BRAF Adds an Additional Piece of the Puzzle to Precision Oncology-Based Treatment Strategies in Lung Cancer

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The recent European Medicines Agency and US Food and Drug Administration approval of combined dabrafenib plus trametinib as effective treatment for patients with BRAF V600E mutations has dramatically altered the natural history of this disease population, highlighting the importance of identifying such patients with lung cancer early during their clinical course. Approval was based on clinical studies that initially demonstrated that the selective BRAF V600 inhibitors dabrafenib or vemurafenib showed clinical activity with an overall response rate (ORR) of 33% and 42% and median progression-free survival (mPFS) of 5.5 months (95% confidence interval [CI], 3.4–7.3) and 7.3 months (95% CI, 3.5–10.8), respectively, as single agents in previously treated patients with BRAF V600E–mutant non–small cell lung cancer (NSCLC).1 2 Similar to melanoma, combined BRAF and MEK inhibition has shown superior efficacy as compared with BRAF inhibitor monotherapy in BRAF V600E–mutant lung cancer. The combination of dabrafenib plus the MEK inhibitor trametinib in patients with previously treated BRAF V600E–mutant NSCLC led to substantial antitumor activity (ORR, 66.7%; 95% CI, 52.9%–78.6%) with durable responses (mPFS, 10.2 months; 95% CI, 6.9–16.7) and a favorable safety profile.3 These results represent a clinically significant improvement over both single-agent dabrafenib and conventional chemotherapy. The same degree of benefit with this combination is also observed in untreated BRAF V600E–mutant NSCLC when compared indirectly with previously treated patients (ORR, 64%; 95% CI, 46%–79% and mPFS, 10.9 months; 95% CI, 7.0–16.6).4 5 Although cross-trial comparisons should be undertaken with caution, the antitumor activity observed with the combination in BRAF V600E–mutant NSCLC (first or second line) seems to be similar to that observed for other targeted therapies, including inhibitors of epidermal growth factor receptor (EGFR; ORR, approximately 70%; mPFS, 9.7–14.7 months) and anaplastic lymphoma kinase (ALK; ORR, 62%–83%; mPFS, 10.4–25.7 months) in EGFR and ALK patient populations, respectively.6–12 The last version of the National Comprehensive Cancer Network guidelines (version 3.2018; February 21, 2018) recommends upfront treatment with the dabrafenib plus trametinib combination, and the European guidelines will soon be updated and will likely include the combination as a standard of care in BRAF V600–mutant NSCLC patients.13 14 The low frequency of this mutation (1%–2%) means that the most practical method for identifying patients with V600E-mutant NSCLC is with a broad molecular panel that includes the oncogenic drivers for which there are approved drugs with the companion diagnostic (EGFR, ALK, ROS1, and now BRAF).

With the 2 abovementioned prospective trials only including NSCLC patients with BRAF V600E mutations,1 4 there is currently no consensus on how to optimally manage patients with BRAF mutations other than V600E. In the EURAC cohort, among patients with non–BRAF V6000–mutant disease, only 1 patient with a BRAF G596V mutation achieved a partial response with vemurafenib.15 More recent studies on melanoma BRAF–mutant cell lines showed a lack of efficacy of vemurafenib, but potential sensitivity to MEK inhibitors, in non–BRAF V6000–mutant cells (BRAF–mutant “group 2,” RAS independent, eg, K601, L597, G469, G464, and “group 3,” with low or absent kinase activity, coexist frequently with mutations in RAS or NF1 loss, eg, G469, G466, D594, G596).16 Further research is needed to assess the efficacy of targeted therapies or immunotherapy for patients with non–BRAF V6000 mutant and until then, the current recommendation should be to expose these patients to a combination of targeted therapy with a MEK or ERK inhibitor.

Activating BRAF mutations are considered an alternative oncogenic driver in NSCLC that are generally mutually exclusive with EGFR mutations, and ALK and ROS1 rearrangements. BRAF mutations, both V600E mutant and non–V506E mutant, are found in around 2% of NSCLCs and lead to a constitutive activation of the downstream MAPK signaling pathway.17 18 The most common of these mutations, BRAF V600E mutant (a glutamate for valine substitution at codon 600), is observed in 70% to 90% of BRAF-mutated melanomas and 50% to 60% of lung adenocarcinomas. The prognostic implications of BRAF V600E mutant are currently unclear. Several studies have associated BRAF V600E–mutant patients with poor outcomes and lower response to platinum-based chemotherapy as compared with those without BRAF mutations.19 20
Furthermore, in the French nationwide program for the systematic genomic characterization of NSCLC, half of the BRAF-mutant patients (106 patients with data) did not have access to a second-line treatment and received only best supportive care. The BRAF-mutant patients who did receive a second-line treatment had poor outcomes: ORR was only 9% and mPFS was 3.1 months (1.4–6.1) for 71 patients with available data. The first-line BRAF-mutant patients showed a modest benefit with standard-of-care chemotherapy with an ORR of 23% (70 patients with data).

Immune checkpoint inhibitors as monotherapy or in combination with chemotherapy have demonstrated significantly prolonged survival for patients with NSCLC, compared to platinum-based chemotherapy, especially those with high tumoral programmed death ligand-1 (PD-L1) expression. However, more than 50% of patients do not respond at all to these therapies. The therapeutic benefit of immune checkpoint inhibitors in BRAF V600-mutant NSCLC is thus far unknown given the rarity of this patient subset and the recent introduction of checkpoint inhibitors as standard therapies. Although patients with EGFR mutations and ALK rearrangements were excluded from the immune checkpoint inhibitor trials, BRAF-mutant patients were not identified in the NSCLC trials with immune checkpoint inhibitors. Clinical trials have not yet been performed to evaluate the therapeutic benefit of immune checkpoint inhibitors alone or in association with BRAF/MEK inhibitors in BRAF V600-mutant NSCLC, although phase III trials are ongoing in BRAF V600–mutant melanoma patients, with the combination dabrafenib and trametinib (NCT02927692) or vemurafenib and cobimetinib (NCT02908672). Results of immune checkpoint inhibitors in NSCLC patients with EGFR mutations or ALK rearrangements suggest that programmed death receptor-1/programmed death ligand-1 (PD-1/PD-L1) inhibitor therapy is less effective in these populations. The BRAF V600 oncogenic drivers arise more commonly in cigarette smokers (higher frequency in comparison to EGFR and ALK patients), so this subgroup may have a higher tumour-mutation burden that might correlate with higher response to checkpoint inhibitors but this awaits further studies.

In conclusion, based on the high ORR and mPFS with BRAF/MEK inhibition in phase II trials, current data support the recommendation of the association of dabrafenib with trametinib in NSCLC BRAF V600E mutant as an earlier line of treatment as standard of care. Immune checkpoint therapy is an option; however, given the lack of data in this population, clinicians should remain prudent about substituting checkpoint inhibitor therapy for the evidenced-based precision medicine treatment strategies.

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