Review Article

A narrative review of the management of BRAF non-V600E mutated metastatic non-small cell lung cancer

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background and Objective: V-raf murine sarcoma viral oncogene homolog B1 (BRAF) mutations occur in approximately 2–4% of patients with non-small cell lung cancer (NSCLC). BRAF non-V600E mutant NSCLC is a rare entity that has yet to be fully characterized. The treatment paradigm is evolving and is currently often extrapolated from data pertaining to V600E mutations. This article serves as a comprehensive review of the clinical characteristics, prognosis, current management and treatment algorthim for patients with NSCLC that harbors BRAF other than the common V600E mutation (non-V600E).

Methods: We performed a review of publications on EMBASE and MEDLINE/PubMed that described the prevalence and characteristic features of this patient subset of NSCLC, with a focus on the current treatment landscape, through October 2021. Non-English publications were excluded. We searched ClinicalTrials.gov for active and past trials pertaining to this patient subset.

Key Content and Findings: BRAF non-V600E mutant NSCLC occurs in females and smokers and is typically mutually exclusive with other driver mutations. Therapeutic choices are guided by extrapolating data from other malignancies and from BRAF-V600E mutant NSCLC. In the absence of any other driver mutations, NSCLC patients with BRAF non-V600E mutations should be treated with front line checkpoint immunotherapy with or without platinum-based chemotherapy. Early enrollment in clinical trials is recommended given the rare nature of this mutation without clear guidelines to steer clinical decisions. For patients who are unable to receive standard chemotherapy, or immunotherapy agents and are not able to participate in clinical trials, tyrosine kinase inhibitors of BRAF and MEK can be employed in some cases depending on the specific mutation and its position in the BRAF gene.

Conclusions: Given the rare nature of BRAF non-V600E mutant NSCLC, without clear guidelines, we offer this review with a proposed treatment algorithm to guide practicing clinicians in formulating evidence-based decisions.

Keywords: Non-small cell lung cancer (NSCLC); BRAF non-V600E mutations; targeted therapy; lung cancer

Received: 15 November 2021; Accepted: 12 April 2022; Published: 30 June 2022.

doi: 10.21037/pcm-21-49

View this article at: https://dx.doi.org/10.21037/pcm-21-49

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Introduction

Lung cancer remains the leading cause of cancer-related deaths worldwide. In the United States, it accounts for a quarter of all deaths (1). The development of targeted therapy following the identification of the heterogenous molecular landscape of non-small cell lung cancer (NSCLC) has revolutionized the treatment paradigm over the past decade with the advent of precision medicine (2). For patients with metastatic NSCLC of the adenocarcinoma (ADC) subtype, molecular testing is performed to screen for actionable driver mutations, such as epidermal growth factor receptor (*EGFR*) and anaplastic lymphoma kinase (*ALK*) mutations, and Kirsten rat sarcoma viral oncogene (*KRAS*) and receptor tyrosine kinase (*ROS1*) translocations. Effective Food and Drug Administration (FDA) approved targeted therapies have dramatically prolonged the life expectancy of patients carrying those alterations. We present the following article in accordance with the Narrative Review reporting checklist (available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-49/rc).

Methods

We searched EMBASE and MEDLINE/PubMed for English-language literature through October 2021 using the terms "non-small cell lung cancer", "lung adenocarcinoma", "BRAF-mutated", "BRAF-V600E mutation", "Non BRAF-V600E mutation", "NSCLC". All searches were conducted between August and October 2021.

This search was independently conducted by the first author I.A. Non-English publications were excluded.

We searched ClinicalTrials.gov for a list of active trials involving patients with BRAF mutations. This search was independently conducted by the second author C.L. Further systematic procedures are outlined in *Table 1*.

BRAF mutations in NSCLC

The V-raf murine sarcoma viral oncogene homolog B1 (BRAF) proto-oncogene belongs to the group of serine-threonine kinases which carries an essential role in the mitogen-activated protein kinase (MAPK) pathway (3). The oncogenic BRAF mutations, located on chromosome 7, have been detected in various cancers including melanoma, colorectal, lung and papillary thyroid cancers. These mutations have long been known to portend poorer prognosis in various tumor types. In a systematic review by (4), BRAF mutations increased the risk of mortality by 2.25 times for patients with colorectal cancer HR =2.25 (95% CI: 1.82–2.83), and by 1.7 times for patients with melanoma (95% CI: 1.37–2.12). Due to its lower frequency in patients with NSCLC, the clinical characteristics and prognostic implications are less defined with conflicting results in the literature.

BRAF mutations occur in approximately 2–4% of patients with NSCLC (5,6). There is a variability in the reported incidence according to the detection methodology employed. Immunohistochemistry (IHC) can screen for BRAF V600E mutations but is limited by the heterogeneity in tumor cells and limited amount of available tissue. Sanger sequencing is the gold standard in precision oncology, but is limited by its ability to only identify alterations with a frequency of 15–20%. Next generation sequencing (NGS) techniques on tissue yield a high sensitivity and acceptable specificity as compared to PCR-based Sanger sequencing. NGS on plasma cell-free DNA is an emerging tool due to rapidity and cost-effectiveness (7). A retrospective series by Marchetti *et al.* (8), evaluated the presence of BRAF mutations in 1,046 NSCLC patients, 739 of which were ADCs and 307 were squamous cell carcinomas (SCCs) and noted the presence of these genomic alterations in 3.5% of the tumors and in 4.9% of lung ADCs.

BRAF mutations are typically exclusive from other driver mutations. They are typically classified into three classes: class 1 mutations signal as *RAS*-independent active monomers (e.g., V600E); class 2 mutations are constitutively active *RAS*-independent dimers; and class 3 mutations have low/absent kinase activity (9). The most common BRAF mutation involves a glutamate substitution for valine at codon 600 (V600E) accounting for approximately 55% of BRAF mutations. The incidence of V600E mutations in ADCs in the study by Marchetti *et al.* was 2.8% (8). They found this to be more prevalent in females (about 9% in females with ADCs), but independent of smoking history. Tumors with this mutation were more aggressive and associated with poorer prognosis.

Forty-five percent of BRAF mutations in NSCLC are non-V600E, one of the many reported such as G469A (35%) or D594G (10%) (10). In contrast to V600E, non-V600E mutations are primarily found in smokers, earlier stages and do not seem to carry a prognostic implication.

While the pathogenic role of BRAF V600E and its targetable nature have been clearly established in many cancers including NSCLC, the rarer non-V600E mutations are still being evaluated for their role in cancer and novel

Table 1 Systematic search strategy

Items	Specification
Date of search (specified to date, month and year)	October 1st, 2021/January 22, 2022
Databases and other sources searched	PubMed/Medline, EMBASE, ClinicalTrials.gov
Search terms used (including MeSH and free text search terms and filters)	"non-small cell lung cancer", "lung adenocarcinoma", "BRAF-mutated", "BRAF-V600E mutation", "Non BRAF-V600E mutation", "NSCLC"
Timeframe	January 1, 2000 to January 22, 2022
Inclusion and exclusion criteria (study type, language restrictions etc.)	Excluded non-English publications
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	IA independently reviewed and selected studies from PubMed/Medline and EMBASE; CSL independently reviewed and selected trials from ClinicalTrials.gov

therapeutics are being tested for tumors harboring these mutations in pre-clinical and clinical trial settings. One estimate suggests that lung cancers with a non-V600 BRAF mutation account for approximately 40,000 annual deaths worldwide (11).

Targeting BRAF mutations

The *BRAF* gene encodes a serine/threonine-protein kinase, which is a key regulator of cell growth and proliferation. The enzymatic kinase domain or the p-loop is located within amino acid residues 457 through 717 of the B-Raf protein. Residues 596–600 is a section within the kinase domain which interacts with the phosphate-binding loop keeping the kinase in a locked position. Upon phosphorylation of this activating loop, mitogen-activated 2 kinase 1 and 2 (MAP2K 1/2) signaling pathway gets triggered which in turn activates other proteins and ultimately results in cell proliferation. L597 and V600 residues specifically interact with other amino acids within the kinase domain to keep it inactive until it gets phosphorylated.

In the study by Tissot *et al.*, the median overall survival (OS) of patients with *BRAF* V600E mutant NSCLC was longer than that of patients with NSCLC harboring a *BRAF* non-V600E mutation (25 *vs.* 13 months, respectively, P=0.153) (12). The OS of stage IV V600E-mutated-patients was also longer than the non-V600E, but this was not statistically significant (16 *vs.* 7 months, P=0.272). Of note, in this study population concurrent KRAS mutations were found among five out of 38 patients carrying *BRAF* non-V600E mutations. This contrasts with *BRAF*-V600E mutations that were mutually exclusive of all other driver mutations. This has been hypothesized to lead to resistance to targeted therapies such as dabrafenib, since *BRAF* inhibition in this case can lead to a feedback loop that activates RAS (13,14).

For metastatic NSCLC with *BRAF* V600E mutations, targeted therapy is preferred as the first-line systemic option, as a combination of dabrafenib (RAF-inhibitor) and trametinib (MEK-inhibitor). An FDA approval and designation of those drugs as Orphan Drugs for the treatment of this specific subset of patients was granted in October 2015 based on the phase II study NCT01336634, for previously treated patients (3), and for treatment naïve patients (4). Subsequently the FDA in 2017 granted regular approval for Dabrafenib and Trametinib combination for metastatic NSCLC with BRAF V600E mutation (15,16). For those patients with PD-L1 >50%: immunotherapy vs targeted therapy vs immunotherapy and chemotherapy combination are all FDA-approved options. Expert opinion still favors that the initial treatment of *BRAF* V600E mutant NSCLC with high PDL1 expression is targeted therapy given durable efficacy and good response rates of immunotherapy in the second line (17).

There is less data to guide the management of *BRAF* non-V600E, however. Management decisions are often guided by extrapolating from studies that focused on other malignancies or studies that predominantly included V600E mutations with few non-V600E patients.

Targeted therapy

Theoretically, many non-V600 *BRAF* mutations are kinase-impaired and thus considered unattractive for RAF-targeted

therapy. A study by Gautschi *et al.* examined 35 NSCLC *BRAF* mutant patients. Only six were non-V600E (G466V, G469A, G469L, G596V, V600K, and K601E) (18). One patient had a co-occurring driver mutation, which was KRAS V12 together with BRAF V600K. Another patient had concomitant HER2 amplification with *BRAF* V600E. No co-occurring alterations of *EGFR*, *ALK*, *MET*, *RET*, or *ROS1* were reported. From the non-V600E group: only the patient with G596V had partial response with vemurafenib monotherapy.

However, a study by Noeparast *et al.*, investigated a patient cohort of NSCLC and demonstrated that non-V600 *BRAF* mutations, resulting in either high or impaired kinase activity, confer sensitivity to combined dabrafenib and trametinib treatment (19).

In trying to understand the specific molecular pathways that compromise non-V600E mutations, consideration can be given to other TKIs not specifically targeting BRAF as an area for future research. For example, sorafenib, an agent with multiple targets that blocks the activation of C-RAF, B-RAF, c-KIT, FLT-3, RET, VEGFR-2, VEGFR-3 and platelet-derived growth factor receptor demonstrated a benefit in one patient A case report of a 56-year-old woman with NSCLC and the *BRAF* G469R mutation was reported by Sereno *et al.* (20). This patient was heavily pretreated with seven lines of therapy and demonstrated a rapid (within 10 days) and durable six months response to sorafenib. A somatic mutation, *ARAF* S214C, was expressed at high levels and was felt to be an indicator of a sorafenib response.

There is also translational data demonstrating a supportive mechanism of action for dasatinib in kinase-inactivating non-V600E BRAF mutations (21).

The role of checkpoint inhibitors

Dudnik *et al.* investigated the association between *BRAF* mutations and PD-L1 expression in 39 patients with NSCLC (22). In their population, a high rate of PD-L1 expression was noted in 42–50% without a statistically significant difference between *BRAF* V600E and non-V600E mutant patients. While utilization of immune checkpoint inhibitors (ICIs) is often controversial in patients with driver-mutations, ICI therapy in their study group was associated with an objective response rate (ORR) of 25% to 33% and a median progression free survival (PFS) of 3.7 to 4.1 months, which was comparable to results observed in NSCLC patients receiving ICI in the second line setting. It was noted that neither the BRAF mutation subtype nor the PD-L1 expression level affected OS. While the study had design limitation such as only 74% of patients underwent PD-L1 testing, 30% only were assessed for MSI status and TMB and only 56% were treated with ICIs, the authors concluded that *BRAF* mutant NSCLC is associated with a high level of PD-L1 expression, low/intermediate TMB and MS-stable status with ICIs carrying a favorable activating against both *BRAF* V600E and *BRAF* non-V600E mutant NSCLC.

In another study by Guisier *et al.*, anti-PD-1 efficacy was assessed in 107 patients, of which 18 patients harbored a BRAF non-V600E mutation (23). This was utilized in the second line setting onwards for 94% of this patient cohort. Response rate was 35% and the duration of response was not reached. While limited by the small numbers of this retrospective study, it was noted that the patients with BRAF non-V600E are prone to respond slightly better to immune checkpoint inhibitors (ICIs) than the patients with BRAF V600E (35% response rate *vs.* 26% respectively) (23).

Further studies are warranted to further confirm these findings. It is hypothesized that the efficacy of ICI in BRAF-mutated NSCLC is likely due to smoking status which is associated with a higher PD-L1 expression and possibly higher mutational burdens.

The role of chemotherapy

Prior to the advent of targeted therapy, traditional platinum-based combination chemotherapy was employed for management of *BRAF*-mutated NSCLC. In the study by Cardarella *et al.* published in 2013, the median PFS of patients with BRAF-mutant advanced NSCLC treated with platinum-based combination chemotherapy was 5.2 months compared with 6.7 months for wild-type patients (P=0.622) (24). Within the *BRAF* cohort, the median PFS was shorter in patients with V600E mutations compared with non-V600E mutations but did not reach statistical significance (4.1 *vs.* 8.9 months; P=0.297).

In this era of personalized lung cancer therapies, chemotherapy is often reserved for the salvage setting following disease progression on targeted and immune therapies.

Future directions

A current area of research is identification of mechanisms of resistance to targeted therapies that eventually arise (2). For V600E-mutant NSCLC, two mechanisms have emerged: (I) loss of full-length *BRAF* V600E in concert with expression

of a truncated form of the mutant protein or (II) enhanced *EGFR* signaling through autocrine activation induced through BRAF-independent c-Jun signaling. Second generation *BRAF* inhibitors such as PLX8394 or using a combination of *BRAF* and *MEK* inhibition have been shown to prevent resistance medication through expression of a *BRAF* V600E splice variant (11).

Mechanisms of resistance for *BRAF* non-V600E mutations are yet to be elucidated and further research is warranted to determine appropriate strategies to overcome development of resistance and to guide appropriate sequencing of therapy. *Table 2* summarizes ongoing trials in

Table 2 Ongoing and future clinical trials for BRAF non-V600 mutated tumors

Protocol name	Phase	Patient population	Treatment regimen	Target sample size (n)	Primary outcomes	Secondary outcomes
NCT02428712 (25)	I/IIA	Advanced solid tumors who are refractory to, relapsed after, or intolerant to standard therapy or for whom no standard therapy exists; cohort 2: BRAF non-V600 mutations	PLX8394	100	PK, safety	DOR, PFS, ORR
NCT03091257 (26)	I	MM patients who relapsed on ≥2 lines of therapy with a BRAF mutation, including non-V600 mutations	Dabrafenib + trametinib	60	ORR	Safety
NCT03843775 (27)	I/II	Metastatic or advanced solid tumor whom no standard therapy is considered to be appropriate confirmed histologically for a BRAF non-V600 mutation	Binimetinib + encorafenib	38	Safety, ORR	
NCT04488003 (28)	II	Locally advanced or metastatic malignancy that has progressed following systemic therapy for which the patient is not a candidate for further treatment; group 3 and 4: BRAF non-V600 mutations	Ulixertinib	528	ORR, PFS	DOR, OS, PK
NCT04249843 (29)	I	Advanced or metastatic solid tumor who have experienced disease progression on ≥1 prior systemic therapy; group 1: BRAF non-V600 mutations	BGB-3245	69	Safety, ORR	DOR, PFS, PK
NCT04439279 (MATCH Treatment Subprotocol R) (30)	II	Advanced refractory solid tumors, lymphomas, or MM with BRAF non-V600 mutations	Trametinib	35	ORR	PFS
NCT04566393 (31)	EA	Solid tumor with a MAPK pathway-alteration, including but not limited to KRAS, NRAS, HRAS, BRAF, MEK, and ERK mutations	Ulixertinib (BVD-523)	N/A	N/A	N/A
NCT03049618 (32)	IIA	Locally advanced or metastatic NSCLC or squamous cell carcinoma of the head and neck that has progressed ≥1 line of platinum-based chemotherapy	Recombinant EphB4-HSA fusion protein + pembrolizumab	42	ORR	DOR, Safety, OS, PFS
NCT03989115 (33)	IB/II	Relapsed or refractory solid tumors OR EGFR+ locally advanced or metastatic NSCLC	RMC-4630 + cobimetinib OR RMC-4630 + osimertinib	168	Safety	PK, ORR, DOR

Table 2 (*continued*)

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Protocol name	Phase	Patient population	Treatment regimen	Target sample size (n)	Primary outcomes	Secondary outcomes
NCT04913285 (34)	I/IB	Metastatic or advanced solid tumor with BRAF OR melanoma NRAS mutation	KIN-2787 ± binimetinib	155	Safety, PK, ORR, DOR	Additional PK
NCT03284502 (35)	IB	Locally advanced or metastatic solid tumors with RAS or RAF mutation	HM95573 + cobimetinib or cetuximab	140	Safety	PK
NCT02974725 (36)	IB	Advanced or metastatic KRAS or BRAF mutated NSCLC or NRAS mutated melanoma	LXH254 + LTT462 or trametinib or ribociclib	331	Safety	ORR, DOR, DCR, PFS, OS, PK
NCT02857270 (37)	I	Advanced or metastatic cancer with an activating MAPK pathway alteration: BRAF mutated metastatic melanoma refractory to or relapsed after treatment with RAF and/or MEK inhibitors OR metastatic melanoma with a NRAS mutation OR BRAF mutated NSCLC	LY3214996	245	Safety	PK, ORR, DOR, PFS, DCR, OS
NCT04892017 (38)	I	Advanced or metastatic solid tumors with RAS or RAF mutations	DCC-3116 ± trametinib	130	Safety, ORR	DPR, PFS, PK
NCT03721120 (LIBELULE) (39)	III	Treatment naïve locally advanced or metastatic NSCLC	Liquid biopsy mutational analysis	286	TTI	Rate of treatment, PFS, QOL

DCR, disease control rate; DOR, duration of response; EA, expanded access; MM, multiple myeloma; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PK, pharmacodynamics; PFS, progression-free survival; QOL, quality of life; TTI, time-to-appropriate treatment initiation.

this population (25-30).

Most clinical trials are focused on *BRAF* V600E mutant NSCLC. Several phase I clinical trials, however, are open to include all forms of *BRAF* mutations in NSCLC and are investigating new targeted therapies.

Conclusions

BRAF non-V600E mutant NSCLC is a rare entity that has yet to be fully characterized. It often occurs in females and smokers and is typically mutually exclusive with other driver mutations.

In the absence of any other driver mutations, NSCLC patients with BRAF non-V600E mutations should be treated with front line checkpoint immunotherapy with or without platinum-based chemotherapy. Early enrollment in clinical trials is recommended given the rare nature of this mutation without clear guidelines to steer clinical decisions. For patients who are unable to receive standard chemotherapy, or immunotherapy agents and are not able to participate in clinical trials, tyrosine kinase inhibitors of BRAF and MEK can be employed in some cases depending on the specific mutation and its position in the BRAF gene.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-49/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://pcm.amegroups.com/article/view/10.21037/pcm-21-49/coif). NS serves as an unpaid editorial board member of *Precision Cancer Medicine* from September 2020 to August 2022. NS reports consulting fee from Boehringer Ingram.

She has been on scientific advisory board for AstraZeneca, Amgen, Takeda, Genentech, Regeneron, and Pfizer within the last 36 months. None of these have any impact on the manuscript. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/pcm-21-49
Cite this article as: Abuali I, Lee CS, Seetharamu N. A narrative review of the management of BRAF non-V600E mutated metastatic non-small cell lung cancer. Precis Cancer Med 2022;5:13.