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REVIEW

Spotlight on dabrafenib/trametinib in the treatment of non-small-cell lung cancer: place in therapy

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Abstract: Advanced non-small-cell lung cancer (NSCLC) remains a challenging disease. The limited utility of chemotherapy indicates the need for additional therapeutic options. Targeted therapy continues to be an important tool in the treatment of NSCLC. Mutations within the RAS–RAF–MEK–MAPK pathway, specifically the BRAF V600E mutation, have become an important target for the subset of NSCLC patients with this mutation. This paper summarizes the clinical evidence that lead to the recent approval of the combination of dabrafenib and trametinib to treat patients with advanced NSCLC who harbor a BRAF V600E mutation.
Keywords: BRAF mutation, MEK, NSCLC, lung cancer, dabrafenib, trametinib

Introduction

Advanced non-small-cell lung cancer (NSCLC) continues to be a significant health burden worldwide. Over 85% of lung cancer cases are NSCLC,[1] with 10%–30% of these cases occurring in nonsmokers.[2] Lung cancer results in 1.6 million deaths annually worldwide and is projected to cause 155,000 deaths in the United States alone in 2017.[3,4] While patients with early-stage disease hold the greatest chance for cure, approximately 70% of NSCLC patients present with advanced or metastatic disease at time of diagnosis.[5] Traditional platinum-based combination chemotherapy results in response rates (RRs) of approximately 20%–40%.[6–10] Unfortunately, durable long-term responses remain elusive, and the median survival for patients with advanced NSCLC remains at only 1 year from diagnosis.

The advent of targeted therapy offers the possibility of prolonged survival beyond the limited response seen with traditional cytotoxic chemotherapy. With the recent approval of dabrafenib and trametinib (TAFINLAR® and MEKINIST®, Novartis Pharmaceuticals Inc., Basel, Switzerland) in combination for advanced NSCLC in patients with a BRAF V600E mutation, we now have an additional tool to treat these patients.

BRAF mutation as a therapeutic target

The BRAF gene is a 2,949 base pair sequence of 18 exons found on chromosome 7q34, encoding a 766 amino acid peptide.[11] The BRAF protein is a member of the Raf family of serine/threonine kinases. BRAF is a critical component of the RAS–RAF–MEK–MAPK pathway whereupon activated BRAF promotes increased cell proliferation and survival.

The normal cascade begins with GTP-bound RAS, which recruits inactive BRAF dimers to the cell membrane, whereupon BRAF is then phosphorylated.[12] Activated

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cytosolic and membrane-bound BRAF then activate MEK1 and MEK2. The MEK proteins then phosphorylate and activate the MAPK/ERK proteins: ERK1 and ERK2.[13] While these events occur within a complex composed of several scaffolding proteins, activated ERK proteins dissociate from the scaffolding proteins and the RAF/MEK/ERK complex to complete a series of downstream effects. Activated ERK1/2 targets include transcription factors, ribosomal proteins, and proteins of the cytoskeleton.[14] These targets are critical to cell growth.

The discovery of activating BRAF mutations within a variety of tumor types has established BRAF as a true protooncogene. Mutations in BRAF are present in as many as 7%–9% of all malignancies.[15] Namely, BRAF mutations have been reported in as many as 97% of hairy cell leukemias,[16] 70% of melanomas,[17] 50% of papillary and anaplastic thyroid cancers,[18] and 10% of colon cancers.[19]

Although many types of BRAF mutations have been observed within the kinase region, the V600 (T1799A) mutation at exon 15 is often seen.[17] The V600E mutation is a single substitution of the T→A nucleotide transversion at codon 600, resulting in the amino acid valine rather than glutamate.[20] This mutation disrupts the hydrophobic interactions between the activating region and the glycine-rich P loop within the BRAF kinase. While these hydrophobic interactions within wild-type BRAF maintain the kinase in an inactive state, the V600E mutation results in constitutive activation of the kinase.[21]

Within NSCLC, BRAF mutations are present in approximately 1.5%–4% of cases. Approximately 50% of BRAF mutations seen in NSCLC are the V600E mutation.[17] A 2016 meta-analysis of 16 studies composed of 11,711 patients with NSCLC revealed a female-to-male predominance (62.5% vs 32.6%) to harbor the BRAF V600E mutation. Additionally, the V600E mutation was found more frequently in never smokers than current or former smokers. Patients with adenocarcinoma NSCLC were over 4.5 times more likely to harbor the V600E mutation when compared to nonadenocarcinoma NSCLC.[22] In contrast, non-V600E BRAF mutations occur almost exclusively in current or former smokers. Notably, BRAF non-V600E mutations also tend to appear with concurrent KRAS mutations.[23]

Early clinical experience of dabrafenib: use as monotherapy and development of resistance

Dabrafenib is an inhibitor of multiple mutated forms of the BRAF kinase. In vitro testing of selectivity of dabrafenib to 270 kinases, including BRAF, showed a 400-fold selectivity of dabrafenib to BRAF in 91% of the kinases tested.[24] In vitro models have demonstrated that dabrafenib significantly decreases ERK phosphorylation, resulting in cell arrest in G1 phase and subsequent cell death.[25]

In the treatment of metastatic melanoma, the phase III, open-label, BREAK-3 trial demonstrated superior efficacy of dabrafenib monotherapy over standard chemotherapy. Of the 733 Stage IV or unresectable Stage III melanoma patients screened for the trial, 250 patients were randomly assigned to receive dacarbazine chemotherapy (1,000 mg/m² intravenously every 3 weeks) or oral dabrafenib monotherapy (150 mg twice daily). In total, 187 patients were assigned to the dabrafenib group and 63 patients were in the dacarbazine group. The median progression-free survival (PFS) for the dabrafenib group was 5.1 months compared to 2.7 months for the dacarbazine group with a hazard ratio of 0.30 (95% confidence interval [CI]: 01.8–0.51; $p<0.0001$).[26] However, most patients in the dabrafenib group developed disease resistance within 1 year following initial disease response (Table 1).[27]

While inherent resistance to BRAF inhibition exists in melanoma, only approximately 10% of BRAF resistance in mutated-BRAF cases are reported to be inherent. The remaining 90% of BRAF inhibition-resistant melanoma cases are acquired.[28] The development of BRAF inhibition resistance is further complicated by tumor heterogeneity and the development of multiple resistance pathways within the same tumor. Universally, all patients develop multiple mechanisms of resistance to BRAF inhibition. Known resistance pathways within melanoma include acquired reactivating mutations within MAPK (NRAS, KRAS, BRAF amplification, BRAF alternative splicing, MEK1/2, and CDKN2A) and alterations within the PI3K–PTEN–AKT pathway.[29] This phenomenon of BRAF inhibitor resistance spurred the advent of targeted combination therapy.

Melanoma and trametinib: the development of combination RAS–RAF–MEK–MAPK pathway targeted therapy

Trametinib is a MAPK kinase/MEK inhibitor. As BRAF is directly upstream from the MEK kinase, activating mutations in BRAF result in constitutively activated MEK with subsequent activation of the MAPK/ERK pathway.[30]

As monotherapy, trametinib was found to be highly active in metastatic melanoma with the results of the multicenter, phase III, open-label, METRIC Study. In that trial, 322

Table 1 Melanoma phase II and III clinical trials using BRAF and MEK inhibition

Author (Study name)	Phase	Agent	Enrollment #	RR	Grade 3 or 4 toxicity
Hauschild et al[27] (BREAK-3)	III	Dabrafenib vs dacarbazine	250	50% (dabrafenib) vs 6% (dacarbazine)	12.8% (dabrafenib) vs 17.4% (dacarbazine)
Flaherty et al[31] (METRIC)	III	Trametinib vs dacarbazine or paclitaxel	322	22% (trametinib) vs 8% (paclitaxel)	29% (trametinib) vs 12% (paclitaxel)
Kim et al[32]	II	Trametinib	97	0% (prior dabrafenib exposure) vs 25% (dabrafenib naïve)	27%
Flaherty et al[33]	I/II	Dabrafenib/trametinib (in 2 cohorts) vs dabrafenib	162	76% (dabrafenib/trametinib) vs 35% (dabrafenib alone)	48% and 58% (in 2 combination cohorts) vs 43% (dabrafenib only)
Long et al[34]	III	Dabrafenib/trametinib vs dabrafenib + placebo	420	67% (dabrafenib/trametinib) vs 51% (dabrafenib + placebo)	35% (dabrafenib/trametinib) vs 37.4% (dabrafenib/placebo)

Abbreviation: RR, response rate.

patients with metastatic melanoma with either V600E or V600K BRAF mutations were randomized to receive either trametinib (2 mg orally) once daily or dacarbazine (1,000 mg/m²) IV or paclitaxel (175 mg/m²) every 3 weeks. The median PFS (4.8 months vs 1.5 months, $p<0.001$) and overall survival (OS) rate at 6 months (81% vs 67%, $p=0.01$) were improved in patients receiving trametinib compared with chemotherapy (Table 1).[31]

Additionally, a phase III trial evaluated trametinib monotherapy in metastatic melanoma patients with known BRAF V600E or V600K mutations previously treated with or without a BRAF inhibitor. Of the 40 patients who previously received a BRAF inhibitor, there were no confirmed treatment responses, although 28% maintained stable disease (SD), and the PFS was 1.8 months. In the BRAF inhibitor-naïve group (57 patients), there was one (2%) complete response (CR), 13 (23%) partial responses (PRs), and 29 patients (51%) with SD, for an overall confirmed RR of 25%, and a median PFS of 4.0 months (Table 1).[32] Theses data lead to United States Food and Drug Administration (FDA) approval of trametinib as monotherapy for BRAF inhibitor-naïve metastatic melanoma patients.

BRAF and MEK inhibition combination therapy was first analyzed by Flaherty et al[33] in an open-label, phase I/II study of 247 patients with metastatic melanoma and BRAF V600 mutations. The phase I portion verified safety of oral dabrafenib (75 or 150 mg twice daily) and trametinib (1, 1.5, or 2 mg daily) in 85 patients. Subsequently, 162 patients were randomized to receive combination therapy with dabrafenib (150 mg) plus trametinib (1 or 2 mg) or dabrafenib monotherapy. Combination therapy allowed for an improved median PFS (9.4 months vs 5.8 months, $p<0.001$) and a higher CR or PR rate (76% vs 54%, $p=0.03$) (Table 1).[33]

In a randomized phase III trial, Long et al[34] randomly assigned 423 previously untreated stage IIIC or stage IV melanoma patients with a BRAF V600E or V600K mutation to receive a combination of dabrafenib (150 mg orally twice daily) and trametinib (2 mg orally once daily) or dabrafenib and placebo. The median PFS was 9.3 months in the combination group vs 8.8 months in the dabrafenib-only group ($p=0.03$). The overall RR was 67% in the dabrafenib/ trametinib group and 51% in the dabrafenib-only group ($p=0.002$). The 6-month OS was 93% with dabrafenib/trametinib and 85% with dabrafenib alone ($p=0.02$) (Table 1).[34] These collective results demonstrated the utility of BRAF/ MEK inhibition combination therapy in melanoma. However, as compared to Flaherty's phase II study, Long's phase III study indicates that while the benefit of combination therapy over dabrafenib monotherapy is clinically and statistically significant, a smaller benefit was seen with a larger study population.

Evidence of BRAF and MEK inhibitor monotherapy and in combination for NSCLC treatment

The success of BRAF and MEK inhibition using dabrafenib, trametinib, and other agents in the treatment of metastatic melanoma generated increased interest in a variety of other malignancies that also harbor BRAF mutations, particularly NSCLC.

Preclinical NSCLC cell line studies have shown that in tumor cells with BRAF V600E and non-V600E mutations, BRAF and MEK inhibitory agents as monotherapy and in combination are proapoptotic. However, BRAF and MEK inhibition in combination has been shown to cause increased apoptosis in V600E- and non-V600E-mutated

NSCLC cell lines as compared to BRAF or MEK inhibitor monotherapy.[35,36]

The first case report in 2012 of BRAF inhibition in NSCLC (off-label) using vemurafenib (BRAF Inhibitor: ZELBORAF®, Genentech, Inc.©, San Francisco, CA, USA) showed a therapeutic response; however, these results were discovered at autopsy as the patient died from complications from heart failure 3 weeks after initiation of treatment (Table 2).[37]

Additionally, a 2014 case report also revealed continued clinical benefit in a NSCLC patient with a BRAF V600E mutation who received second-line vemurafenib following standard chemotherapy. Upon progression, vemurafenib was discontinued, and the patient received docetaxel thereafter. However, upon the development of malignant ascites, the patient was switched to dabrafenib and had continued disease response for approximately 3 months before disease progression (Table 2).[38]

Within the context of a clinical trial, dabrafenib was first evaluated by Planchard et al[39] in a multicenter, nonrandomized, open-label, phase II study published in 2016. The study enrolled 78 patients with Stage IV NSCLC who had already received first-line systemic chemotherapy. Patients received 150 mg orally of dabrafenib twice daily. The primary endpoint was overall response (PR or CR), and secondary endpoints were OS, PFS, duration of response, disease control for longer than 12 weeks, pharmacokinetics, and safety and tolerability of dabrafenib. At a median follow-up of 10.7 months, the median exposure to dabrafenib was 4.6 months. Overall response by investigator assessment was observed in 26 of 78 (33%; 95% CI: 23%–45%) previously treated patients, with each of these responses being PRs. However, 73% of responses were reported during the first assessment at 6 weeks. Median PFS was 5.5 months. Disease control was achieved in 58% of patients.

Notably, 83 (99%) of 84 patients had at least one adverse event, while 45 (54%) of 84 patients experienced grade 2 or greater adverse events. The most common grade 3 adverse event was the development of cutaneous squamous cell carcinoma or basal cell carcinoma, which was seen in 12% and 5% of patients, respectively. Only 6% of patients had adverse events that resulted in the discontinuation of dabrafenib. The most common adverse events were grade 1–2 pyrexia (33% of patients) and hyperkeratosis (29% of patients).[39]

This study also evaluated the combination of dabrafenib and trametinib in BRAF V600E mutated NSCLC as two separate cohorts not included in the phase II dabrafenib monotherapy results. These patients were also evaluated within a phase II, multicenter, randomized, open-label study that enrolled 57 patients who received dabrafenib 150 mg twice daily (oral) and trametinib 2 mg daily (oral) in continuous 21 day cycles. As in the dabrafenib monotherapy study, the primary endpoint was overall response (PR or CR). Early results reported that 36 of 57 patients (63.2% [95% CI: 49.3–75.6]) achieved an investigator-assessed overall response. With 9 patients (16%) maintaining SD, the investigators found that 45 (78.9%) of enrolled patients maintained disease control (CR + PR + SD). PFS was 9.7 months (6.9–19.6), while the duration of response was 9.0 months (6.9–18.3). The most common adverse event, as in the dabrafenib monotherapy study, was grade 1–2 pyrexia (reported in 44% of patients). Serious adverse events were reported in 32 of 57 (56%) patients and included pyrexia (16%), anemia (5%), confusional state (4%), decreased appetite (4%), hemoptysis (4%), hypercalcemia (4%), nausea (4%), and cutaneous squamous cell carcinoma (4%). The most common grade 3–4 adverse events were neutropenia (9%), hyponatremia (7%), and anemia (5%).[40]

In the updated results published online ahead of print in September 2017, the investigators reported that of the

Table 2 NSCLC case reports and clinical trials using BRAF and MEK inhibition

Author	Phase	Agent	Enrollment #	RR (%)	Grade 3 or 4 toxicity (%)
Gautschi et al[37]	Case report	Vemurafenib	1	PR	N/A
Schmida et al[38]	Case report	Vemurafenib followed by dabrafenib on progression	1	PR	Skin toxicity
Pervere et al[42]	Case report	Dabrafenib/trametinib	2	Patient 1: CR at 1 year Patient 2: PR at 10 months	N/A
Planchard et al[39]	II	Dabrafenib	78	33	42
Planchard et al[40]	II	Dabrafenib/trametinib	57	63.2	56
Planchard et al[41]	II	Dabrafenib/trametinib	36	64	69

Abbreviations: CR, complete response; NSCLC, non-small-cell lung cancer; PR, partial response; RR, response rate; N/A, not available.

36 patients enrolled (median follow-up 15.9 months) and treated with first-line dabrafenib plus trametinib, an overall response was achieved in 23 patients (64%, 95% CI: 46–79), with two (6%) patients achieving a CR and 21 patients (58%) achieving a PR. All patients had one or more adverse event of any grade, and 25 (69%) had one or more grade 3 or 4 events. The most common grade 3 or 4 adverse event was pyrexia (11%). Serious adverse events occurring in more than two patients included alanine aminotransferase increase (14%), pyrexia (11%), aspartate aminotransferase increase (8%), and ejection fraction decrease (8%). One fatal serious adverse event deemed unrelated to study treatment was reported (cardiorespiratory arrest).[41] The FDA-approved dabrafenib and trametinib in combination for metastatic NSCLC with a BRAF V600E mutation on June 22, 2017, based on these results under the Study designations of BRF113928 / CDRB436E2201/NCT01336634 (Table 2).

Limitations of this study discussed by the investigators include the following: small sample size, nonrandomization of the study, and lack of quality of life indicators within the study results. However, the investigators are reviewing the quality of life information of these patients, and it is expected that these findings will be reported in the future. Despite these limitations, the results from this trial demonstrate a clear benefit with the therapy combination of dabrafenib/trametinib in the treatment of BRAF V600E mutated NSCLC to warrant further investigation.

Future directions

Currently, the FDA approval of dabrafenib and trametinib in combination for BRAF V600E-mutated NSCLC patient is limited to patients with metastatic disease in first, second, or third line. However, the study that led to the current approval did not fully evaluate utility in the first-line setting. Additionally, the dabrafenib/trametinib combination has yet to be evaluated head-to-head with chemotherapy or other targeted therapies as first-line therapy. The role of this combination in the neoadjuvant or adjuvant settings remains unclear in early or locally advanced disease. No current clinical trials are underway evaluating the dabrafenib/trametinib combination, but further study is warranted to evaluate these current knowledge gaps. Similarly, the role of this targeted therapy used concurrently or sequentially with radiotherapy remains unknown.

Conclusion

The BRAF pathway has proven to be important in a variety of malignancies. The combination of dabrafenib and trametinib

is now available for the treatment of metastatic NSCLC, with clear evidence of patient benefit. However, the role of this targeted therapy combination outside of the metastatic setting or with other treatment modalities remains unclear. Despite these unresolved issues, the dabrafenib/trametinib combination therapy has emerged as a viable tool to treat a carefully selected subset of NSCLC patients.

Disclosure

The authors report no conflicts of interest in this work.

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