Perspective

Adding to the targeted therapy toolbox: *BRAF* and MEK inhibition in the treatment of *BRAF* V600E metastatic non-small cell lung cancer

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Planchard D, Besse B, Groen HJ, 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;17:984-93.

Abstract: Mutations in the *BRAF* oncogene are found in approximately 2–4% of non-small cell lung cancer (NSCLC). The most common mutation is associated with substitution of glutamic acid for valine at position 600 (V600E) within the BRAF kinase. Targeted therapy against the BRAF V600E mutant kinase has shown efficacy in other solid tumors including melanoma. In this setting, dual inhibition of both BRAF and the downstream mitogen-activated protein kinase kinase (MEK) improves survival compared to BRAF inhibition alone. Planchard *et al*. published two recent phase 2 trials evaluating the clinical activity and safety profile of second-line BRAF monotherapy (dabrafenib) and BRAF-MEK combination therapy (dabrafenib plus trametinib), respectively, in patients with stage IV *BRAF* V600E mutant NSCLC. Here, we review the pertinent findings from each of these studies, discuss their significance in context of the current literature, and consider their potential impact on the management of patients with NSCLC in the clinical setting.

Keywords: Non-small cell lung cancer (NSCLC); BRAF V600E; dabrafenib; trametinib

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Knowledge of the role of oncogenic driver mutations in tumor initiation and maintenance has transformed the treatment of non-small cell lung cancer (NSCLC). Given the availability of targeted therapies that are approved for first-line use, guidelines now recommend that all patients with non-squamous lung cancer undergo routine testing for mutations in the epidermal growth factor receptor (EGFR) gene and rearrangements in the *anaplastic lymphoma kinase* (*ALK*) gene (1-4). The success of targeted therapies for *EGFR*- and *ALK*-mutated NSCLC as well as the historically poor outcomes of patients with advanced disease has led to increased interest in identifying additional driver mutations in lung cancer that may similarly be targets for novel therapies. One such potential target is the *BRAF* oncogene, which encodes a serine-threonine protein kinase within the mitogen-activated protein kinase (MAPK) signaling pathway that regulates cell growth (5). Mutations in *BRAF* occur in 2–4% of NSCLC with predominance in adenocarcinoma (6-9). The clinical characteristics of patients with *BRAF* mutant NSCLC tend to be similar to those of patients with *BRAF* wildtype NSCLC. *BRAF* mutations occur in both males and females but favor older patients (age >60) and current or former smokers (8,10). At least half of *BRAF* mutations in NSCLC are characterized by the substitution of glutamic acid for valine at position 600 (V600E) within the BRAF protein, leading to constitutive activation of the kinase and subsequent tumorigenesis (7,9). Although the remaining non-V600E *BRAF* mutations are similarly

Table 1 Summary of Studies Evaluating the Efficacy of Targeted Therapy in BRAF Mutant NSCLC

Study results	Gautschi *et al*.	Falchook *et al.*	Hyman *et al.*	Planchard *et al.*	Planchard *et al.*
Study type	Retrospective	Phase 1	Phase 2 "basket trial"	Phase 2	Phase 2
Number of patients	35[a]	1	20[d]	78	59[e]
ORR	53%[b]	–[c]	42%	33%	63.2%
DCR	85%	–	–	58%	78.9%
PFS	5 months	–	7.3 months	5.5 months	9.7 months
OS	10.8 months	–	–	12.7 months	–

[a], within this cohort, 34 patients were included in the survival analysis, of which 29 had NSCLC harboring V600E mutations; [b], although outcomes were assessed in patients with any *BRAF* mutation including non-V600E mutations, only one patient with a non-V600E mutation achieved a partial response to targeted therapy; [c], the single enrolled patient with NSCLC achieved a partial response to therapy; [d], within this cohort, 19 patients were included in the survival analysis, of which 18 had NSCLC harboring V600E mutations; [e], within this cohort, 57 patients were included in the survival analysis. ORR, objective or overall response rate; DCR, disease control rate; PFS, progression free survival; OS, overall survival.

thought to drive tumorigenesis in NSCLC, the efficacy of targeted therapies against these mutations is questionable, and clinical trials in other solid tumors have focused on patients with *BRAF* V600E mutations in particular (11-13).

Inhibitors of the V600E mutant BRAF kinase, including dabrafenib and vemurafenib, were initially approved for melanoma, which harbors *BRAF* mutations in >40% of cases (14,15). Based on the efficacy of BRAF inhibitors in this clinical setting and the success of other targeted therapies in NSCLC, there has been interest in pivoting towards the use of BRAF inhibitors for *BRAF* V600E mutant lung cancer. In *Lancet Oncology*, Planchard *et al.* recently published the two largest phase 2 studies to date evaluating the clinical activity and safety profile of BRAF monotherapy and combination BRAK-MEK inhibition, respectively, in previously treated NSCLC (16,17). A third cohort of patients receiving BRAF-MEK combination therapy in the first-line setting has yet to be reported. In the first of the two published studies, 78 patients with stage IV NSCLC who had progressed after one or more systemic therapies were enrolled from August 2011 to February 2014. Notable inclusion criteria included the presence of a *BRAF* V600E mutation as identified locally by Clinical Laboratory Improvement Amendments (CLIA) approved methods and an ECOG performance status 0-2. Patients with brain metastases that were <1 cm in size, untreated, and asymptomatic were allowed to enroll. All patients received dabrafenib 150 mg twice daily as monotherapy unless adverse events merited a dose reduction. By investigator assessment, the primary endpoint of overall response was achieved in 26 of 78 patients (33%; 95% CI: 23–45%, all partial responses). The majority of these responses (73%) were detectable by the time of the first patient assessment at 6 weeks from baseline. Disease control, defined as the number of patients achieving a response or stable disease for ≥12 weeks after the initiation of therapy, was reported in 45 patients (58%; 95% CI: 46–67%). Median progression-free survival (PFS) was 5.5 months, and median overall survival (OS) was 12.7 months.

In the second study, 59 patients with stage IV NSCLC who had progressed after one or more platinum-based systemic chemotherapy regimens were enrolled from December 2013 to January 2015. Inclusion and exclusion criteria were similar to the cohort described above. All patients were treated with dabrafenib 150 mg twice daily plus trametinib 2 mg daily unless dose reduction was warranted due to adverse events. Trametinib inhibits the mitogen-activated protein kinase kinase (MEK), a downstream effector of RAF within the MAPK pathway. An investigator-assessed overall response was documented in 36 of 57 eligible patients (63.2%; 95% CI: 49.3–75.6%), including two complete responses. Disease control was documented in 45 patients (78.9%; 95% CI: 66.1–88.6%), and PFS was 9.7 months. Although median duration of response was 9.0 months at the time of data cutoff, 18 of 36 responses were still ongoing, and the majority of these patients (approximately 16 of 18) had already been on therapy for at least 6 months. Survival data for this cohort is incomplete.

Prior to these results, studies of BRAF inhibition in NSCLC had been limited (*Table 1*). Early support for BRAF inhibition in NSCLC came from case reports of patients treated off-label with dabrafenib or vemurafenib

(18-21). Subsequently, a retrospective analysis of the European BRAF cohort (EURAF) by Gautschi *et al.* reported outcomes in patients with *BRAF*-mutant NSCLC who had received BRAF monotherapy as first- or second-line treatment (13). Among 34 patients, 29 with V600E mutations, overall response rate (ORR) was 53% and disease control rate (DCR) was 85%. Although these results were striking, validation by prospective studies has been necessary. In a phase 1 study of dabrafenib monotherapy in various solid tumors, Falchook *et al.* accrued a single patient with NSCLC who achieved a partial response to dabrafenib with an 83% reduction in tumor size (22). In a larger phase 2 "basket trial" of vemurafenib in non-melanoma tumors, the ORR in a cohort of 20 patients with *BRAF*-mutant NSCLC (18 with V600E mutations) was 42%, and median PFS was 7.3 months (23). Data supporting MEK inhibition in NSCLC is even more limited by comparison. In a trial of patients with NSCLC, small cell lung cancer, and thymic malignancies treated with selumetinib monotherapy, the ORR was 11% in nine patients with NSCLC (24). However, the study included patients with mutations in any one of multiple RAS/RAF proteins including KRAS, HRAS, NRAS, or BRAF.

These few prospective trials have been limited by small patient numbers, which reflects the low incidence of *BRAF* mutations in NSCLC. Additionally, many of these studies were conducted as "basket trials" that included patients with multiple tumor types, which limits the inferences that can be drawn about the efficacy of therapy in lung cancer in particular. The studies conducted by Planchard *et al.* likely benefitted from multiple centers of enrollment as well as a more widespread understanding of the role of multiplex genotyping in improving patient outcomes in lung cancer (25). As a result, Planchard *et al.* were able to enroll relatively larger numbers of patients with *BRAF*-mutant NSCLC in each of their two cohorts reported thus far. With respect to the clinical characteristics of the patients enrolled, there was also fairly good correspondence with previous descriptions of individuals with *BRAF* V600E mutant NSCLC in the literature. In prior studies, median age at diagnosis has ranged from 63–67 years with *BRAF* mutations occurring predominantly in adenocarcinoma, which matches the cohorts enrolled in each of the studies from Planchard *et al.* (8-10). The percentage of never-smokers in each of the two cohorts (28% and 37%, respectively) was also similar to what has been reported previously (8,9,26).

With a sizeable cohort and fairly representative sample of patients enrolled, the results from Planchard *et al.* should set the current standard upon which the efficacy of BRAF monotherapy and BRAF-MEK combination therapy is judged. However, in considering whether dabrafenib or dabrafenib plus trametinib should be used routinely in the second-line treatment of *BRAF*-mutant NSCLC, it is important to understand what is known about the efficacy of currently approved second-line therapies since the studies from Planchard *et al.* were not randomized or controlled. When comparing results across trials, one must keep in mind that earlier studies of second-line therapy included patients with NSCLC regardless of tumor genotype whereas the studies from Planchard *et al.* were designed to evaluate only the subset of patients with NSCLC harboring *BRAF* V600E mutations. This caveat is especially important given that long-term survival of *BRAF* V600E mutant NSCLC has been described in select cases (27,28). In addition, at least one study has demonstrated a trend toward better outcomes among patients with NSCLC whose tumors harbor any *BRAF* mutation compared to those harboring other driver mutations or no mutations at all (10). On the other hand, in a nationwide French study of patients with NSCLC whose tumors were profiled for oncogenic mutations, outcomes among patients with *BRAF* mutant NSCLC receiving second-line therapy were poor (ORR 9%), with the majority receiving best supportive care only (26).

Per current guidelines, approved second-line therapies following disease progression include single-agent or combination chemotherapy (pemetrexed, docetaxel, gemcitabine, or ramucirumab plus docetaxel), targeted therapy (erlotinib) and newer immunotherapies (nivolumab, pembrolizumab) (1). Second-line chemotherapy agents in NSCLC have generally yielded poor results. Accounting for methodological differences, studies of single-agent gemcitabine reported ORRs ranging from 13–19% with median OS 26–34 weeks (29,30). Single-agent docetaxel by comparison was demonstrated in separate trials to be superior to best supportive care and single-agent vinorelbine or ifosfamide, respectively, but the highest ORR was only 10.8% and the longest median OS was 7.0 months in either of the two studies (31,32). Better outcomes were noted in a trial of docetaxel alone *vs.* docetaxel plus ramucirumab in which an ORR of 14% was reported for single-agent docetaxel (33). However, the authors of that study attributed such findings to the enrollment of patients with better performance status. Furthermore, the combination of ramucirumab and docetaxel was superior with respect to

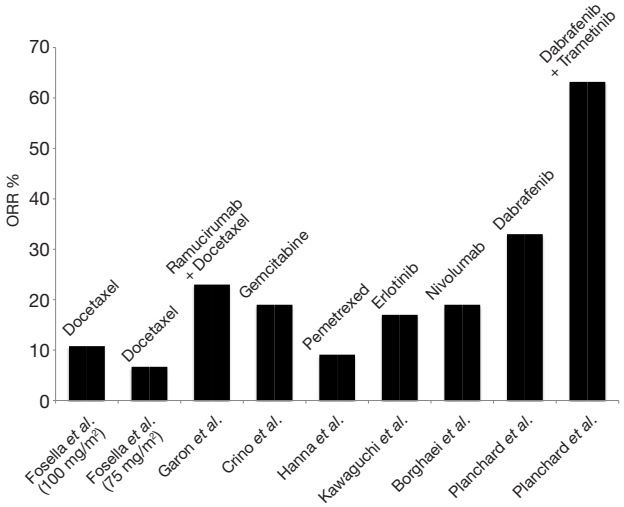

Figure 1 The objective or overall response rates (%; complete or partial response) for currently approved second-line therapies in NSCLC are shown along with the response rates recorded in the two recent studies by Planchard *et al*. For each therapy for which multiple clinical trials have been performed, one representative trial is shown. The response rates for two different doses of docetaxel that were studied in the same trial from Fosella *et al*. are both shown. Molecular testing in NSCLC is key to identifying appropriate patients with *BRAF* mutant NSCLC who would benefit from second-line treatment with targeted therapy over other approved agents.

ORR (23% *vs.* 14%), DCR (64% *vs.* 53%), and median OS (10.5 *vs.* 9.1 months) compared to single-agent docetaxel. Single-agent pemetrexed has been comparable in regards to ORR (9.1% *vs.* 8.8%) and OS (8.3 *vs.* 7.9 months) compared to docetaxel (34).

As a second-line treatment option, erlotinib compared to placebo results in a greater ORR (8.9% *vs.* <0.1%) and median OS (6.7 *vs.* 4.7 months) (35). Compared to single-agent chemotherapy, however, the benefit of targeted therapy in this setting is less clear. A comparison of pemetrexed *vs.* erlotinib, for example, demonstrated similar outcomes with chemotherapy and targeted therapy (36). In the TAILOR study, ORR (15.5% *vs.* 3%) and DCR (44.3% *vs.* 22%) were higher in patients with wildtype *EGFR* NSCLC who were treated with docetaxel compared to erlotinib, and thus the benefit of targeted therapy in patients with wildtype tumors is questionable (37). With respect to newer anti-PD-1 immunotherapies, nivolumab compared to docetaxel has been associated with longer OS (12.2 *vs.* 9.4 months) and higher ORR (19% *vs.* 12%) (38). Herbst *et al.* reported similar benefits with pembrolizumab with median OS 10.4 months (2 mg/kg dose of pembrolizumab) and 12.7 months (10 mg/kg dose) and an ORR of 18% at both dosages (39). However, the study excluded patients with negative PD-1 expression <1% and found that the best outcomes were experienced by patients with PD-1 expression >50%.

In the context of these studies, dabrafenib monotherapy and dabrafenib plus trametinib both compare favorably to currently approved second-line therapies. The response rates reported for both dabrafenib alone and dabrafenib plus trametinib are higher than that which has been traditionally reported with either single-agent chemotherapy or erlotinib in *EGFR* wild-type patients in the second-line setting. Additionally, the median OS of 12.7 months in patients with *BRAF* mutant NSCLC receiving dabrafenib monotherapy is longer than the survival typically reported with second-line chemotherapy. While newer anti-PD-1 immunotherapies are promising, their efficacy is dependent on PD-1 expression in tumor cells, and it is unclear if they will represent a treatment option for all patients with *BRAF*-mutant NSCLC. Although some variability in results may be explained by differences in patient populations, enrollment sizes, and methods between studies, targeted therapy nonetheless seems to represent a significant treatment addition for the subset of patients with *BRAF* V600E mutant NSCLC. This furthermore highlights the importance of molecular testing in patients with NSCLC. To optimize the benefits of *BRAF* targeted therapy, clinicians must be able to accurately identify patients with NSCLC harboring targetable *BRAF* V600E mutations who would be candidates to receive dabrafenib or dabrafenib plus trametinib over other standard second-line therapy options for which responses are less robust (*Figure 1*).

For oncologists tasked with making treatment decisions for patients with *BRAF* V600E mutant NSCLC, the next dilemma is selecting between BRAF monotherapy *vs.* BRAF-MEK combination therapy. In melanoma, acquired resistance to BRAF monotherapy leads to eventual drug failure and disease progression (12). Preclinical studies in melanoma cell lines have demonstrated multiple mechanisms of acquired resistance including new mutations in *NRAS* or *MEK* and increased expression of COT, CRAF, or PDGF-α (40-45). The rationale for the combined use of BRAF and MEK inhibition is to delay acquired resistance by blocking two sites along the MAPK pathway, and studies in melanoma have demonstrated better outcomes with BRAF-MEK combination therapy compared to

BRAF monotherapy (46). Planchard *et al.* caution against directly comparing the results of their two cohorts since each was studied independently. However, each study employed a similar methodological design and had a similar median duration of follow-up. The comparable baseline characteristics of each cohort with respect to age, sex, performance status, percentage of non-smokers, and histology also makes direct comparisons more palatable. It is worth noting that with respect to ethnicity, the two cohorts were not as well balanced with a greater percentage of patients of Asian ethnicity enrolled in the cohort receiving dabrafenib monotherapy (22% *vs.* 7%). The potential effect of this discrepancy on outcomes is not clear.

Across nearly all metrics, dabrafenib plus trametinib was superior with a higher ORR, higher DCR, and longer PFS than dabrafenib monotherapy. While the duration of response in each therapy group was similar (9.0 months for dabrafenib plus trametinib *vs.* 9.6 months for dabrafenib), 18 of the 36 patients receiving dabrafenib plus trametinib who achieved a response remained on therapy at the time of data cutoff. In addition, among all patients receiving dabrafenib plus trametinib, 17 out of 57 (30%) remained on therapy for >12 months. As pointed out by Planchard *et al.*, the response rate of dabrafenib plus trametinib compared to that of dabrafenib monotherapy is closer to the response rates typically reported with other targeted therapies such as erlotinib and crizotinib, although some of these latter studies were conducted using targeted therapy as first-line treatment (2-4,47-50). With this in mind, combined dabrafenib plus trametinib should likely be the preferred option wherever possible but until a head-to-head trial of BRAF monotherapy and BRAF-MEK combination therapy is conducted in NSCLC, clinician experience, patient preference, and the safety profile of each therapy should always be considered. The poor outcomes of patients receiving second-line treatment for NSCLC in general should make even dabrafenib monotherapy an attractive option in cases where combination therapy is contraindicated.

The documented adverse events occurring in patients receiving dabrafenib monotherapy were similar to those reported in melanoma. Planchard *et al.* reported adverse events of grade 2 or worse in 45 of 84 (54%) patients. By comparison, in a phase 3 trial of dabrafenib monotherapy in melanoma patients, adverse events grade 2 or greater occurred in 53% of patients, the most common of which were skin-related, pyrexia, fatigue, headache, and arthralgia (12). The rate of grade 3 squamous cell carcinoma of the skin was less common in this study of patients with melanoma compared to the Planchard *et al.* cohort (12% *vs.* 4%). In the two studies from Planchard *et al.*, patients receiving combination dabrafenib plus trametinib compared to those receiving dabrafenib monotherapy had higher rates of adverse events leading to drug discontinuation (12% *vs.* 6%), drug interruption (61% *vs.* 43%), and dose reduction (35% *vs.* 18%), which has been similarly reported in comparisons of BRAF monotherapy and BRAF-MEK combination therapy in melanoma (46). Serious adverse events were also more common in the cohort receiving combination therapy (56% *vs.* 42%). However, squamous cell carcinoma was much less common, occurring in only 4% of patients. Regardless of these differences, Planchard *et al.* reported that both therapies were tolerated well overall. With respect to serious adverse events, it is worth noting that one patient receiving dabrafenib monotherapy who was also on a factor Xa inhibitor died from an intracranial hemorrhage while one patient with a history of a cranial artery aneurysm receiving dabrafenib plus trametinib experienced a subarachnoid hemorrhage. Only the intracranial hemorrhage was attributed to the study drug. Although rare, three patients with cerebral hemorrhage were reported in a trial of dabrafenib plus trametinib in melanoma, and at least one case report of intracranial hemorrhage occurring in a patient receiving dabrafenib plus trametinib therapy has been described previously (46,51). While causality has not been established, the potential for such serious adverse events should be noted as use of dabrafenib and trametinib increases.

Conclusions

In conclusion, the recent studies from Planchard *et al.* shed new light onto the efficacy of targeted therapy as second-line treatment in patients with stage IV *BRAF* V600E mutant NSCLC. As existing second-line therapy options in NSCLC have traditionally been associated with poor outcomes, dabrafenib monotherapy and combination dabrafenib plus trametinib should be considered in the management of patients with NSCLC harboring *BRAF* V600E mutations. Areas for future research remain and include direct head-to-head comparisons of BRAF monotherapy and combination BRAF-MEK inhibition, long-term follow-up of the safety profile of these targeted therapies, evaluation of the efficacy of dabrafenib and trametinib in the first-line treatment setting, and explorations of treatment options for patients with tumors harboring less common *BRAF* mutations.

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Footnote

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