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Dabrafenib in combination with trametinib in the treatment of patients with BRAF V600-positive advanced or metastatic non-small cell lung cancer: clinical evidence and experience

Arjun Khunger, Monica Khunger and Vamsidhar Velcheti

Abstract: Mutations in the BRAF oncogene are found in 2–4% of all non-small cell lung cancer (NSCLC) patients. The most common activating mutation present within the BRAF oncogene is associated with valine substitution for glutamate at position 600 (V600E) within the BRAF kinase. BRAF-targeted therapies are effective in patients with melanoma and NSCLC harboring BRAF V600E mutation. In both melanoma and NSCLC, dual inhibition of both BRAF and the downstream mitogen-activated protein kinase (MEK) improves response rates compared with BRAF inhibition alone. BRAF-MEK combination therapy (dabrafenib plus trametinib) demonstrated tolerability and efficacy in a recent phase II clinical trial and was approved by the European Medicines Agency and United States Food and Drug Administration for patients with stage IV NSCLC harboring BRAF V600E mutation. Here, in this review, we outline the preclinical and clinical data for BRAF and MEK inhibitor combination treatment for NSCLC patients with BRAF V600E mutation.

Keywords: BRAF V600E, dabrafenib, non-small cell lung cancer (NSCLC), trametinib

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Introduction

Over the past decade, there has been a significant increase in the understanding of the genetic and molecular mechanisms underlying lung cancer, causing a paradigm shift in the diagnosis and management of non-small cell lung cancer (NSCLC). All patients with advanced NSCLC undergo routine genomic testing for clinically actionable genomic alterations.[1] The success of genotype-directed therapies particularly for epidermal growth factor receptor (EGFR) mutated and anaplastic lymphoma kinase (ALK) rearranged NSCLC patients has made the identification of these clinically actionable alterations imperative.[2,3] Several such potentially actionable genomic alterations like BRAF, MET exon 14 skipping mutations, HER2, RET and NTRK gene rearrangements are now identified through more frequent clinical use of comprehensive genomic sequencing. In patients with NSCLC, BRAF mutations occur in approximately 2–4% of patients with lung adenocarcinoma.[4–7] More than 50% of mutations in the BRAF oncogene are associated with substitution of glutamate-to-valine amino acid at codon 600 position (V600E, i.e. Val600Glu) within exon 15 of the kinase domain that leads to a 500-fold increase in the kinase activity of BRAF as compared with its wild type.[8] Recently the European Medicines Agency and United States Food and Drug Administration (US FDA) approved the use of B-Raf proto-oncogene, serine/threonine kinase (BRAF) inhibitor, dabrafenib in combination with a mitogen-activated protein kinase (MEK) inhibitor, trametinib in patients with NSCLC harboring a BRAF V600E mutation.

Correspondence to:
Vamsidhar Velcheti
Department of Hematology and Oncology, Taussig Cancer Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195, USA
velchev@ccf.org

Arjun Khunger
Department of Hematology and Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA

Monica Khunger
Department of Internal medicine, Cleveland Clinic, Cleveland, OH, USA

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BRAF V600E mutation occurs in equal frequency in both men and women, however, is more common in older patients (age > 60 years), adenocarcinoma and current and former smokers.[9–13] This contrasts with EGFR mutation and ALK rearrangement, which tend to be more prevalent in younger patients and lifetime nonsmokers.[14–16] However, a few studies indicate no significant influence of smoking habits or sex on BRAF mutation.[17,18] In addition, clinical outcomes associated with BRAF V600E and non-V600E mutations are not clearly understood. Due to paucity of clinical studies in BRAF-mutant NSCLC, clinical characteristics of patients harboring BRAF mutations are not well defined and should not be used as a guide for selection of patients to undergo mutational screening.

Biology of BRAF-mutant NSCLC

The mitogen-activated protein kinase (MAPK) pathway (also commonly referred to as the Ras-Raf-MEK-ERK pathway) is a group of signal transducer kinases involved in promoting cell growth, proliferation and inhibition of apoptosis. In normal conditions, growth factor ligands bind to the cell surface tyrosine kinase receptors, leading to its dimerization and autophosphorylation. This leads to subsequent phosphorylation of downstream adaptor proteins that ultimately causes activation of Ras GTPase. Activation of Ras protein induces downstream activation of the RAF oncogene. BRAF is a member of RAF family of serine/threonine protein kinase with two other isoforms, ARAF and CRAF. Activation of BRAF activates a second protein kinase called MEK (dual specificity MAPK 1; MAP2K1). MEK causes phosphorylation and activation of extracellular signal-regulated kinase (ERK), which get translocated into nucleus, bind and phosphorylate transcription factors, thereby leading to gene expression[19,20] (Figure 1). In BRAF-mutant NSCLC, the Ras-Raf-MEK-ERK pathway is rendered constitutively active by V600E mutation in the BRAF oncogene, leading to uncontrolled signaling and tumor growth.[8]

BRAF and MEK inhibitors in melanoma

BRAF mutations are found in approximately 50% patients with melanoma, with BRAF V600 mutation being the most common.[21,22] Thus, the early preclinical and clinical evidence of BRAF and MEK inhibition was first developed in the context of BRAF-mutant melanoma. In BRAF V600E melanoma cell lines and patient-derived xenograft models' inhibition of both BRAF and MEK with small molecule tyrosine kinase inhibitors reduce ERK signaling, resulting in cell cycle arrest and decreased cell proliferation.[23,24]

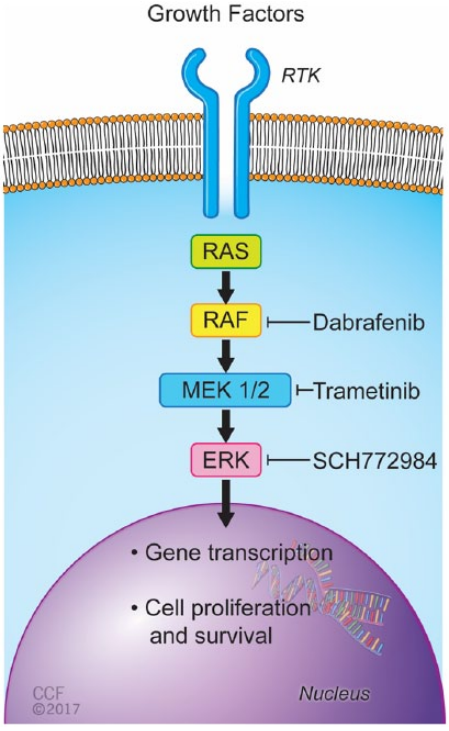

Figure 1. Mechanism of action of dabrafenib and trametinib: binding of BRAF and MEK inhibitors generates a blockade point in MAPK pathway at two different levels, inhibiting oncogenic downstream signaling and causing cell cycle arrest.
MAPK: mitogen-activated protein kinase.

Vemurafenib was the first BRAF inhibitor to be approved by the US FDA in 2011 for metastatic BRAF V600E-mutant melanoma. It was based on the results of a phase III study which showed superior progression-free survival (PFS) of 5.3 months and overall survival (OS) of 13.6 months with vemurafenib as compared with 1.6 months PFS and 9.7 months OS with dacarbazine in patients with BRAF V600E-mutated metastatic melanoma.[25] In 2013, a second BRAF inhibitor, dabrafenib was approved by the US FDA after the results of a phase III trial with dabrafenib, in BRAF V600E-mutated melanoma patients.[26] Dabrafenib had longer PFS of 5.1 months as compared with 2.7 months with dacarbazine, further establishing the superiority of BRAF inhibitors as

compared with chemotherapy. Both vemurafenib and dabrafenib were well tolerated with only mild toxicities in both these clinical trials. However, longer follow up suggested that patients treated with BRAF inhibitors developed disease progression within 6 months of initiation of treatment due to development of resistance.[26,27] Also, a considerable number of patients developed secondary skin cancers, including squamous cell carcinoma and keratoacanthoma, mainly due to paradoxical activation of the MAPK pathway in BRAF nonmutant cells.[28]

Trametinib is a MEK1/2 inhibitor which blocks MEK1/2 kinase activity and prevents RAF-dependent MEK phosphorylation.[29] It was approved initially as a monotherapy in treatment of advanced BRAF V600-mutant melanoma in 2013 based on the results of the phase III METRIC study.[30] In this study, 322 patients with BRAF V600E or V600K-mutated advanced or metastatic melanoma who had no more than one prior chemotherapy regimen and no prior BRAF or MEK inhibitor drugs, were randomized to trametinib 2 mg once daily or chemotherapy with dacarbazine or paclitaxel. Trametinib was associated with statistically significant improvement in response rate (22% *versus* 8%) and median PFS of 4.8 months as compared with 1.5 months with chemotherapy. However, a later study by Kim and colleagues noted no statistically significant response of trametinib in patients who were previously treated with a BRAF inhibitor, indicating that BRAF inhibitor resistance mechanisms also confer resistance to MEK inhibitor monotherapy.[31]

Although BRAF-mutant cancers responded well to initial therapy, acquired resistance to BRAF inhibitors was inevitable in the majority of patients leading to treatment failure.[32] Also, studies demonstrated that isolated BRAF inhibition led to the development of Ras-driven secondary tumors, so it was imperative to use combination therapies.[33,34]

In preclinical models of BRAF-mutant melanoma, synergistic antitumor activity and delay in emergence of acquired resistance was noted with combination of BRAF inhibitors with MEK inhibitors.[35–37] This established the need for simultaneous inhibition of the MAPK pathway with the use of BRAF inhibitors. A randomized, open-label, phase III study by Long and colleagues in BRAF V600-mutant melanoma patients showed superiority of the dabrafenib plus trametinib compared with dabrafenib alone.[38] Patients in the combination arm had a median PFS of 11 months and OS of 25.1 months as compared with PFS of 8.8 months and OS of 18.7 months in dabrafenib-only treated patients. Also, the incidence of secondary skin cancers was lower in the combination arm (2%) as compared with the dabrafenib-only arm (9%). Based on these promising results, combination of dabrafenib plus trametinib was approved by the US FDA in patients with metastatic melanoma with BRAF V600E mutation.

BRAF and MEK inhibitors in NSCLC

Based on the experience and success of BRAF inhibitors in melanoma, similar studies were performed in BRAF-mutated NSCLC. Early *in vitro* studies demonstrated considerable efficacy in treatment of BRAF V600-mutated NSCLC using a single-agent BRAF inhibitor.[39] In addition, various preclinical studies also demonstrated that BRAF mutations predicted sensitivity of NSCLC cells to MEK inhibitors.[40,41] Like melanoma models, a combination of BRAF and MEK inhibition was synergistic and delayed emergence of acquired resistance in NSCLC harboring BRAF V600E mutation.[39]

Early case reports documented a partial response (PR) to the isolated use of BRAF inhibitors in BRAF V600E-mutated NSCLC patients.[42–44] Similarly, durable response was noted in a case report, which employed combination therapy of BRAF and MEK inhibitors.[45] In the retrospective EURAF study, 35 patients with advanced NSCLC harboring BRAF mutations were treated with different BRAF inhibitors including vemurafenib, dabrafenib, or sorafenib as a single agent, outside of a clinical trial setting.[46] Rapid tumor response was observed, with 2 patients noted to have complete response, 16 patients had a PR and 11 patients achieved stable disease. Only four patients were reported to have progressive disease after treatment. Overall, for BRAF inhibition therapy, PFS was 5 months and median OS was 10.8 months. Overall, six patients harboring non-V600E mutations were noted to have poor response rate to BRAF inhibitor therapy as compared with patients harboring V600E mutation, and only one out of the six patients having a G596V mutation experienced a PR with vemurafenib therapy. The phase II VE-BASKET trial was an initial prospective study which assessed

response to vemurafenib monotherapy in BRAF V600-mutated nonmelanoma solid tumors, including NSCLC.[47] A total of 20 patients with BRAF-mutant NSCLC (90% BRAF V600E) were enrolled and almost all had received one or more prior systemic chemotherapy. It was observed that 42% of patients had a PR and median PFS was 7.3 months. Also, 12-month PFS and OS was 23% and 66% respectively.

In a multicenter, single arm, nonrandomized phase II study (BRF113928; ClinicalTrials.gov identifier: NCT01336634), potential efficacy and safety of dabrafenib was sequentially evaluated in patients with BRAF V600E-mutant NSCLC, both as a single agent and in combination with trametinib. In cohort A of this trial, dabrafenib was given as a monotherapy in a population of predominantly pretreated patients.[48] A total of 84 patients were incorporated into this cohort. Notable inclusion criteria was presence of a BRAF V600E mutation and an Eastern Cooperative Oncology Group performance status of 0–2. Patients with brain metastases that were <1 cm in size, untreated, and asymptomatic were allowed enrollment. By investigator assessment, the primary endpoint of objective response rate (ORR) was 33% and the disease control rate (DCR) was 58%. Median PFS and OS were 5.5 months and 12.7 months respectively. Adverse effects most commonly reported were pyrexia (36%), asthenia (30%), hyperkeratosis (30%) and decreased appetite (28%). Most common grade 3–4 adverse events were cutaneous squamous cell carcinoma observed in 10 patients (12%) and basal cell carcinoma in 4 patients (5%).

In cohort B of this trial, dabrafenib was administered in combination with trametinib in previously treated patients with BRAF V600E-mutant NSCLC.[49] Dabrafenib (150 mg twice daily) with trametinib (2 mg once daily) combination resulted in an ORR of 63.2% and DCR of 79%. Median PFS was 9.7 months and 65% of the patients achieved >6-month PFS. Serious adverse effects were noted in 32 patients ($>50\%$) and included pyrexia (16%), anemia (5%), decreased appetite (4%), and squamous cell carcinoma (4%). However, it was noted that 33 patients (58%) received at least 80% of the planned dose of dabrafenib and 43 (75%) received at least an 80% of the planned dose of trametinib suggesting that combination therapy had a manageable adverse effect profile. Importantly, secondary squamous cell carcinoma and basal cell carcinoma developed in only two patients each (Table 1).

Though there are no studies directly comparing dabrafenib monotherapy with dabrafenib and trametinib combination therapy, the two cohorts in this study had similar inclusion criteria, methodology and duration of follow up. Across all metrics, dabrafenib plus trametinib was superior with a higher ORR and longer PFS compared with dabrafenib monotherapy. Updated analysis presented at a median follow up of 16.2 months also demonstrated superior OS of combination therapy over dabrafenib monotherapy (18.2 months *versus* 12.7 months respectively).[50] However, it has to be noted that among the two cohorts, patients receiving dabrafenib plus trametinib combination therapy compared with those receiving dabrafenib monotherapy had higher rates of adverse events leading to drug discontinuation (12% *versus* 6%), drug interruption (61% *versus* 43%), and dose reduction (35% *versus* 18%), which has been similarly reported in comparisons of BRAF monotherapy and BRAF-MEK combination therapy in melanoma. However, squamous cell carcinoma was much less common, occurring in only 4% of patients in the combination arm as compared with 12% in the dabrafenib monotherapy arm. In June 2017, the US FDA approved the combination therapy of dabrafenib and trametinib for patients with metastatic NSCLC with BRAF V600E mutation.

Recently, Planchard and colleagues reported the results of cohort C of this phase II study, evaluating the clinical efficacy of dabrafenib plus trametinib combination in 36 treatment-naïve patients with BRAF V600E-mutant NSCLC.[51] The study demonstrated promising results with ORR of 64% and DCR of 75%, further confirming the durable clinical activity of dabrafenib and trametinib combination in BRAF-mutant NSCLC. The median PFS and OS were 10.9 months and 24.6 months respectively, slightly improved as compared with the previously treated cohort (cohort B) of this trial. Also, the side effect profile was largely similar to that recorded in cohort B of the study, with adverse events leading to permanent discontinuation, dose interruption and dose reduction in 22%, 75% and 39% of the patients respectively. Thus, it could be reasonably concluded that these results offer a level of flexibility to

Table 1. Summary of results of all studies in BRAF-mutated NSCLC patients treated with a BRAF or MEK inhibitor.

Study results	EURAF study[46] (*n* = 35)	VE-BASKET study, Hyman and colleagues.[47] (*n* = 20)	Planchard and colleagues.[48] Patients receiving dabrafenib 150 mg BD PO as second-line or later treatment (*n* = 78)	Planchard and colleagues.[49] Patients receiving dabrafenib (150 mg BD PO) plus trametinib (2 mg OD PO) as second-line or later treatment (*n* = 57)	Planchard and colleagues.[51] Patients receiving dabrafenib (150 mg BD PO) plus trametinib (2 mg OD PO) as first-line treatment (*n* = 36)
Age (years)	63 (42–85)	61 (48–83)	66 (28–85)	64 (58–71)	67 (62–74)
Male	18 (51%)	14 (70%)	39 (50%)	29 (51%)	14 (39%)
Smoking history					
Never smoker	14 (40%)	7 (35%)	29 (37%)	16 (28%)	10 (28%)
Smoker ⩽30 pack-years	-	-	25 (32%)	22 (54%)	17 (47%)
Smoker >30 pack-years	-	-	24 (31%)	19 (46%)	7 (19%)
Overall response rate (complete response + partial response)	18 (53%; 35–70%)	8 (42%; 20–67%)	26 (33%; 23–45%)	36 (63.2%; 49.3–75.6%)	23 (64%; 46–79%)
Disease control rate (complete response + partial response + stable disease)	29 (85%; 69–95%)	16 (84%; 60–97%)	45 (58%; 46–67%)	45 (78·9%; 66.1–88.6%)	27 (75%; 58–88%)
Progression-free survival (months)	5.0	7.3 (3.5–10.8)	5.5 (3.4–7.3)	9.7 (6.9–19.6)	10.9 (7.0–16.6)
Duration of response (months)	-	-	9.6 (5.4–15.2)	9.0 (6.9–18.3)	10.4 (8.3–17.9)
Overall survival	10.8	Not estimable	12.7 (7.3–16.3)[50]	18.2 (14.3–not estimable)[50]	24.6 (12.3–not estimable)
Adverse effects (grade 3–4)	-	Pyrexia - 0 (0%) Asthenia - 4 (20%) Anemia - N/A Squamous cell carcinoma - 7 (35%) Dyspnea - 3 (15%) Rash - 1 (5%) Hypertension - 3 (15%)	Pyrexia - 2 (2%) Asthenia - 5 (6%) Anemia - 2 (2%) Squamous cell carcinoma - 10 (12%) Dyspnea - 2 (2%) Rash - 1 (1%) Hypertension - 1 (1%)	Pyrexia - 1 (2%) Asthenia - 2 (4%) Anemia - 3 (5%) Squamous cell carcinoma - 2 (4%) Dyspnea - 2 (4%) Rash - 1 (2%) Hypertension - 0 (0%)	Pyrexia - 4 (11%) Asthenia - 1 (3%) Anemia - 1 (3%) Squamous cell carcinoma - 1 (3%) Dyspnea - 2 (6%) Rash - 1 (3%) Hypertension - 4 (11%)

BD, twice daily; MEK, mitogen-activated protein kinase; N/A, not applicable; PO, orally; NSCLC, non-small cell lung cancer.

physicians to give the combination therapy either as first-line or following chemotherapy, tailored to individual patient needs.

There remain several unanswered questions for the dabrafenib and trametinib combination, particularly pertaining to the resistance mechanisms

to BRAF and MEK inhibition. For instance, in melanoma, it has been noted that acquired resistance to BRAF and MEK inhibitors is frequently associated with persistence of ERK signaling, and the use of competitive ERK inhibitor, SCH772984 has demonstrated significant activity in cells that became resistant to combination of BRAF and MEK inhibitors.[52] SCH772984 prevents phosphorylation and activation of ERK1 and ERK2 by MEK1/MEK2 kinase and sensitizes resistant tumor cells to BRAF-MEK combination therapy. Use of this selective ERK inhibitor in combination therapy can add a new weapon to the arsenal of drugs against BRAF V600E-mutant NSCLC.

Another critical area that demands attention from oncology community is the exploration of BRAF pathway inhibitors in patients with non-V600E mutant NSCLC, which make up almost half of the total patient population with BRAF-mutant NSCLC.[4,5] Unlike the BRAF V600E mutation, biochemistry of the various altered BRAF proteins in non-V600E mutations varies substantially. It has been observed that BRAF non-V600E mutations that are located outside the activation segment of BRAF kinase domain are refractory to BRAF kinase inhibitors.[46] Also, a number of BRAF non-V600E mutations are kinase inactivating or are kinase dead (D594G, G466V), but are still capable of activating the MAPK/ERK pathway through transactivation of CRAF.[53] Since the majority of BRAF non-V600E mutant cells drive hyperactivation of ERK, it has been postulated that cells resistant to BRAF kinase inhibitors may be sensitive to downstream inhibition of MAPK signaling using MEK inhibitors or ERK inhibitors. A clinical trial testing trametinib alone in BRAF non-V600E tumors, including lung cancer is currently ongoing (NCI-MATCH trial; ClinicalTrials.gov identifier; NCT02465060). Also, a preclinical study has shown that combination of dabrafenib and trametinib possess antiproliferative effects against BRAF non-V600 mutant NSCLC cell lines, having either impaired or elevated kinase activity.[54] However, no clinical study testing the combination in this target population has been conducted as of yet. Other treatment strategies that are currently being investigated include concurrent use of an EGFR inhibitor with a MEK inhibitor and the use of a next-generation BRAF inhibitor PLX8394 to achieve sustainable suppression of downstream MEK-ERK signaling in non-V600E BRAF mutations.[55,56]

Over the past decade, molecular diagnostic testing has become a critical component for evaluation of patients with NSCLC. Technological advances have led to the integration of next-generation sequencing platforms into routine clinical practice, thus providing a powerful tool to detect multiple actionable driver mutations using a single sample. In addition, several advances have been made in ctDNA and circulating tumor cell (CTC)-based tests offering a potential alternative for detection of BRAF V600E mutation, however tissue based testing for BRAF is still considered the gold standard.[57,58] A joint guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology currently recommends inclusion of BRAF molecular testing as part of expanded testing panel but it did not recommend genetic testing of BRAF as a routine stand-alone assay.[59]

In conclusion, the recent studies by Planchard and colleagues have established the clinical efficacy of dabrafenib and trametinib combination in patients with stage IV BRAF V600E-mutant NSCLC and have added another milestone towards personalized and precision medicine. This treatment approach offers higher response rates and longer PFS along with improved tolerability and toxicity profile as compared with cytotoxic chemotherapy. Opportunities for future research include evaluation of intracranial activity of dabrafenib and trametinib combination in the target population with brain metastasis, and exploration of treatment options for patients who develop resistance to treatment or who harbor BRAF mutations other than the V600E mutation.

Clinical practice points

1. BRAF mutations occur in approximately 2–4% of patients with stage IV NSCLC and they tend to be mutually exclusive of other major driver gene mutations such as EGFR and KRAS oncogenic mutations.
2. Prognostic impact of BRAF mutation is not clearly defined, mainly due to small patient numbers and patient heterogeneity across various studies.
3. Combination of dabrafenib and trametinib has higher response rate and more durable responses as compared with chemotherapy in both first-line and second-line treatment of NSCLC.

4. Adverse effects of the combination therapy can be managed through dose reduction or interruption without permanent discontinuation of therapy, as derived from experiences from melanoma.

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