# Ongoing Progress in *BRAF*-Mutated Non–Small Cell Lung Cancer

Pamela Abdayem, MD, and David Planchard, MD
Gustave Roussy, Département de médecine oncologique, Villejuif, France

Corresponding author:
David Planchard, MD
Gustave Roussy
Département de médecine oncologique
114, rue Édouard-Vaillant
F-94805 Villejuif, France
Tel: 00 33 1 42 11 42 11
Email: David.planchard@gustaveroussy.fr

**Abstract:** Activating *BRAF* mutations are detected in 1.5% to 4.5% of patients with non–small cell lung cancer (NSCLC). These mutations involve the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway, and affect proliferation, differentiation, transcriptional regulation, and survival of cancer cells. Today, the combination of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib is the preferred first-line treatment option in patients with advanced *BRAF* V600–mutated NSCLC, with an objective response rate of 64%, a median progression-free survival of 10.2 months, a median overall survival of 24.6 months, and a median duration of response of 10.4 months, according to a pivotal phase 2 study. These outcomes remain inferior to those achieved with other targeted therapies in advanced NSCLC with other driver alterations. First-generation BRAF inhibitors are not active in the class II and III *BRAF* mutations that form the other half of *BRAF* mutations in NSCLC. New RAF inhibitors are being investigated in early trials. Novel treatment combinations, particularly with immune checkpoint inhibitors, are also underway. Patient referral to expert centers and enrollment in basket trials as well as serial tissue and liquid biopsies are needed to improve the understanding and the treatment outcomes of this relatively rare disease subset.

Keywords
BRAF, driver mutations, MEK, non–small cell lung cancer, non-V600, V600E

## Introduction

Sustained proliferative signaling, a hallmark of cancer, is one of the main mechanisms of oncogenesis, particularly in non–small cell lung cancer (NSCLC) with oncogene addiction.[1] The advent of molecular testing, particularly next-generation sequencing (NGS), has reshaped the course of NSCLC, a disease that has a poor prognosis and until recently had few therapeutic options. Patients with driver mutations who are treated with targeted therapies achieve impressive response rates and survival outcomes. The *BRAF* mutation is 1 of 9 actionable driver alterations that should be looked for at diagnosis of either advanced adenocarcinoma of the lung (regardless of smoking history) or squamous cell carcinoma of the lung (current or former smokers with a ≤15 pack-year smoking history).

Clinical trials evaluating the efficacy of the BRAF inhibitor

dabrafenib (Tafinlar, Novartis) in combination with the downstream MEK inhibitor trametinib (Mekinist, Novartis) in metastatic *BRAF* V600E–mutated (MT) NSCLC led to rapid approval of the combination in this clinical setting by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[2,3] Dual BRAF and MEK inhibition is currently a standard of care in this molecular subtype of NSCLC. In this review, we present an overview of the clinical and molecular characteristics of *BRAF*-MT NSCLC, the current treatment modalities in *BRAF*-driven advanced NSCLC, the current challenges of treatment and how to overcome them, and the next-generation targeted treatments against this molecular subtype.

## Biology of *BRAF*-MT Tumors

The mitogen activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway known as the RAS/RAF/MEK/ERK signal transduction cascade is one of the main oncogenic pathways in cancer. RAS-guanosine triphosphate (GTP) promotes the formation of active homodimers or heterodimers of the serine/threonine protein kinases ARAF, BRAF, and CRAF. These enzymes catalyze the phosphorylation and activation of MEK1 and MEK2, which in turn activate ERK1 and ERK2. The activation of the MAPK/ERK pathway is involved in many cellular processes, including cell proliferation, differentiation, transcriptional regulation, and survival.[4,5] ARAF and CRAF have been reported as oncogenic drivers in some cancers.[6,7]

*BRAF* is a gene that encodes the serine/threonine protein kinase BRAF. There are approximately 300 *BRAF* mutations. A *BRAF* mutation can be found in 6% of all patients with cancer, mainly those with colorectal adenocarcinoma, melanoma, lung adenocarcinoma, glioblastoma, thyroid gland papillary carcinoma, and hairy cell leukemia.[8-10] Activating *BRAF* mutations and fusions, found in 5.5% and 0.47% of all cancers, respectively, are responsible for the constitutive activation of the MAPK/ERK pathway, which enhances cell growth, proliferation, and survival.[4,8,11] They principally involve the activation loop next to the V600 codon or the phosphate-binding loop at residues 464 to 469.[7] The substitution of glutamic acid for valine at amino acid 600, initially reported in 2002 and known as the *BRAF* V600E mutation, is the most common *BRAF* mutation. It occurs in 3.05% of tumors, according to My Cancer Genome, and is responsible for constitutive BRAF protein kinase activity.[8,12]

Activating *BRAF* mutations, which are found in 1.5% to 4.5% of NSCLC tumors, are generally mutually exclusive from epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*)/*ROS1*/*RET* rearrangements, and *MET* exon 14 skipping mutations.[3,4,13,14] Although the frequency of *BRAF* mutations is much higher in melanoma (nearly 50% of patients) than in NSCLC, the overall number of patients is comparable between the 2 groups owing to the high incidence of lung cancer.[14] In a study by Sheikine and colleagues that involved comprehensive genomic profiling of 23,396 patients with lung cancer, *BRAF* alterations were found in 4.5% of the tumor samples and included *BRAF* V600E mutations (37.4%), *BRAF* non-V600E activating mutations (38%), *BRAF* inactivating mutations (18%), and *BRAF* rearrangements (4.3%; mainly fusions [2.8%]).[15]

Three functional classes of *BRAF* mutations exist, based on different signaling mechanisms and kinase activities:

(1) Class I (kinase activated, codon 600): Class I consists of V600E/K/D-MT kinase-activating RAS-independent monomers (ie, they do not require dimerization to activate MEK1/2) with constitutive high BRAF kinase activity. This class includes nearly 50% of *BRAF* mutations in NSCLC and more than 80% of *BRAF* mutations in melanoma.

(2) Class II (kinase-activated, non–codon 600): Class II consists of kinase-activating RAS-independent dimers with high/intermediate BRAF kinase activity involving codons outside 600 (eg, *K601E, L597R/Q/R, G469A/V/R/E, G464V*).

(3) Class III (kinase-impaired): Class III consists of kinase-inactivating RAS-dependent heterodimers requiring additional upstream signaling (eg, *G596R, D594G, N581, G466V, D287Y*).[16] The inactive kinase domain prevents autophosphorylation of inactivating residues, and thus prolongs the active conformation state.[17] SHP2 is a non–receptor protein tyrosine phosphatase that functions downstream of multiple receptor tyrosine kinases and promotes RAS activation after induction by growth factor signals. Class III is the only class that is sensitive to SHP2 inhibitors in monotherapy because these agents block the upstream signaling that is essential for the cascade activation.[18]

A real-world clinical genomic analysis from the Tempus database identified 1160 patients with solid tumors who had *BRAF* class II or III mutations. NSCLC tumors with class II or III mutations were mostly microsatellite stable. The median tumor mutational burden (TMB) class increased with the *BRAF* class.[19]

There is an unmet need to tailor therapy for *BRAF*-driven disease based on co-occurring alterations. In the previously mentioned study from Sheikine and colleagues that provides one of the largest assessments of *BRAF* alterations in lung cancer, alterations of *SETD2*, *SMAD4,* and *PI3KCA* were significantly more frequent in *BRAF* V600E–altered tumors than in tumors with other *BRAF*

alterations. In contrast, alterations in *KEAP1*, *NF1*, *MET*, *RICTOR*, *KRAS*, *MYC*, *STK11,* and *TP53* were significantly more common in non–V600E *BRAF*–altered tumors.[15] Negrao and colleagues conducted an analysis of 305 unique *BRAF* non-V600 mutations using genomic profiles of 1589 *BRAF*-altered NSCLC cell-free DNA samples from the Guardant Health Clinical Laboratory database. They confirmed that *TP53*, *EGFR*, *KRAS*, and *NF1* were among the most frequently co-altered genes in *BRAF*-MT and *BRAF*–focally amplified tumors. *KRAS* mutations were common in class III *BRAF*-MT specimens, and *NF1* mutations were significantly more associated with class II *BRAF* mutations compared with class I.[20] A genomic analysis of tumor samples from cohorts B and C of the phase 2 multicenter open-label study that led to the adoption of anti-BRAF and anti-MEK therapy as the standard of care in *BRAF*-MT NSCLC revealed that 18% of the patients (n=11) had concomitant somatic mutations and/or genetic alterations in addition to *BRAF* V600E.[21] These mutations consisted of:

(1) Alterations within the phosphatidylinositol 3-kinase (PI3K) pathway (n=4). In these patients, a trend towards decreased progression-free survival (PFS) and overall survival (OS) was shown.

(2) *IDH1* R132X mutations (n=4)

(3) *BRAF* G466V mutation (n=1)

(4) *KRAS* G13C mutation (n=1)

(5) *cMET* exon 14 skipping mutation (n=1)

A pooled analysis of five phase 1 and 2 trials of vemurafenib (Zelboraf, Genentech/Daiichi Sankyo) as monotherapy and in combination with either crizotinib (Xalkori, Pfizer), sorafenib, or everolimus or both paclitaxel and carboplatin in *BRAF* V600E–MT advanced or metastatic nonmelanoma tumors (with 13% of 99 total patients having NSCLC) was recently presented at the 2022 annual meeting of the American Association for Cancer Research. No significant added clinical benefit and poor tolerance were noted when vemurafenib was combined with other targeted agents or cytotoxic therapy.[22]

## Clinical Profile of *BRAF*-MT NSCLC

Epidemiologic data should be interpreted with caution given the rare nature of the *BRAF* mutation, the small sample sizes, and the heterogeneity of the studies. In NSCLC, the prevalence of *BRAF* mutations is higher in White patients (2%-4%) than in Asian patients (0.8%-2%), and the proportion of V600E mutations has been reported to be lower in Asian patients (30%-40% vs ≈50%-70%).[4] *BRAF*-MT NSCLC tumors are almost restricted to a nonmucinous adenocarcinoma histologic subtype.[23] There are no associations between *BRAF* mutations and other clinical characteristics, such as age and sex.[24,25] The prognostic significance of a *BRAF* mutation in NSCLC is also unclear, with studies reporting conflicting outcomes.[26-28]

Patients with *BRAF*-MT NSCLC have a higher prevalence of smoking compared with those who have other driver alterations. Whereas the majority of non-V600E–altered patients are heavy smokers (average daily consumption of ≥20 cigarettes), 20% to 30% of V600E-MT patients are never smokers.[10] Nevertheless, looking at other contrasting results from small-scale studies, one can conclude that *BRAF* mutations occur at a similar incidence in smokers and never smokers.[28] All patients with advanced adenocarcinoma of the lung should therefore be screened for the *BRAF* mutation.

Although class I mutations are predominant in melanoma, 50% to 80% of *BRAF*-altered NSCLC tumors have non-V600 alterations.[29] In a large retrospective analysis of 236 patients with *BRAF*-MT NSCLC (n=107 class I, n=75 class II, and n=54 class III), Dagogo-Jack and colleagues found that class II and III mutations had more aggressive clinical features than class I mutations. These mutations were associated with more brain metastases and *RAS* co-alterations, as well as shorter PFS with chemotherapy. The OS rate also was shorter, although this was driven by fewer extrathoracic metastases and higher use of targeted therapies in class I patients.[16] Indeed, the odds of class I mutations were higher among tumors with pleural involvement (odds ratio [OR], 4.39; 95% CI, 1.11-17.4) and lower among tumors with abdominal metastases (OR, 0.25; 95% CI, 0.07-0.92).[30] In the aforementioned real-world clinical genomic analysis from the Tempus database, treatments (chemotherapy, immune checkpoint inhibitors [ICIs], or combinations of these agents, in both the first- and second-line settings) were discontinued earlier in patients with class II and III mutations compared with those harboring class I mutations, suggesting less benefit and/or less tolerability with the therapies used.[19]

## Treatment of *BRAF*-MT NSCLC

### *Evidence*

Selective first-generation (type I) BRAF inhibitors such as vemurafenib, dabrafenib, and encorafenib bind to the adenosine triphosphate–binding pocket of the active conformation of BRAF, especially BRAF V600E. The latter is active as a monomer, in contrast with wild-type RAF, which signals as a dimer.[17] The efficacy of type I inhibitors was initially demonstrated in metastatic V600E-MT melanoma.[10] The addition of the MEK inhibitor trametinib to the BRAF inhibitor dabrafenib significantly improved OS, PFS, and overall response rate (ORR) compared with dabrafenib plus placebo in metastatic melanoma because the drugs affect distinct targets within the same MAPK

**Table.** Main Published Studies in *BRAF*-MT Advanced NSCLC

| Author (y) | Design | Patients | Best Response | Median PFS, mo | Median OS, mo | Other Findings | AEs |
|---|---|---|---|---|---|---|---|
| Hyman et al (2015)[31] | Basket study; vemurafenib 960 mg PO 2×/d | 20 w/NSCLC (18 *BRAF* V600E, 1 *BRAF* V600G, 1 *BRAF* V600?) | CR: 0%; PR: 42%; ORR: 42%; SD: 42% | 7.3 | NR | – | Rash (68%), fatigue (56%), arthralgia (40%) |
| Subbiah et al (2019)[33] | Basket study; vemurafenib 960 mg PO 2×/d | 62 w/NSCLC (8 L1, 54 ≥L2) | ORR: 37.1%; ORR L1: 37.5%; ORR ≥L2: 37% | 6.5 | 15.4 | mDOR: 7.2 mo | Most common all-G AE: nausea (40%); G 3/4 events: 77%; 2 G 5, not related to vemurafenib; AEs leading to tx interruption in 40% of pt; tx discontinuation in 6 pt; cutaneous SCC: 26% |
| Gautschi et al (2015)[13] | Retrospective multicenter cohort study; vemurafenib or dabrafenib or sorafenib[a] | 35 (5 L1) | ORR: 53%; DCR: 85% | 5 | 10.8; L1: 25.3 for *V600E* mutations and 11.8 for non-*V600E* mutations | 83% had V600E-MT | – |
| Mazieres et al (2020)[34] | NSCLC cohort of phase 2 open-label basket study; vemurafenib 960 mg 2×/d | 118 ≥L2 (101 *BRAF* V600, 17 *BRAF* non-V600) | ORR: 44.8% (*BRAF* V600 cohort); ORR: 0%– cohort stopped (*BRAF* non-V600 cohort) | 5.2 (*BRAF* V600); 1.8 (*BRAF* non-V600) | 10 (*BRAF* V600); 5.2 (*BRAF* non-V600) | 23 pt (19% of *BRAF* V600 and 27% of non-V600) had ECOG PS 2 | All for *BRAF* V600: SAEs: 36%; TRAEs of any G: asthenia (56%), decreased appetite (46%), acneiform dermatitis (37%), nausea (35%), diarrhea (35%); G ≥3 TRAEs: cutaneous SCC (8.8%), dermatitis (6.6%), increased GGT (6.6%); 27 tx discontinuation owing to toxicity; 3 G 5: dehydration, pneumonia, neutropenic sepsis |
| Planchard et al (2016)[59] | Cohort A of phase 2, multicenter, nonrandomized open-label study; dabrafenib 150 mg 2×/d | 84 (6 L1, 78 ≥L2) | OR: 4 of 6 (L1); ORR: 33% (≥L2); SD: 24% (≥L2) | 5.5 | 12.7 | mDOR: 9.6 mo by investigator assessment | SAEs: 42%; G ≥3 AEs: cutaneous SCC (12%), asthenia (5%), BCC (5%); 1 treatment-related death from intracranial hemorrhage |

**Table.** (*Continued*) Main Published Studies in *BRAF*-MT Advanced NSCLC

| Author (y) | Design | Patients | Best Response | Median PFS, mo | Median OS, mo | Other Findings | AEs |
|---|---|---|---|---|---|---|---|
| Planchard et al (2016)[3] | Cohort B of phase 2, multicenter, nonrandomized open-label study; dabrafenib 130 mg PO 2×/d and trametinib 2 mg PO 1×/d | 57 (progression following ≥1 prior platinum-based CT) | ORR: 63.2% (4 of 5 patients who had an ECOG PS of 2 achieved an OR) | 9.7 | – | 100% *BRAF* V600E; mDOR: 9 mo; median time to first response: 6 wk by investigator assessment | SAEs (56%): pyrexia (16%), anemia (5%), confusion (4%), decreased appetite (4%), hemoptysis (4%), hypercalcemia (4%), nausea (4%), cutaneous SCC (4%); G 3-4 AEs: neutropenia (9%), hyponatremia (7%), anemia (5%); tx discontinuation owing to toxicity: 12%[b] (tx interruption 61%, dose reduction 35%) |
| Planchard et al (2017)[2] | Cohort C of phase 2, multicenter, nonrandomized open-label study of dabrafenib 130 mg PO 2×/d and trametinib 2 mg PO 1×/d | 36 (L1) | CR: 6%; PR: 58%; ORR: 64% | 10.2 | 24.6 | – | G 3-4 AEs (69%): pyrexia (11%), increased ALT (11%), HTN (11%), vomiting (8%); SAEs: increased ALT (14%), pyrexia (11%), increased AST (8%), decreased EF (8%); 1 treatment-unrelated death (cardiorespiratory arrest) |
| Planchard et al (2020)[21] | Updated results for cohorts B and C; dabrafenib 130 mg PO 2×/d and trametinib 2 mg PO 1×/d | 57 cohort B; 36 cohort C | ORR: 68.4% (cohort B); ORR: 63.9% (cohort C) | 10.2 (cohort B); 10.8 (cohort C) | 18.2 (cohort B); 17.3 (cohort C) | mDOR: 9.8 mo (cohort B); 10.2 mo (cohort C) by investigator assessment | – |

[a]Vemurafenib in 29 patients, dabrafenib in 9 patients, sorafenib in 1 patient. Thirty-one patients had 1 BRAF inhibitor, 3 patients had vemurafenib followed by dabrafenib, and 1 patient had sorafenib followed by dabrafenib.

[b]None of the 5 ECOG PS 2 patients.

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BCC, basal cell carcinoma; CR, complete response; CT, computed tomography scan; d, day; DCR, disease control rate; ECOG PS, Eastern Cooperative Oncology Group performance status; EF, ejection fraction; G, grade; GGT, gamma-glutamyl transferase; HTN, hypertension; L1, first-line; L2, second-line; mDOR, median duration of response; mo, month(s); MT, mutated; NR, not reached; NSCLC, non–small cell lung cancer; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; PR, partial response; pt, patient(s); SAEs, serious adverse events; SCC, squamous cell carcinoma; SD, stable disease; TRAEs, treatment-related adverse events; tx, treatment; V600?, V600 unknown; wk, weeks(s); y, year.

pathway, and trametinib overcomes the reactivation of ERK signaling, which is the most common mechanism of resistance to BRAF inhibitors.[31]

In a basket trial, the selective BRAF V600 inhibitor vemurafenib achieved a response rate of 42%, a median PFS (mPFS) of 7.3 months, and an unreached median OS (mOS) in 20 pretreated NSCLC patients.[32] In the histology-independent VE-BASKET study, vemurafenib monotherapy achieved an ORR of 37% in *BRAF* V600-MT NSCLC patients as well as durable activity,

with median PFS and OS times of 6.5 and 15.4 months, respectively.[33] Other trials testing vemurafenib were published and showed its efficacy in *BRAF* V600-MT NSCLC, with ORR rates ranging from 37.1% to 53%, mPFS times from 5 to 6.5 months, and mOS times from 10 to 15.4 months.[13,33,34]

After demonstrating encouraging clinical activity of dabrafenib monotherapy in *BRAF* V600E-MT advanced NSCLC (cohort A), including a 33% ORR and an mPFS of 5.5 months, Planchard and colleagues led a phase 2, multicenter, nonrandomized open-label study of dabrafenib at 150 mg twice daily and trametinib at 2 mg once daily in patients with stage IV *BRAF* V600E-MT NSCLC that progressed following at least 1 platinum-based chemotherapy regimen (cohort B). They reported a confirmed ORR of 66.7%, an mPFS of 10.9 months, and an mOS of 18.2 months.[3,21] The results of cohort C that included treatment-naive patients with advanced *BRAF* V600E-MT NSCLC showed an ORR of 64%, an mPFS of 10.2 months, an mOS of 24.6 months, and a median duration of response of 10.4 months.[2,21] The Table summarizes the findings of these pivotal studies in advanced *BRAF*-MT NSCLC. In summary, the addition of MEK inhibitors to BRAF inhibitors has significantly improved treatment outcomes in advanced *BRAF*-MT NSCLC; yet response rates remain lower than those achieved with other targeted therapies such as EGFR or ALK inhibitors in *EGFR*-MT or *ALK*-rearranged disease, respectively.

In the European BRAF (EURAF) cohort, rapid and significant tumor responses were achieved in older patients who were heavily pretreated and who received anti-BRAF treatment, thus encouraging physicians to administer treatment to older patients who have altered performance status.[13]

### *Central Nervous System Activity*

According to a study of 146 patients by Geukes and colleagues, BRAF inhibitors with or without MEK inhibitors are active in melanoma brain metastases, with an intracranial disease control rate of 65% at 8 weeks in symptomatic patients (vs 70% extracranially). A median intracranial PFS of 5.8 months was achieved with the combination of dabrafenib and trametinib (vs 5.7 months for dabrafenib monotherapy and 3.6 months for vemurafenib monotherapy).[35] Given the scarcity of clinical studies in lung cancer, the beneficial effect of BRAF and MEK inhibitors on brain metastatic *BRAF*-MT NSCLC could be extrapolated from melanoma studies.

### *Safety*

Safety data from studies that evaluated BRAF inhibitors with or without MEK inhibitors in advanced NSCLC are summarized in the Table. BRAF inhibitors may cause pyrexia, whereas MEK inhibitors may result in gastrointestinal toxicity. Uncomplicated pyrexia and gastrointestinal toxicities can usually be managed with good patient education and supportive care. Through the blockage of paradoxical activation of the MAPK pathway in *BRAF* wild-type cells, the addition of MEK inhibitors to BRAF inhibitors significantly reduces the risk of cutaneous squamous cell carcinoma compared with BRAF inhibitor monotherapy (4% vs 12% in the phase 2 study by Planchard and colleagues).[3] On the other hand, MEK inhibitors can cause interstitial lung disease in approximately 2% of cases. When this occurs, the MEK inhibitor should be discontinued while maintaining BRAF inhibition.

### *Current Recommendations*

Despite the lack of randomized clinical trial data, the EMA and the FDA have approved dabrafenib in combination with trametinib for the treatment of patients with *BRAF* V600 mutation–positive advanced or metastatic NSCLC.

According to the latest guidelines from the European Society for Medical Oncology (ESMO), the combination of dabrafenib and trametinib is the preferred first-line treatment in stage IV lung carcinoma with *BRAF* V600E mutations (level of evidence: III; grade of recommendation: A; ESMO Magnitude of Clinical Benefit Scale version 1.1 [ESMO-MCBS v1.1]: 2). Immunochemotherapy (level of evidence: V; grade of recommendation: B) or platinum-based chemotherapy alone (in nonsmokers) could be administered after systemic progression on targeted therapies. Oligoprogressive disease could benefit from local treatment such as radiation therapy or surgery while continuing dabrafenib and trametinib. Platinum-based chemotherapy is another frontline option (level of evidence: IV; grade of recommendation: A); in that case, dabrafenib and trametinib could be administered in a second-line setting.[36] Of note, the ESMO-MCBS v1.1 is calculated for every new therapy/indication approved by the EMA since January 2016. Levels of evidence (I to V) and grades of recommendation (A to E) for the ESMO guidelines are adapted from the Infectious Diseases Society of America–US Public Health Service Grading System.[37,38]

According to 2021 guidelines from the American Society of Clinical Oncology, dabrafenib and trametinib or standard treatment may be offered as first-line therapy in the nondriver mutation setting (type: informal consensus; evidence quality: low; strength of recommendation: moderate). There are no randomized controlled trials comparing targeted therapies with standard-of-care chemotherapy or chemoimmunotherapy. In the second-line setting, dabrafenib and trametinib may be offered if not given in the frontline setting (type: informal consensus;

evidence quality: low; strength of recommendation: moderate) or dabrafenib or vemurafenib alone may be offered (type: informal consensus; evidence quality: low; strength of recommendation: weak).[12]

The NSCLC panel of the National Comprehensive Cancer Network added dabrafenib or vemurafenib monotherapy as an option to preferred first-line treatment with dabrafenib and trametinib, mainly when the latter combination is not tolerated. Chemotherapy regimens, with or without ICIs, also remain "useful in certain circumstances."[39]

### *Immunotherapy*

Tumors with driver alterations are known to respond poorly to ICIs. These tumors often occur in never smokers, and generally have lower TMB and lower programmed death ligand 1 (PD-L1) expression. *BRAF*-MT tumors seem to be an exception to this common finding. In a retrospective analysis of 22 patients with *BRAF*-MT advanced NSCLC who were treated with ICIs, *BRAF*-MT NSCLC was associated with a high PD-L1 expression, a low/intermediate TMB, and a microsatellite stable status. Treatment outcomes with ICIs were not influenced by the level of PD-L1 expression nor by the *BRAF* mutation class; they were comparable with those seen in the general NSCLC population.[40] In the retrospective IMMUNOTARGET registry study, 38 patients with *BRAF*-MT who received ICIs had an ORR and an mOS of 28% and 13.6 months, respectively.[41] Similarly, in a study of 210 patients enrolled in the Italian Expanded Access Program of second-line nivolumab, mOS was 11.0, 11.2, and 10.3 months in the overall population, the *BRAF*–wild type subgroup, and the *BRAF*-MT (5% of patients) subgroup, respectively. *BRAF*-MT patients had an ORR of 9%.[42] Whether the efficacy of ICIs is caused by the higher proportion of smoker patients in the *BRAF*-driven subgroup (mainly V600E mutations), or possibly to the higher PD-L1 expression and TMB, the conclusion remains the same: ICIs should not be discarded as a second- or later-line treatment option in *BRAF*-MT NSCLC.

### *Resistance to BRAF Inhibitors*

Secondary resistance mechanisms to BRAF inhibitors, which have been studied primarily in melanoma, most commonly involve the same MAPK pathway through reactivation of ERK signaling either upstream or downstream of BRAF kinase through:

- *BRAF* splice variants (16%)
- *BRAF* gene amplification (13%)
- *NRAS/KRAS* (20%) or *MEK1/2* mutations (7%)

that induce a BRAF-independent reactivation of ERK signaling[14,43]

Indeed, molecular analyses of tumor and liquid biopsies of 8 patients with NSCLC who progressed on dabrafenib/trametinib and were included in the MATCH-R (from "Matching Resistance") institutional prospective trial revealed 3 molecular events, all within the MAPK pathway, that were potentially responsible for resistance: *MEK1* K57N, *NRAS* Q61R, and *KRAS* Q61R mutations.[44] Similarly, Sheikine and colleagues reported a small subset of *BRAF* V600E-MT NSCLC tumors with available specimens before and after treatment (7 patients). The putative resistance alterations that were identified involved *KRAS* (G12D, K61H, G12R, V14I), *NRAS* (Q61K), a rearrangement in the setting of V600E as well as a concomitant splice site mutation in the remaining allele of *SMARCA4*, and a homozygous deletion of *MAP2K4*.[15] The combination of MEK1/2 inhibitors (eg, trametinib, cobimetinib [Cotellic, Genentech], binimetinib [Mektovi, Pfizer]) with BRAF inhibitors delays the emergence of MAPK-related resistance mechanisms through inhibition of ERK signaling.[10]

Other less-common resistance mechanisms include the activation of other pathways—such as PI3K/mammalian target of rapamycin (mTOR)—through activating mutations in AKT and PTEN loss of function, thus bypassing the MAPK pathway.[14] Based on the finding that the activation of the PI3K/mTOR pathway is a mechanism of primary and acquired resistance to BRAF-targeted therapy, Subbiah and colleagues combined vemurafenib and the mTOR inhibitor everolimus in a phase 1 study of *BRAF*-MT advanced solid tumors. Among the 20 patients who were enrolled, 11 were heavily pretreated with prior BRAF or MEK inhibitors, 4 (22%) had a partial response, and 9 (50%) had stable disease as the best response.[33]

## The Future of *BRAF*-MT NSCLC

### *Encorafenib and Binimetinib*

The phase 3 COLUMBUS trial showed that the BRAF inhibitor encorafenib and the MEK inhibitor binimetinib had favorable efficacy and better tolerability compared with vemurafenib monotherapy in *BRAF*-MT melanoma.[45] Encorafenib/binimetinib plus the anti–EGFR monoclonal antibody cetuximab (Erbitux, Lilly) was also evaluated in metastatic *BRAF* V600E-MT colorectal cancer, a subtype with a poor prognosis. This combination resulted in a significantly longer mOS (9 months with the triplet vs 5 months with cetuximab plus chemotherapy).[46] An open-label, multicenter, multicohort phase 2 study of the combination of encorafenib and binimetinib in patients with previously treated and untreated *BRAF* V600E-MT NSCLC called ENCO-BRAF is currently running in France (NCT04526782). Another similar international phase 2 trial of the same combination in the frontline setting or as second-line therapy after chemotherapy or immunotherapy with or without chemotherapy is

also actively recruiting patients (NCT03915951). Of note, participants with other *BRAF* V600 mutations are eligible for the latter study.

### *Next-Generation RAF Inhibitors*

Currently used first-generation (type I and type I 1/2) RAF inhibitors are effective in the treatment of patients with class I *BRAF* V600 mutations. However, these agents paradoxically activate the MAPK signaling pathway, thus leading to renewed tumor growth as well as additional cancer growth in noncancerous wild-type BRAF tissues. Type II RAF inhibitors target DFG-out and αC-helix–in conformations of RAF proteins, leading to their ability to block both active RAF dimers and active RAF monomers at similar potencies without inducing paradoxical activation. Among the studied type II RAF inhibitors are AZ628, belvarafenib, CCT196969, CCT241161, LY3009120, and TAK-580 (MLN2480). In contrast with the first-generation inhibitors, these drugs are less selective for mutated *BRAF* and can induce toxicities in nonmalignant cells.[17] Among the type II RAF inhibitors that are being evaluated in *BRAF* V600-MT NSCLC, we cite HLX208, which has high bioavailability (NCT05065398); XP-102, which is 100 times more potent than vemurafenib (NCT05275374); PF-0728489, also known as ARRY-461, which is highly brain-penetrant (NCT04543188); ABM-1310, which is brain-penetrant (NCT04190628); LXH254 (NCT02974725); KIN-2787 (NCT04913285); and DAY101 (NCT04985604). The corresponding early trials are shown in the eTable (see www.hematologyandoncology.net).

On the other hand, paradox breakers—such as PLX7904 and PLX8394—are a class of BRAF inhibitors that inhibit ERK1/2 in *BRAF* V600E-MT cells without driving paradoxical activation of ERK1/2 in RAS-MT cell lines. They are more specific for mutated RAF (mainly *BRAF* V600-MT) than wild-type RAF proteins, and could replace first-generation RAF inhibitors without paradoxically inducing tumor genesis. They also remain active in cases of dimerization-mediated resistance to vemurafenib.[17] PLX8394 is currently being evaluated in an ongoing basket trial of *BRAF* V600-MT gliomas and (in extension cohort 2) non–V600-MT solid tumors (NCT02428712).

### *Non-V600 Mutations*

First-generation BRAF inhibitors such as dabrafenib, encorafenib, and vemurafenib target class I *BRAF* mutations but are not effective against class II or III mutations, which constitute approximately 50% of *BRAF* mutations (34% all cancers included) in NSCLC and 34% of *BRAF* mutations, all cancers included. Interestingly, Negrao and colleagues reported an objective durable response at 1 year to dabrafenib and trametinib in a patient with a class II mutation (L597R).[20] Class-specific therapies are needed to target these different subsets. The studied strategies include single-agent ERK inhibition, combined BRAF and MEK inhibition, and MEK with receptor tyrosine kinase inhibition.[47-49]

Among the type II novel RAF inhibitors that are being evaluated in *BRAF* non–V600-MT NSCLC, we cite LXH254 in combination with LTT462 (ERK1/2 inhibitor), trametinib or ribociclib (Kisqali, Novartis; NCT02974725), KIN-2787 (specifically designed to inhibit class II and III in addition to class I mutations) in combination with binimetinib (NCT04913285), belvarafenib as monotherapy and in combination with cobimetinib (NCT04589845, NCT03284502), and DAY101 as monotherapy and in combination with the selective MEK1/2 inhibitor pimasertib (NCT04985604).

RAMP202 is an ongoing phase 2 study of the dual RAF/MEK inhibitor VS-6766, as a single agent and in combination with the FAK inhibitor defactinib, in recurrent *KRAS*-MT and *BRAF*-MT NSCLC (NCT04620330). DCC-3116, a first-in-class selective inhibitor of ULK1/2 kinases and autophagy, is currently being tested as monotherapy and in combination with trametinib in NSCLC tumors with *KRAS, NRAS,* and *BRAF* mutations (NCT04892017).[50] PF-07284892 (ARRY-558), a small-molecule inhibitor of SHP2 that may block MAPK signaling, is being evaluated as monotherapy and in combination with binimetinib in class III *BRAF*-MT NSCLC (NCT04800822). Information regarding these ongoing trials is also featured in the eTable.

### *Combining ICIs With Targeted Therapies*

The aim of combining ICIs and targeted therapies in *BRAF*-MT advanced NSCLC is to achieve high response rates (through targeted therapies) and durable responses (through ICIs). Most of the evidence on the efficacy and safety of the triplet therapy comes from trials in advanced melanoma. In a phase 1 multicenter, open-label study of 50 patients with advanced melanoma, Ribas and colleagues showed that durvalumab (Imfinzi, AstraZeneca) can be safely combined with trametinib with or without dabrafenib.[51] Results from parts 1 and 2 of the COMBI-i trial showed a promising and durable ORR (75%) and an unreached mPFS with more than 15 months of follow-up in 36 patients with advanced *BRAF* V600-MT melanoma treated with the triplet dabrafenib, trametinib, and spartalizumab.[52] Results of the randomized phase 3 part of the study are awaited (NCT02967692). The results of KEYNOTE-022, a double-blind randomized phase 2 trial of dabrafenib (150 mg twice daily) and trametinib (2 mg daily) with pembrolizumab (2 mg/kg) or placebo every 3 weeks in treatment-naive *BRAF* V600E/K-MT advanced melanoma were recently reported.[53] The trial

did not meet its prespecified endpoint (required *P* value of .0025), as the improvement of PFS in the triplet group (n=60) was not statistically significant (16.0 vs 10.3 months; hazard ratio [HR], 0.66; *P*=.043). Also, there was an unexpected 8.4% increase in the response rate in the doublet compared with the triplet arm. This could be explained by the imbalance in the baseline patient characteristics as the triplet arm had a higher tumor burden (more visceral metastases, distant metastases with elevated lactate dehydrogenase, and metastatic sites), and therefore a lower ORR and a poorer prognosis. The randomization had been stratified for baseline lactate dehydrogenase levels but not for M1c stage. Nevertheless, the median duration of response was longer in the triplet arm than in the doublet arm, at 18.7 vs 12.5 months, respectively. Grade 3 to 5 treatment-related adverse events were reported in 58.3% and 26.7% of patients receiving triplet and doublet therapies, respectively. Most immune-related adverse events resolved with treatment modification or discontinuation. Grade 3 or 4 increases in aspartate aminotransferase and alanine transaminase resolved with dose modifications. Grade 5 pneumonitis occurred in 1 patient in the triplet group (1.7%). The triplet arm had a worse toxicity profile; however, most toxicities resolved after dose reduction and/or discontinuation of the targeted therapies and/or pembrolizumab. RNA sequencing of biopsies showed increased CD8+ T cells, a T cell–inflamed transcriptome as well as increased expression of histocompatibility class I and II molecules in patients who received triple therapy, which is concordant with an enhanced immune response.[53]

IMspire150 is a randomized, double-blind, placebo-controlled phase 3 study of vemurafenib, cobimetinib, and either atezolizumab or placebo (added at cycle 2) in 514 patients with *BRAF* V600-MT advanced melanoma. PFS was significantly longer in patients who received atezolizumab vs placebo, at 15.1 vs 10.6 months (HR, 0.78; 95% CI, 0.63-0.97; *P*=.025). Reassuringly, the safety profile and treatment discontinuation rates (13% vs 16%) were comparable in both treatment arms.[54] Treatment with BRAF inhibitors results in a paradoxical activation of cells with wild-type *BRAF*, including lymphocytes that could increase the risk of autoimmune toxicities.[55] The main concern in combining ICIs and BRAF inhibitors is the increase in immune-related adverse events, especially pneumonitis, which could be fatal in NSCLC patients—who usually have pre-existing respiratory frailty. Indeed, the addition of ipilimumab to either vemurafenib or dabrafenib and trametinib in melanoma patients was quite toxic (eg, hepatotoxicity, colonic perforation), which led to discontinuation of both trials.[56,57] Fortunately, as stated previously, MEK inhibitors block the paradoxical activation of the MAPK pathway, thus improving the toxicity profile when they are combined with BRAF inhibitors with or without ICIs. Landscape 1011 is a phase 1b/2 umbrella study that is currently testing (among other arms) the combination of sasanlimab, a subcutaneously administered monoclonal antibody that blocks the interaction between PD-1 and PD-L1/PD-L2, with encorafenib and binimetinib in advanced *BRAF* V600E-MT NSCLC (NCT04585815). B-FAST is another ongoing trial of atezolizumab combined with vemurafenib and cobimetinib in treatment-naive patients with a *BRAF* V600 mutation as detected by 2 blood-based NGS circulating tumor DNA (ctDNA) assays (NCT03178552).

### *Liquid Biopsy in* BRAF-*MT NSCLC*

Liquid biopsy is a simple noninvasive analysis of either plasma circulating tumor cells, ctDNA, or other analytes. This approach to biopsy resolves the main issues associated with standard tissue biopsies: tissue scarcity and damage; complications related to the intervention, especially in older, unfit patients; and tumor heterogeneity, given that the collected tumor cells/DNA may be derived from several tumor sites.[23] Ortiz-Cuaran and colleagues reported the results of serial ctDNA testing before treatment with anti-BRAF agents upon response and progression. They detected the *BRAF* V600E mutation in ctDNA in 72.7% and 54.3% of samples at baseline and at disease progression on BRAF inhibitors, respectively. Serial monitoring of ctDNA mirrored the observed overall clinical and radiologic tumor response. At baseline, *BRAF* mutations were associated with liver and adrenal metastases. Patients with concomitant activating mutations of *FGFR2* and *CTNNB1* progressed earlier while on BRAF tyrosine kinase inhibitors. Although the reactivation of the MAPK pathway remained the most frequently described resistance mechanism, other alterations in the PI3K pathway, as well as in *IDH1*, *FGFR2*, and *CTNNB1*, were found.[58] Today, real-time polymerase chain reaction and NGS are the most commonly used methods to assess for *BRAF* mutations in tissue biopsies. These methods could also be used on ctDNA in the blood or other fluids (pleural and cerebrospinal fluid). Despite the use of sensitive assays to detect circulating *BRAF* mutations, false negatives remain an important obstacle to the validation of liquid biopsy as an alternative to tissue biopsy. They are mostly linked to the variable amounts of ctDNA shed into the plasma depending on tumor burden and location (eg, cerebral vs noncerebral, thoracic vs extrathoracic).

## Conclusion

Together with immunotherapy, precision medicine is a pillar of modern thoracic oncology. Twenty years after

the initial report of the *BRAF* V600E mutation, patients with *BRAF*-MT metastatic NSCLC have better survival outcomes, primarily because of the combination of dabrafenib and trametinib in first- and later-line settings. We still have much room for improvement, however. The rarity of *BRAF* mutations in lung cancer, the heterogeneity of the disease, and the retrospective design of many of the studies explain the general lack of understanding when it comes to *BRAF*-MT NSCLC, as well as the delayed development of targeted therapies in comparison with other driver mutations in lung cancer, such as *EGFR* and *ALK*. The routine implementation of molecular profiling in both early and advanced NSCLC is a must in 2022. Large-scale analyses are needed to fully determine the clinical and prognostic characteristics of *BRAF*-MT disease. Patients with *BRAF*-MT NSCLC should be referred to expert centers where they can be enrolled in clinical trials of new drugs and new treatment combinations. They should also be encouraged to participate in translational research protocols in which serial tissue and liquid biopsies are collected before and during treatment, including at response and at progression.

### *Disclosures*

*Dr Abdayem has received nonfinancial support from Pierre Fabre and Eli Lilly; personal fees from AstraZeneca; and research funding from Cegedim Health Data outside the submitted work. Dr Planchard has received personal fees, nonfinancial support, and other from AstraZeneca, Pfizer, and Roche; personal fees and other from Bristol Myers Squibb, Boehringer Ingelheim, Daiichi Sankyo, Eli Lilly, and Merck; personal fees from Celgene and Peer CME; personal fees and nonfinancial support from Prime Oncology; and other funding from MedImmune, Sanofi-Aventis, Taiho Pharma, and Novocure outside the submitted work.*

## References


1. Hanahan D. Hallmarks of cancer: new dimensions. *Cancer Discov*. 2022;12(1):31-46.
2. Planchard D, Smit EF, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously untreated $BRAF^{V600E}$-mutant metastatic non-small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol*. 2017;18(10):1307-1316.
3. Planchard D, Besse B, Groen HJM, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol*. 2016;17(7):984-993.
4. Litvak AM, Paik PK, Woo KM, et al. Clinical characteristics and course of 63 patients with BRAF mutant lung cancers. *J Thorac Oncol*. 2014;9(11):1669-1674.
5. Roskoski R Jr. Targeting oncogenic Raf protein-serine/threonine kinases in human cancers. *Pharmacol Res*. 2018;135:239-258.
6. Araujo LH, Amann J, Imielinski M, Greulich H, Meyerson M, Carbone DP. Oncogenic ARAF as a new driver in lung adenocarcinoma [ASCO abstract 11034]. *J Clin Oncol*. 2014;32(15)(suppl).
7. Holderfield M, Deuker MM, McCormick F, McMahon M. Targeting RAF kinases for cancer therapy: BRAF-mutated melanoma and beyond. *Nat Rev Cancer*. 2014;14(7):455-467.
8. AACR Project GENIE Consortium. AACR Project GENIE: powering precision medicine through an international consortium. *Cancer Discov*. 2017;7(8):818-831.
9. Forbes SA, Bindal N, Bamford S, et al. COSMIC: mining complete cancer genomes in the Catalogue of Somatic Mutations in Cancer. *Nucleic Acids Res*. 2011;39(database issue)(suppl 1):D945-D950.
10. Tabbò F, Pisano C, Mazieres J, et al; BOLERO Consortium. How far we have come targeting BRAF-mutant non-small cell lung cancer (NSCLC). *Cancer Treat Rev*. 2022;103:102335.
11. BRAF. My Cancer Genome. https://www.mycancergenome.org/content/gene/braf/. Accessed April 30, 2022.
12. 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.
13. Gautschi O, Milia J, Cabarrou B, et al. Targeted therapy for patients with BRAF-mutant lung cancer: results from the European EURAF Cohort. *J Thorac Oncol*. 2015;10(10):1451-1457.
14. Leonetti A, Facchinetti F, Rossi G, et al. BRAF in non-small cell lung cancer (NSCLC): pickaxing another brick in the wall. *Cancer Treat Rev*. 2018;66:82-94.
15. Sheikine Y, Pavlick D, Klempner SJ, et al. BRAF in lung cancers: analysis of patient cases reveals recurrent BRAF mutations, fusions, kinase duplications, and concurrent alterations [published online April 19, 2018]. *JCO Precis Oncol*. doi:10.1200/PO.17.00172.
16. 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.
17. Cook FA, Cook SJ. Inhibition of RAF dimers: it takes two to tango. *Biochem Soc Trans*. 2021;49(1):237-251.
18. 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 (Basel)*. 2019;11(9):E1381.
19. Severson P, Kellner W, Franovic A, et al. Real-world clinical genomic analysis of patients with BRAF mutated cancers identifies BRAF class II and III as a population of unmet medical need [ESMO Targeted Anticancer Therapies Congress abstract 40P]. *Ann Oncol*. 2022;33(1)(suppl).
20. Negrao MV, Raymond VM, Lanman RB, et al. Molecular landscape of BRAF-mutant NSCLC reveals an association between clonality and driver mutations and identifies targetable non-V600 driver mutations. *J Thorac Oncol*. 2020;15(10):1611-1623.
21. Planchard D, Besse B, Groen H, et al. Updated overall survival (OS) and genomic analysis from a single-arm phase II study of dabrafenib (D) + trametinib (T) in patients (pts) with BRAF V600E mutant (Mut) metastatic non-small cell lung cancer (NSCLC) [ASCO abstract 9593]. *J Clin Oncol*. 2020;38(15)(suppl).
22. Nelson BE, Roszik J, Janku F, et al. B-Raf V600E harboring non-melanoma cancers treated with vemurafenib monotherapy and in combination with everolimus/sorafenib/crizotinib/paclitaxel+ carboplatin: a pooled analysis of five phase 1/2 studies [AACR abstract 5237]. *Cancer Res*. 2022;82(12)(suppl).
23. Abdayem P, Planchard D. Update on molecular pathology and role of liquid biopsy in nonsmall cell lung cancer. *Eur Respir Rev*. 2021;30(161):200294.
24. Cardarella S, Ogino A, Nishino M, et al. Clinical, pathologic, and biologic features associated with BRAF mutations in non-small cell lung cancer. *Clin Cancer Res*. 2013;19(16):4532-4540.
25. 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.
26. 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.
27. Tissot C, Couraud S, Tanguy R, Bringuier PP, Girard N, Souquet PJ. Clinical characteristics and outcome of patients with lung cancer harboring BRAF mutations. *Lung Cancer*. 2016;91:23-28.
28. Villaruz LC, Socinski MA, Abberbock S, et al. Clinicopathologic features and outcomes of patients with lung adenocarcinomas harboring BRAF mutations in the Lung Cancer Mutation Consortium. *Cancer*. 2015;121(3):448-456.
29. Dankner M, Rose AAN, Rajkumar S, Siegel PM, Watson IR. Classifying BRAF alterations in cancer: new rational therapeutic strategies for actionable mutations. *Oncogene*. 2018;37(24):3183-3199.
30. Mendoza DP, Dagogo-Jack I, Chen T, et al. Imaging characteristics of BRAF-mutant non-small cell lung cancer by functional class. *Lung Cancer*. 2019;129:80-84.
31. 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(9992):444-451.
32. Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmela-

noma cancers with BRAF V600 mutations. *N Engl J Med*. 2015;373(8):726-736.
33. 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(3):1-9.
34. Mazieres J, Cropet C, Montané L, et al. Vemurafenib in non-small-cell lung cancer patients with $BRAF^{V600}$ and $BRAF^{nonV600}$ mutations. *Ann Oncol*. 2020;31(2):289-294.
35. Geukes Foppen MH, Boogerd W, Blank CU, van Thienen JV, Haanen JB, Brandsma D. Clinical and radiological response of BRAF inhibition and MEK inhibition in patients with brain metastases from BRAF-mutated melanoma. *Melanoma Res*. 2018;28(2):126-133.
36. Planchard D, 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(suppl 4):iv192-iv237.
37. Cherny NI, Dafni U, Bogaerts J, et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Ann Oncol*. 2017;28(10):2340-2366.
38. Dykewicz CA; Centers for Disease Control and Prevention (U.S.); Infectious Diseases Society of America; American Society of Blood and Marrow Transplantation. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis*. 2001;33(2):139-144.
39. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: non-small cell lung cancer. v.3.2022. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Updated March 16, 2022. Accessed May 13, 2022.
40. Dudnik E, Peled N, Nechushtan H, et al; Israel Lung Cancer Group. 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.
41. 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.
42. 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.
43. Chan XY, Singh A, Osman N, Piva TJ. Role Played by signalling pathways in overcoming BRAF inhibitor resistance in melanoma. *Int J Mol Sci*. 2017;18(7):e1527.
44. 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(132):211-223.
45. Dummer R, Ascierto PA, Gogas HJ, et al. Encorafenib plus binimetinib versus vemurafenib or encorafenib in patients with BRAF-mutant melanoma (COLUMBUS): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2018;19(5):603-615.
46. Kopetz S, Grothey A, Yaeger R, et al. Encorafenib, binimetinib, and cetuximab in *BRAF* V600E-mutated colorectal cancer. *N Engl J Med*. 2019;381(17):1632-1643.
47. 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.
48. Sullivan RJ, Infante JR, Janku F, et al. First-in-class ERK1/2 inhibitor ulixertinib (BVD-523) in patients with MAPK mutant advanced solid tumors: results of a phase I dose-escalation and expansion study. *Cancer Discov*. 2018;8(2):184-195.
49. 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.
50. Bogdan M, Timson MJ, Al-Hashimi H, Zhan Y, Smith BD, Flynn DL. DCC-3116, a first-in-class selective inhibitor of ULK1/2 kinases and autophagy, synergizes with EGFR inhibitors osimertinib and afatinib in NSCLC preclinical models [AACR-NCI-EORTC Virtual International Conference on Molecular Targets and Cancer Therapeutics abstract P084]. *Mol Cancer Ther*. 2021;20(12)(suppl).
51. Ribas A, Butler M, Lutzky J, et al. Phase I study combining anti-PD-L1 (MEDI4736) with BRAF (dabrafenib) and/or MEK (trametinib) inhibitors in advanced melanoma [ASCO abstract 3033]. *J Clin Oncol*. 2015;33(15)(suppl).
52. Long GV, Lebbe C, Atkinson V, et al. The anti–PD-1 antibody spartalizumab (S) in combination with dabrafenib (D) and trametinib (T) in previously untreated patients (pts) with advanced BRAF V600–mutant melanoma: updated efficacy and safety from parts 1 and 2 of COMBI-I [ASCO abstract 9531]. *J Clin Oncol*. 2019;37(15)(suppl).
53. Ascierto PA, Ferrucci PF, Fisher R, et al. Dabrafenib, trametinib and pembrolizumab or placebo in BRAF-mutant melanoma. *Nat Med*. 2019;25(6):941-946.
54. Gutzmer R, Stroyakovskiy D, Gogas H, et al. Atezolizumab, vemurafenib, and cobimetinib as first-line treatment for unresectable advanced $BRAF^{V600}$ mutation-positive melanoma (IMspire150): primary analysis of the randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020;395(10240):1835-1844.
55. Huynh S, Mortier L, Dutriaux C, et al. Combined therapy with anti-PD1 and BRAF and/or MEK inhibitor for advanced melanoma: a multicenter cohort study. *Cancers (Basel)*. 2020;12(6):1666.
56. Puzanov I. Combining targeted and immunotherapy: BRAF inhibitor dabrafenib (D) ± the MEK inhibitor trametinib (T) in combination with ipilimumab (Ipi) for V600E/K mutation-positive unresectable or metastatic melanoma (MM). *J Transl Med*. 2015;13(1):K8.
57. Ribas A, Hodi FS, Callahan M, Konto C, Wolchok J. Hepatotoxicity with combination of vemurafenib and ipilimumab. *N Engl J Med*. 2013;368(14):1365-1366.
58. Ortiz-Cuaran S, Mezquita L, Swalduz A, et al. MA21.07 Circulating tumor DNA analysis depicts potential mechanisms of resistance to BRAF-targeted therapies in BRAF+ non-small cell lung cancer. *J Thorac Oncol*. 2019;14(10):S337.
59. 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.
60. Subbiah V, Gutierrez M, Anders CK, et al. Trial in progress: phase 1a/b study of PF-07284890 (brain-penetrant BRAF inhibitor) with/without binimetinib in patients with BRAF V600-mutant solid tumors [ASCO abstract TPS3152]. *J Clin Oncol*. 2021;39(15)(suppl).
61. Monaco KA, Delach S, Yuan J, et al. LXH254, a potent and selective ARAF-sparing inhibitor of BRAF and CRAF for the treatment of MAPK-driven tumors. *Clin Cancer Res*. 2021;27(7):2061-2073.

## Supporting Online Material

**eTable.** Ongoing Early Studies in *BRAF*-Mutant NSCLC

| Name (Identifier) | *BRAF* Mutation | Design | Drug(s) | Setting | Comment | Status |
|---|---|---|---|---|---|---|
| ENCO-BRAF (NCT04526782) | *BRAF* V600E | Phase 2, multicenter, open-label, multicohort | Encorafenib and binimetinib | Pretreated and tx-naive *BRAF* V600E-MT NSCLC | Encorafenib: BRAF inhibitor; binimetinib: MEK inhibitor | Recruiting |
| OCEAN II (NCT05195632) | *BRAF* V600E | Phase 2, multicenter, single-arm | Encorafenib and binimetinib | First- or second-line setting; BRAF and MEK inhibitor–naive | – | Not yet recruiting |
| LAND-SCAPE 1011 (NCT04585815) | *BRAF* V600E | Phase 1b/2, open-label umbrella | Substudy A: sanlimab with encorafenib and binimetinib | Advanced NSCLC with *BRAF* V600E mutation; any line (phase 1b); previously untreated (phase 2) | Sasanlimab: subcutaneous monoclonal antibody that targets and inhibits programmed death ligand 1 | Recruiting |
| (NCT03915951) | Mainly *BRAF* V600E; other *BRAF* V600 mutations will be considered | Phase 2, open-label | Encorafenib and binimetinib | First- or second-line setting | – | Recruiting |
| (NCT05065398) | *BRAF* V600 | Phase 2, multicenter, open-label | HLX208 | Pretreated BRAF V600-MT NSCLC; *BRAF* and MEK inhibitor–naive | HLX208: small-molecule BRAF inhibitor | Recruiting |
| ENHANCE (NCT05275374) | *BRAF* V600 | Phase 1/2a | XP-102; XP-102 and trametinib | Pretreated *BRAF* V600-MT cancers (melanoma, colorectal, NSCLC, thyroid); previous BRAF + MEK inhibitors permitted | XP-102: highly potent and selective RAF inhibitor that binds to the DFG-out (inactive) conformation of the BRAF kinase (100× higher potency than vemurafenib, does not affect wild-type cells) | Recruitment starts in 2022 |
| NAUTIKA1 (NCT04302025) | *BRAF* V600 | Phase 2, multicenter, multicohort | *BRAF* cohort: vemurafenib and cobimetinib | NSCLC stages IB-III, neoadjuvant treatment for 8 wk, then if pathological response or lack of progression, 4 cycles of chemotherapy followed by up to 2 y of vemurafenib and cobimetinib | – | Recruiting |
| B-FAST (NCT03178552) | *BRAF* V600 | Phase 2-3, multicenter, global, open-label, multicohort | Cohort E: atezolizumab, cobimetinib, and vemurafenib | First-line setting, *BRAF* V600 mutation detected in blood | – | Recruiting |

**eTable.** (*Continued*) Ongoing Early Studies in *BRAF*-Mutant NSCLC

| Name (Identifier) | *BRAF* Mutation | Design | Drug(s) | Setting | Comment | Status |
|---|---|---|---|---|---|---|
| (NCT04543188) | *BRAF* V600 | Phase 1a/b, multicenter, open-label | PF 07284890 (ARRY 461); PF 07284890 (ARRY 461) and binimetinib | *BRAF* V600-MT solid tumors, including NSCLC, +/- brain involvement; prior BRAF inhibitor allowed (part B cohort 3) | PF 07284890 (ARRY 461): potent, selective, highly brain-penetrant, small-molecule inhibitor of *BRAF* V600 mutations[60] | Recruiting |
| (NCT04190628) | *BRAF* V600 | Phase 1, first-in-human, open-label | ABM-1310 (part A); ABM-1310 and cobimetinib | *BRAF* V600-MT solid tumors; progressive disease or intolerance following BRAF and MEK inhibitors | ABM-1310: highly selective brain-penetrant BRAF inhibitor | Recruiting |
| (NCT02428712) | *BRAF* non-V600 | Phase 2a, extension cohort 2 | PLX8394 | Extension cohort 2: *BRAF* non–V600-MT solid tumors; prior BRAF inhibitor tx allowed | PLX8394: paradox breaker | Recruiting |
| (NCT02974725) | Class I-III | Phase 1b, multicenter, open-label | LXH254 and LTT462; LXH254 and trametinib; LXH254 and ribociclib | Pretreated *KRAS* or *BRAF*-MT NSCLC or *NRAS*-MT melanoma; prior tx with BRAF/MEK inhibitors allowed for *BRAF* V600-MT NSCLC | LXH254: type II novel RAF inhibitor of dimerized BRAF and CRAF as well as monomeric BRAF while largely sparing ARAF[61]; LTT462: small-molecule inhibitor of ERK1/2 | Active, not recruiting |
| (NCT04913285) | Class I-III In part B dose expansion, patients with *BRAF* class I mutations are excluded | Phase 1/1b, multicenter, open-label | KIN-2787; KIN-2787 and binimetinib | *BRAF/NRAS*-MT advanced or metastatic solid tumors | KIN-2787: next-generation pan-RAF small-molecule kinase inhibitor | Recruiting |
| (NCT04800822) | Class III | Phase 1, multicenter, open-label | Part 1: PF-07284892 (ARRY-558); part 3, cohort 7: PF-07284892 and binimetinib | Part 1: *BRAF* class III-MT solid tumors; part 3, cohort 7: *BRAF* class III-MT solid tumors previously treated with SOC | PF-072284892: small-molecule inhibitor of SHP2 that may block MAPK signaling | Recruiting |
| TAPISTRY (NCT04589845) | Cohort I: class II; cohort J: class III | Phase 2, global, multicenter, open-label, multicohort | Cohort I: belvarafenib; cohort J: belvarafenib | Cohort I: pretreated BRAF class II mutant/fusion-positive tumors; cohort J: pretreated BRAF class III mutant tumors | Belvarafenib: potent, selective RAF dimer (type II) inhibitor | Recruiting |

**eTable.** (*Continued*) Ongoing Early Studies in *BRAF*-Mutant NSCLC

| Name (Identifier) | *BRAF* Mutation | Design | Drug(s) | Setting | Comment | Status |
|---|---|---|---|---|---|---|
| (NCT03284502) | Cohort 1, basket: not specified (class I); cohort 2: class II-III | Phase 1b, multicenter, open-label | Expansion cohorts 1 and 2: belvarafenib and cobimetinib | Pretreated locally advanced or metastatic solid tumors with *RAS*-MT or *RAF*-MT; no prior RAF, MEK, or ERK inhibitor for class II-III mutations | – | Recruiting |
| (NCT04985604) | Not specified | Phase 1b/2, multicenter, open-label, umbrella | DAY101; DAY101 and pimasertib | Pretreated solid tumors with MAPK pathway alteration; prior dabrafenib and trametinib or vemurafenib allowed for *BRAF* V600-MT NSCLC | DAY101: highly selective type 2 pan-RAF kinase inhibitor; pimasertib: selective MEK1/2 inhibitor | Recruiting |
| (NCT04892017) | Not specified | Phase 1, multicenter, open-label, first-in-human | DCC-3116; DCC-3116 and trametinib | Cohort 2 NSCLC with *KRAS*, *NRAS*, or *BRAF* mutation; *BRAF* V600E/K, must have received prior SOC | DCC-3116: first-in-class selective inhibitor of ULK1/2 kinases and autophagy[50] | Recruiting |
| RAMP202 (NCT04620330) | Not specified | Phase 1b/2, multicenter, nonrandomized, open-label | VS-6766; VS-6766 and defactinib | Pretreated *KRAS*-MT or *BRAF*-MT NSCLC; prior BRAF/MEK inhibitors allowed | VS-6766: dual RAF/MEK inhibitor, vertical inhibition of MAPK pathway with a single drug; defactinib: FAK inhibitor | Recruiting |

ERK, extracellular signal-regulated kinase; MAPK; mitogen activated protein kinase; MT, mutated; NSCLC, non–small cell lung cancer; SOC, standard of care; tx, treatment; y, years.