. 2017;548(7666):234–238. https://doi.org/10.1038/nature23291
6. Dagogo-Jack I, Martinez P, Yeap BY, et al. Impact of BRAF mutation class on disease characteristics and clinical outcomes in BRAF-mutant lung cancer. *Clin Cancer Res*. 2019;25(1):158–165. https://doi.org/10.1158/1078-0432.CCR-18-2062
7. Marchetti A, Felicioni L, Malatesta S, et al. Clinical features and outcome of patients with non-small-cell lung cancer harboring BRAF mutations. *J Clin Oncol*. 2011;29(26):3574–3579. https://doi.org/10.1200/JCO.2011.35.9638
8. Wiesweg M, Preuß C, Roeper J, et al. BRAF mutations and BRAF mutation functional class have no negative impact on the clinical outcome of advanced NSCLC and associate with susceptibility to immunotherapy. *Eur J Cancer*. 2021;149:211–221. https://doi.org/10.1016/j.ejca.2021.02.036
9. Litvak AM, Paik PK, Woo KM, et al. Clinical characteristics and course of 63 patients with *BRAF* mutant lung cancer. *J Thorac Oncol*. 2014;9(11):1669–1674. https://doi.org/10.1097/JTO.0000000000000344
10. Perrone F, Mazzaschi G, Minari R, et al. Multicenter observational study on metastatic non-small cell lung cancer harboring *BRAF* mutations: focus on clinical characteristics and treatment outcome of V600E and non-V600E subgroups. *Cancers*. 2022;14(8):2019. https://doi.org/10.3390/cancers14082019
11. Paik PK, Arcila ME, Fara M, et al. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. *J Clin Oncol*. 2011;29(15):2046–2051. https://doi.org/10.1200/JCO.2010.33.1280
12. Li S, Li L, Zhu Y, et al. Coexistence of EGFR with KRAS, or BRAF, or PIK3CA somatic mutations in lung cancer: a comprehensive mutation profiling from 5125 Chinese cohorts. *Br J Cancer*. 2014;110:2812–2820. https://doi.org/10.1038/bjc.2014.210
13. Ding X, Zengli Z, Tao J, et al. Clinicopathologic characteristics and outcomes of Chinese patients with non-small-cell lung cancer and BRAF mutation. *Cancer Med*. 2017;6:555–562. https://doi.org/10.1002/cam4.1014
14. Planchard P, Popat S, Kerr K, et al. Metastatic non-small cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29:iv192–iv237. https://doi.org/10.1093/annonc/mdy275
15. Capper D, Preusser M, Habel A, et al. Assessment of BRAF V600E mutation status by immunohistochemistry with a mutation-specific monoclonal antibody. *Acta Neuropathol*. 2011;122(1):11–19. https://doi.org/10.1007/s00401-011-0841-z
16. Ilie M, Long E, Hofman V, et al. Diagnostic value of immunohistochemistry for the detection of the BRAFV600E mutation in primary lung adenocarcinoma Caucasian patients. *Ann Oncol*. 2013;24(3):742–748. https://doi.org/10.1093/annonc/mds534

17. Seto K, Haneda M, Masago K, et al. Negative reactions of BRAF mutation-specific immunohistochemistry to non-V600E mutations of BRAF. *Pathol Int*. 2020;70(5):253–261. https://doi.org/10.1111/pin.12903
18. Hofman V, Benzaquen J, Heeke S, et al. Real-world assessment of the BRAF status in non-squamous cell lung carcinoma using VE1 immunohistochemistry: a single laboratory experience (LPCE, Nice, France). *Lung Cancer*. 2020;145:58–62. https://doi.org/10.1016/j.lungcan.2020.04.024
19. Wolff HB, Steeghs EMP, Mfumbilwa ZA, et al. Cost-effectiveness of parallel versus sequential testing of genetic aberrations for stage IV non-small-cell lung cancer in the Netherlands. *JCO Precis Oncol*. 2022;6:e2200201. https://doi.org/10.1200/PO.22.00201
20. Zou D, Ye W, Hess LM, et al. Diagnostic value and cost-effectiveness of next-generation sequencing-based testing for treatment of patients with advanced/metastatic non-squamous non-small-cell lung cancer in the United States. *J Mol Diagn*. 2022;24(8):901–914. https://doi.org/10.1016/j.jmoldx.2022.04.010
21. Dall'Olio FG, Conci N, Rossi G, et al. Comparison of sequential testing and next generation sequencing in advanced lung adenocarcinoma patients – a single centre experience. *Lung Cancer*. 2020;149:5–9. https://doi.org/10.1016/j.lungcan.2020.08.008
22. Guibert N, Pradines A, Casanova A, et al. Detection and monitoring of the BRAF mutation in circulating tumor cells and circulating tumor DNA in BRAF-mutated lung adenocarcinoma. *J Thorac Oncol*. 2016;11(9):e109–e112. https://doi.org/10.1016/j.jtho.2016.05.001
23. Raymond V, Bivona T, Lanman R, et al. OA12.05 spectrum of 1014 somatic BRAF alterations detected in cell-free DNA of patients with advanced non-small cell lung cancer. *J Thor Oncol*. 2017;12:s1777–s1778. https://doi.org/10.1016/j.jtho.2017.09.397
24. Bracht JWP, Karachaliou N, Bivona T, et al. *BRAF* mutations classes I, II, and III in NSCLC patients included in the SLLIP trial: the need for a new pre-clinical treatment rationale. *Cancers*. 2019;11(9):1381. https://doi.org/10.3390/cancers11091381
25. Sugimoto A, Matsumoto S, Udagawa H, et al. A large-scale prospective concordance study of plasma- and tissue-based next-generation targeted sequencing for advanced non-small cell lung cancer (LC-SCRUM-Liquid). *Clin Cancer Res*. 2022;6:CCR-22-1749. https://doi.org/10.1158/1078-0432.CCR-22-1749
26. ClinicalTrials.gov. Evaluation of the feasibility and clinical relevance of liquid biopsy in patients with suspicious metastatic lung cancer. https://clinicaltrials.gov/ct2/show/NCT03721120. Accessed October 3, 2022.
27. Leighl NB, Page RD, Raymond VM, et al. Clinical utility of comprehensive cell-free dna analysis to identify genomic biomarkers in patients with newly diagnosed metastatic non-small cell lung cancer. *Clin Cancer Res*. 2019;25(15):4691–4700. https://doi.org/10.1158/1078-0432.CCR-19-0624
28. Liu L, Liu H, Shao D, et al. Development and clinical validation of a circulating tumor DNA test for the identification of clinically actionable mutations in nonsmall cell lung cancer. *Genes Chromosomes Cancer*. 2018;57(4):211–220. https://doi.org/10.1002/gcc.22522
29. Aggarwal C, Thompson JC, Black TA, et al. Clinical implications of plasma-based genotyping with the delivery of personalized therapy in metastatic non-small cell lung cancer. *JAMA Oncol*. 2019;5(2):173–180. https://doi.org/10.1001/jamaoncol.2018.4305
30. US FDA. Guardant360 CDx – P200010/S002. https://www.fda.gov/medical-devices/recently-approved-devices/guardant360-cdx-p200010s002. Accessed October 3, 2022.
31. US FDA. FoundationOne Liquid CDx – P190032. https://www.fda.gov/medical-devices/recently-approved-devices/foundationone-liquid-cdx-p190032. Accessed October 3, 2022.
32. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. *Lancet*. 2012;380:358–365. https://doi.org/10.1016/S0140-6736(12)60868-X
33. McArthur GA, Chapman PB, Robert C, et al. Safety and efficacy of vemurafenib in BRAF(V600E) and BRAF(V600K) mutation-positive melanoma (BRIM-3): extended follow-up of a phase 3, randomised, open-label study. *Lancet Oncol*. 2014;15:323–332. https://doi.org/10.1016/S1470-2045(14)70012-9
34. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med*. 2011;364:2507–2516. https://doi.org/10.1056/NEJMoa1103782
35. Long GV, Stroyakovskiy D, Gogas H, et al: Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicentre, double-blind, phase 3 randomised controlled trial. *Lancet*. 2015;386:444–451. https://doi.org/10.1016/S0140-6736(15)60898-4
36. Ascierto PA, McArthur GA, Dreno B, et al. Cobimetinib combined with vemurafenib in advanced BRAF(V600)-mutant melanoma (coBRIM): updated efficacy results from a randomised, double-blind, phase 3 trial. *Lancet Oncol*. 2016;17:1248–1260. https://doi.org/10.1016/S1470-2045(16)30122-X
37. Planchard D, Kim TM, Mazieres J, et al. Dabrafenib in patients with BRAF(V600E)-positive advanced non-small-cell lung cancer: a single-arm, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(5):642–650. https://doi.org/10.1016/S1470-2045(16)00077-2

38. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAFV600E-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol*. 2016;17:984–993. https://doi.org/10.1016/S1470-2045(16)30146-2
39. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol*. 2017;18:1307–1316. https://doi.org/10.1016/S1470-2045(17)30679-4
40. Planchard D, Besse B, Groen HJM, et al. Phase 2 study of dabrafenib plus trametinib in patients with BRAF V600E-mutant metastatic NSCLC: updated 5-year survival rates and genomic analysis. *J Thor Oncol*. 2022;17:103–115. https://doi.org/10.1016/j.jtho.2021.08.011
41. Johnson BE, Baik CS, Mazieres J. Clinical outcomes with dabrafenib plus trametinib in a clinical trial versus real-world standard of care in patients with *BRAF*-mutated advanced NSCLC. *JTO Clin Res Rep*. 2022;3(5):100324. https://doi.org/10.1016/j.jtocrr.2022.100324
42. Salama AKS, Li S, Macrae ER, et al. Dabrafenib and trametinib in patients with tumors with *BRAFV600E* mutations: results of the NCI-MATCH trial subprotocol H. *J Clin Oncol*. 2020;38(33):3895–3904. https://doi.org/10.1200/JCO.20.00762
43. European Medicines Agency. Tafinlar. https://www.ema.europa.eu/en/medicines/human/EPAR/tafinlar#authorisation-details-section. Accessed October 3, 2022.
44. US FDA. FDA grants regular approval to dabrafenib and trametinib combination for metastatic NSCLC with BRAF V600E mutation. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-dabrafenib-and-trametinib-combination-metastatic-nsclc-braf-v600e. Accessed October 3, 2022.
45. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med*. 2015;373:726–736. https://doi.org/10.1056/NEJMoa1502309
46. Subbiah V, Gervais R, Riely G, et al. Efficacy of vemurafenib in patients with non-small-cell lung cancer with *BRAF* V600 mutation: an open-label, single-arm cohort of the histology-independent VE-BASKET study. *JCO Precis Oncol*. 2019;3:PO 18.00266. https://doi.org/10.1200/PO.18.00266
47. Mazieres J, Cropet C, Montané L, et al. Vemurafenib in non-small-cell lung cancer patients with BRAFV600 and BRAFnonV600 mutations. *Ann Oncol*. 2020;31:289–294. https://doi.org/10.1016/j.annonc.2019.10.022
48. Auliac JB, Bayle S, Do P, et al. Efficacy of dabrafenib plus trametinib combination in patients with *BRAF* V600E-mutant NSCLC in real-world setting: GFPC 01-2019. *Cancers*. 2019;12(12):3608. https://doi.org/10.3390/cancers12123608
49. Gautschi O, Milia J, Cabarrou B, et al. Targeted therapy for patients with BRAF-mutant lung cancer results from the European EURAF cohort. *J Thor Oncol*. 2015;10:1451–1457. https://doi.org/10.1097/JTO.0000000000000625
50. Mu Y, Ke Y, Xuezhi H, et al. Clinical characteristics and treatment outcomes of 65 patients with BRAF-mutated non-small cell lung cancer. *Front Oncol*. 2020;10:603. https://doi.org/10.3389/fonc.2020.00603
51. Riely GJ, Ahn MJ, Felip E, et al. Encorafenib plus binimetinib in patients with $BRAF^{V600}$-mutant non-small cell lung cancer: phase II PHAROS study design. *Future Oncol*. 2022;18(7):781–791. https://doi.org/10.2217/fon-2021-1250
52. Dankner M, Lajoie M, Moldoveanu D, et al. Dual MAPK inhibition is an effective therapeutic strategy for a subset of class II BRAF mutant melanomas. *Clin Cancer Res*. 2018;24(24):6483–6494. https://doi.org/10.1158/1078-0432.CCR-17-3384
53. Noeparast A, Teugels E, Giron P, et al. Non-V600 BRAF mutations recurrently found in lung cancer predict sensitivity to the combination of trametinib and dabrafenib. *Oncotarget*. 2016;8(36):60094–60108. https://doi.org/10.18632/oncotarget.11635
54. Rajkumar S, Berry D, Heney KA, et al. Melanomas with concurrent BRAF non-p.V600 and NF1 loss-of-function mutations are targetable by BRAF/MEK inhibitor combination therapy. *Cell Rep*. 2022;39(1):110634. https://doi.org/10.1016/j.celrep.2022.110634
55. Menzer C, Menzies AM, Carlino MS, et al. Targeted therapy in advanced melanoma with rare BRAF mutations. *J Clin Oncol*. 2019;37(33):3142–3151. https://doi.org/10.1200/JCO.19.00489
56. Nebhan C, Douglas BJ, Sullivan RJ, et al. Efficacy and safety of trametinib in non-V600 BRAF mutant melanoma: a phase II study. *Oncologist*. 2021;26:731.e1498. https://doi.org/10.1002/onco.13795
57. Dankner M, Wang Y, Fazelzad R, et al. Clinical activity of mitogen-activated protein kinase-targeted therapies in patients with non-V600 BRAF-mutant tumors. *JCO Precis Oncol*. 2022;6:e2200107. https://doi.org/10.1200/PO.22.00107
58. Gautschi O, Peters S, Zoete V, et al. Lung adenocarcinoma with BRAF G469L mutation refractory to vemurafenib. *Lung Cancer*. 2013;82(2):365–367. https://doi.org/10.1016/j.lungcan.2013.08.012
59. Casadei Gardini A, Chiadini E, Faloppi L, et al. Efficacy of sorafenib in BRAF-mutated non-small-cell lung cancer (NSCLC) and no response in synchronous BRAF wild type-hepatocellular carcinoma: a case report. *BMC Cancer*. 2016;16:429. https://doi.org/10.1186/s12885-016-2463-2
60. Sereno M, Moreno V, Rubio JM, et al. A significant response to sorafenib in a woman with advanced lung adenocarcinoma and a BRAF non-V600 mutation. *Anticancer Drugs*. 2015;26:1004–1007. https://doi.org/10.1097/CAD.0000000000000277
61. Dagogo-Jack I. Durable response to dabrafenib combined with trametinib in a patient with NSCLC harboring a *BRAF* G469A mutation. *J Thor Oncol*. 2021;15(10):e174–e176. https://doi.org/10.1016/j.jtho.2020.07.007

62. Sen B, Peng S, Tang X, et al. Kinase-impaired BRAF mutations in lung cancer confer sensitivity to dasatinib. *Sci Transl Med*. 2012;136:136ra70. https://doi.org/10.1126/scitranslmed.3003513
63. Turshudzhyan A, Vredenburgh J. A rare p.T599dup BRAF mutant NSCLC in a non-smoker. *Curr Oncol*. 2020;28(1):196–202. https://doi.org/10.3390/curroncol28010021
64. Citarella F, Russano M, Perrone G, et al. Ineffective target therapy in non-small cell lung cancer harboring BRAF G466R mutation: a case report and biological rationale. *Prec Canc Med*. 2022;5:19. https://doi.org/10.21037/pcm-21-24
65. Rose AAN, Ayodele O, Genta S, et al. Preliminary results of BEAVER: an investigator-initiated phase II study of binimetinib and encorafenib for the treatment of advanced solid tumors with non-V600E BRAF mutations (mts). *J Clin Oncol*. 2021;29(Suppl. 15):e15038. https://doi.org/10.1200/JCO.2021.39.15_suppl.e15038
66. Schadendorf D, Robert C, Dummer R, et al. Pyrexia in patients treated with dabrafenib plus trametinib across clinical trials in BRAF-mutant cancers. *Eur J Cancer*. 2021;153:234–241. https://doi.org/10.1016/j.ejca.2021.05.005
67. Shimada Y, Sato Y, Tachikawa R, et al. Gastrointestinal perforation following dabrafenib and trametinib administration in non-small cell lung carcinoma with BRAF V600E mutation: a case report and literature review. *Invest New Drugs*. 2021;39:1702–1706. https://doi.org/10.1007/s10637-021-01135-0
68. Mourad N, Lourenço N, Delyon J, et al. Severe gastrointestinal toxicity of MEK inhibitors. *Mel Res*. 2019;29:556–559. https://doi.org/10.1097/CMR.0000000000000618
69. Gelsomino F, Di Federico A, Tardio ML, et al. Drug-induced colitis on BRAF and MEK inhibitors for BRAF V600E-mutated non-small cell lung cancer: a case report. *Invest New Drugs*. 2022;40(1):190–193. https://doi.org/10.1007/s10637-021-01166-7
70. Waliany S, Zhu H, Wakelee H, et al. Pharmacovigilance analysis of cardiac toxicities associated with targeted therapies for metastatic NSCLC. *J Thor Oncol*. 2021;16:2029–2039. https://doi.org/10.1016/j.jtho.2021.07.030
71. Méndez-Martínez S, Calvo P, Ruiz-Moreno O, et al. Ocular adverse events associated with MEK inhibitors. *Retina*. 2019;39:1435–1450. https://doi.org/10.1097/IAE.0000000000002451
72. Choe CH, McArthur GA, Caro I, et al. Ocular toxicity in BRAF mutant cutaneous melanoma patients treated with vemurafenib. *Am J Ophtalm*. 2014;158:831–837.e2. https://doi.org/10.1016/j.ajo.2014.07.003
73. Chalmers A, Cannon L, Akerley W. Adverse event management in patients with BRAF V600E-mutant non-small cell lung cancer treated with dabrafenib plus trametinib. *Oncologist*. 2019;24:963–972. https://doi.org/10.1634/theoncologist.2018-0296
74. Giraud V, Longvert C, Houlle-Crepin S, et al. Relapsing pneumonitis due to two distinct inhibitors of the MAPK/ERK pathway: report of a case. *BMC Cancer*. 2015;15:732. https://doi.org/10.1186/s12885-015-1754-3
75. Chic N, Mezquita L, Aldea M, et al. Successful switch to vemurafenib plus cobimetinib after dabrafenib plus trametinib toxicity in $BRAF^{V600E}$-mutant metastatic non-small-cell lung cancer. *Clin Lung Cancer*. 2021;22(1):e54–e56. https://doi.org/10.1016/j.cllc.2020.07.013
76. 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(8):1128–1137. https://doi.org/10.1016/j.jtho.2018.04.024
77. Dudnik E, Bshara E, Grubstein A, et al. Rare targetable drivers (RTDs) in non-small cell lung cancer (NSCLC): Outcomes with immune check-point inhibitors (ICPi). *Lung Cancer*. 2018;124:117–124. https://doi.org/10.1016/j.lungcan.2018.07.044
78. Offin M, Pak T, Mondaca S, et al. Molecular characteristics, immunophenotype, and immune checkpoint inhibitor response in BRAF non-V600 mutant lung cancers. *J Thorac Oncol*. 2019;14(10):S455. https://doi.org/10.1016/j.jtho.2019.08.942
79. 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(8):1321–1328. https://doi.org/10.1093/annonc/mdz167
80. 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(4):628–636. https://doi.org/10.1016/j.jtho.2019.12.129
81. Guaitoli G, Tiseo M, Di Maio M, et al. Immune checkpoint inhibitors in oncogene-addicted non-small cell lung cancer: a systematic review and meta-analysis. *Transl Lung Cancer Res*. 2021;10(6):2890–2916. https://doi.org/10.21037/tlcr-20-941
82. Rihawi K, Giannarelli D, Galetta D, et al. BRAF mutant NSCLC and immune checkpoint inhibitors: results from a real-world experience. *J Thorac Oncol*. 2019;14(3):e57–e59. https://doi.org/10.1016/j.jtho.2018.11.036
83. Negrao MV, Skoulidis 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(8):e002891. https://doi.org/10.1136/jitc-2021-002891
84. Murciano-Goroff YR, Pak T, Mondaca S, et al. Immune biomarkers and response to checkpoint inhibition of $BRAF^{V600}$ and BRAF non-V600 altered lung cancers. *Br J Cancer*. 2022;126(6):889–898. https://doi.org/10.1038/s41416-021-01679-1
85. Fehrenbacher L, Spira A, Ballinger M, et al. Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): a multicentre, open-label, phase 2 randomised controlled trial. *Lancet*. 2016;387:1837–1846. https://doi.org/10.1016/S0140-6736(16)00587-0

86. 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. https://doi.org/10.1016/S0140-6736(16)32517-X
87. Di Federico A, De Giglio A, Gelsomino F, et al. Genomic landscape, clinical features and outcomes of non-small cell lung cancer patients harboring *BRAF* alterations of distinct functional classes. *Cancers*. 2022;14(14):3472. https://doi.org/10.3390/cancers14143472
88. 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(19):1823–1833. https://doi.org/10.1056/NEJMoa1606774
89. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078–2092. https://doi.org/10.1056/NEJMoa1801005
90. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379(21):2040–2051. https://doi.org/10.1056/NEJMoa1810865
91. Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(2):198–211. https://doi.org/10.1016/S1470-2045(20)30641-0
92. NCCN Guidelines. Non-small cell lung cancer. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed March 9, 2023.
93. Hendriks LE, Kerr KM, Menis J, et al. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023:34(4):358-376. https://doi.org/10.1016/j.annonc.2022.12.013
94. Hanna NH, Robinson AG, Temin S, et al. Therapy for stage IV non-small-cell lung cancer with driver alterations: ASCO and OH (CCO) joint guideline update. *J Clin Oncol*. 2021;39(9):1040–1091. https://doi.org/10.1200/JCO.20.03570
95. Hendriks LE, Kerr KM, Menis J, et al. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023:34(4):339-357. https://doi.org/10.1016/j.annonc.2022.12.009
96. Antonia SJ, Villegas A, Daniel D, et al. Durvalumab after chemoradiotherapy in stage III non–small-cell lung cancer. *N Engl J Med*. 2017;377:1919–1929. https://doi.org/10.1056/NEJMoa1709937
97. Antonia SJ, Villegas A, Daniel D, et al. Overall survival with durvalumab after chemoradiotherapy in stage III NSCLC. *N Engl J Med*. 2018;379:2342–2350. https://doi.org/10.1056/NEJMoa1809697
98. 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. https://doi.org/10.1016/j.jtho.2020.12.015
99. 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(5):868–872. https://doi.org/10.1016/j.jtho.2020.12.020
100. Aredo JV, Mambetsariev I, Hellyer JA, et al. Durvalumab for stage III EGFR-mutated NSCLC after definitive chemoradiotherapy. *J Thorac Oncol*. 2021;16(6):1030–1041. https://doi.org/10.1016/j.jtho.2021.01.1628
101. Riudavets M, Auclin E, Mosteiro M, et al. Durvalumab consolidation in patients with unresectable stage III non-small cell lung cancer with driver genomic alterations. *Eur J Cancer*. 2022;167:142–148. https://doi.org/10.1016/j.ejca.2022.02.014
102. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386(21):1973–1985. https://doi.org/10.1056/NEJMoa2202170
103. Cascone T, Provencio M, Sepesi B, et al. Checkmate 77T: a phase III trial of neoadjuvant nivolumab (NIVO) plus chemotherapy (chemo) followed by adjuvant nivo in resectable early-stage NSCLC. *J Clin Oncol*. 2020;38(Suppl. 15):TPS9076. https://doi.org/10.1200/JCO.2020.38.15_suppl.TPS9076
104. O'Brien M, Paz-Ares L, Marreaud S, et al. Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB-IIIA non-small-cell lung cancer (PEARLS/KEYNOTE-091): an interim analysis of a randomised, triple-blind, phase 3 trial. *Lancet Oncol*. 2022;23(10):1274–1286. https://doi.org/10.1016/S1470-2045(22)00518-6
105. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. 2021;398(10308):1344–1357. https://doi.org/10.1016/S0140-6736(21)02098-5
106. Wu YL, Tsuboi M, He J, et al. Osimertinib in resected *EGFR*-mutated non-small-cell lung cancer. *N Engl J Med*. 2020;383(18):1711–1723. https://doi.org/10.1056/NEJMoa2027071
107. ClinicalTrials.gov. A global study to assess the effects of osimertinib in participants with EGFRm stage IA2-IA3 NSCLC following complete tumour resection. https://clinicaltrials.gov/ct2/show/NCT05120349. Accessed November 1, 2022.
108. Tsuboi M, Weder W, Escriu C, et al. Neoadjuvant osimertinib with/without chemotherapy versus chemotherapy alone for *EGFR*-mutated resectable non-small-cell lung cancer: NeoADAURA. *Future Oncol*. 2021;17(31):4045–4055. https://doi.org/10.2217/fon-2021-0549
109. Solomon BJ, Ahn JS, Barlesi F, et al. ALINA: a phase III study of alectinib versus chemotherapy as adjuvant therapy in patients with stage IB-IIIA anaplastic lymphoma kinase-positive (ALK+) non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2019;37(Suppl. 15):TPS8569. https://doi.org/10.1200/JCO.2019.37.15_suppl.TPS8569

110. Leonetti A, Minari R, Boni L, et al. Phase II, open-label, single-arm, multicenter study to assess the activity and safety of alectinib as neoadjuvant treatment in surgically resectable stage III ALK-positive NSCLC: ALNEO trial. *Clin Lung Cancer*. 2021;22(5):473–477. https://doi.org/10.1016/j.cllc.2021.02.014
111. Wang JR, Zafereo ME, Dadu R, et al. Complete surgical resection following neoadjuvant dabrafenib plus trametinib in *BRAFV600E*-mutated anaplastic thyroid carcinoma. *Thyroid*. 2019;29(8):1036–1043. https://doi.org/10.1089/thy.2019.0133
112. Amaria RN, Prieto PA, Tetzlaff MT, et al. Neoadjuvant plus adjuvant dabrafenib and trametinib versus standard of care in patients with high-risk, surgically resectable melanoma: a single-centre, open-label, randomised, phase 2 trial. *Lancet Oncol*. 2018;19(2):181–193. https://doi.org/10.1016/S1470-2045(18)30015-9
113. Long GV, Saw RPM, Lo S, et al. Neoadjuvant dabrafenib combined with trametinib for resectable, stage IIIB-C, $BRAF^{V600}$ mutation-positive melanoma (NeoCombi): a single-arm, open-label, single-centre, phase 2 trial. *Lancet Oncol*. 2019;20(7):961–971. https://doi.org/10.1016/S1470-2045(19)30331-6
114. Liu C, Lu M, Yang Y, et al. Case report: major pathologic response induced by neoadjuvant treatment using BRAF and MEK inhibitors in a patient with stage IIIA lung adenocarcinoma harboring BRAF V600E-mutation. *Front Oncol*. 2022;12:961539. https://doi.org/10.3389/fonc.2022.961539
115. Sun C, Wang L, Huang S, et al. Reversible and adaptive resistance to BRAF(V600E) inhibition in melanoma. *Nature*. 2014;508(7494):118–122. https://doi.org/10.1038/nature13121
116. Long GV, Fung C, Menzies AM, et al. Increased MAPK reactivation in early resistance to dabrafenib/trametinib combination therapy of BRAF-mutant metastatic melanoma. *Nat Commun*. 2014;5:5694. https://doi.org/10.1038/ncomms6694
117. Ortiz-Cuaran S, Mezquita L, Swalduz A, et al. Circulating tumor DNA genomics reveal potential mechanisms of resistance to BRAF-targeted therapies in patients with *BRAF*-mutant metastatic non-small cell lung cancer. *Clin Cancer Res*. 2020;26(23):6242–6253. https://doi.org/10.1158/1078-0432.CCR-20-1037
118. Facchinetti F, Lacroix L, Mezquita L, et al. Molecular mechanisms of resistance to BRAF and MEK inhibitors in $BRAF^{V600E}$ non-small cell lung cancer. *Eur J Cancer*. 2020;132:211–223. https://doi.org/10.1016/j.ejca.2020.03.025
119. Girotti MR, Lopes F, Preece N, et al. Paradox-breaking RAF inhibitors that also target SRC are effective in drug-resistant BRAF mutant melanoma. *Cancer Cell*. 2015;27(1):85–96. Erratum in: Cancer Cell 2017;31(3):466. https://doi.org/10.1016/j.ccell.2014.11.006
120. Su PL, Lin CY, Chen YL, Chen WL, Lin CC, Su WC. Durable response to combined dabrafenib and trametinib in a patient with BRAF K601E mutation-positive lung adenocarcinoma: a case report. *JTO Clin Res Rep*. 2021;2(8):100202. https://doi.org/10.1016/j.jtocrr.2021.100202
121. Saalfeld FC, Wenzel C, Aust DE, Wermke M. Targeted therapy in BRAF p.K601E-driven NSCLC: case report and literature review. *JCO Precis Oncol*. 2020;4:1163–1166. https://doi.org/10.1200/PO.20.00187