Editorial

Dual inhibition of BRAF and MEK in BRAF-mutated metastatic non-small cell lung cancer

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Lung cancer is one of the leading causes of cancer-related death worldwide. Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of lung cancers, and about 70% are diagnosed as advanced disease (1). Until recently, systemic chemotherapy has been the standard treatment for patients with metastatic NSCLC with limited efficacy; however, identification of driver mutations, such as epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) rearrangements, and the development of tyrosine kinase inhibitors for each genetic alteration markedly changed current clinical practice (2,3).

KRAS mutations are the most common mutations in NSCLC; however, targeted therapy is not available for this mutation because of the absence of known allosteric sites within the molecule and its extremely high affinity to its effectors (4). Therefore, researchers' interests are being focused on the downstream pathway of KRAS. BRAF is a member of the RAF family of serine/threonine protein kinases, constituting the RAS-RAF-MEK-ERK-MAP kinase pathway. This pathway can be constitutively activated by *BRAF* mutations that have been found in several cancer types including melanoma, colorectal cancer, and NSCLC (5). So far, more than 40 different mutations have been identified and the most common is the V600E point mutation. The $BRAF^{V600E}$ mutation is the most important variant because, at present, it is the only treatable mutation of *BRAF* (6).

BRAF mutations are commonly observed in melanoma patients (roughly 50%) and over 90% of the mutations are $BRAF^{V600E}$ (6). Vemurafenib is the first FDA-approved BRAF inhibitor based on the results of a phase 3 study showing the superiority of vemurafenib to standard chemotherapy with dacarbazine (7). Dabrafenib is another potent BRAF inhibitor, and a phase 3 study comparing dabrafenib and dacarbazine demonstrated significantly higher efficacy of dabrafenib in terms of response rate and progression-free survival (PFS), leading to the second FDA-approved BRAF inhibitor (8). Toxicities of both vemurafenib and dabrafenib were generally mild; however, the problem was that a considerable number of patients treated with BRAF inhibitors experienced secondary skin cancer (squamous-cell carcinoma or keratoacanthoma) resulting from a paradoxical activation of the MAPK pathway in *BRAF* mutation-negative cells (7,8).

In contrast to melanoma, the frequency of *BRAF* mutations in NSCLC is extremely low. The percentage of positive *BRAF* mutations in NSCLC is approximately 2% to 4%, and about 50% are V600E mutations (i.e., $BRAF^{V600E}$ is detected in roughly 1.5% of NSCLC, especially in adenocarcinoma) (9). Previous evidence suggested that BRAF inhibitors are also clinically active in NSCLC patients with *BRAF* mutations. In a phase 2 study of vemurafenib, 8 of 19 patients achieved partial response (response rate: 42%) and median PFS was 7.3 months (10), and, in a phase 2 study of dabrafenib, 26 of 78 patients achieved partial response (response rate: 33%) and median PFS was 5.5 months (11); however, similar to the clinical study in melanoma, secondary squamous-cell carcinoma developed in 12% of patients treated with dabrafenib in the latter study.

Although the initial response is good in *BRAF*-mutant patients, acquired resistance to BRAF inhibitors is inevitable, and one of the most important resistance mechanisms is reactivation of the MAPK pathway (12).

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Based on the preclinical data that dual inhibition of BRAF and MEK had a synergistic effect and delayed the emergence of resistance (13,14), combination of both BRAF and MEK inhibitors has been extensively evaluated in *BRAF*-mutated melanoma. In a randomized phase 3 study comparing dabrafenib and trametinib, a MEK inhibitor, with dabrafenib and placebo, the response rate was 69% in the combination arm and 53% in the dabrafenib alone arm (P=0.0014). Survival data were also significantly improved in the combination arm. Median overall survival (OS) was 25.1 months in the combination arm and 11.0 months in the dabrafenib alone arm, respectively [hazard ratio (HR) 0.71; P=0.0107]. Median PFS was 11.0 months in the combination arm and 8.8 months in the dabrafenib alone arm, respectively (HR 0.67; P=0.0004). In addition, the incidence of secondary skin cancer decreased in the combination arm: the incidence was 3% in the combination arm and 9% in the dabrafenib alone arm (15). Based on these results, the combination of dabrafenib and trametinib became the first FDA-approved combination therapy for metastatic melanoma with the $BRAF^{V600E}$ mutation.

In the latest issue of Lancet Oncology, Planchard *et al.* reported the results of a phase 2 study of dabrafenib plus trametinib in $BRAF^{V600E}$-mutant NSCLC patients who were previously treated with systemic chemotherapy (16). Doses of the two agents were the same as the doses successfully used in the preceding melanoma study. The primary endpoint was investigator-assessed overall response. Secondary endpoints were investigator-assessed PFS, OS, and safety. Fifty-nine patients were enrolled in the study and 57 were eligible. Among the 57 eligible patients, 56 (98%) had adenocarcinoma and 41 (72%) were current or former smokers, agreeing with the previously reported characteristics of *BRAF*-mutant NSCLC patients. Confirmed overall responses were achieved in 36 patients, resulting in the response rate of 63.2%. Tumor response was durable in most cases, irrespective of number of previous chemotherapy regimens. Median PFS was 9.7 months and 65% of the patients achieved 6-month PFS. Common adverse events included pyrexia (46%), nausea (40%), vomiting (35%), and diarrhea (33%). Serious adverse events were reported in 32 (56%) of the patients, including pyrexia (16%), anemia (5%), and confused state (4%). Adverse events led to permanent discontinuation in 7 patients (12%); however, the fact that 33 patients (58%) received at least 80% of the planned dose of dabrafenib and 43 (75%) received at least an 80% dose of the planned dose of trametinib suggested that these toxicities were manageable in most of the patients. Importantly, secondary squamous-cell carcinoma developed in only 2 patients (4%). Furthermore, no patients had documented new brain metastases as part of their progression suggesting the potency of this combination regimen for brain metastases.

Compared with the results of dabrafenib monotherapy in the same patient population (12), response rate (33% *vs.* 63.2%) and PFS (5.5 months *vs.* 9.7 months) were numerically better in the combination regimen. In addition, although incidence of some toxicities, including pyrexia, was higher in the combination regimen, secondary skin cancer developed in fewer patients (12% *vs.* 4%). Considering the rarity of the disease, randomized study is not realistic, and these results together with the results in the melanoma studies strongly support the superiority of dabrafenib plus trametinib to dabrafenib alone in NSCLC patients with the $BRAF^{V600E}$ mutation. Indeed, the FDA has granted a breakthrough therapy designation to the combination of dabrafenib and trametinib as a potential treatment for patients with $BRAF^{V600E}$-mutant NSCLC.

Now, patient accrual into the phase 2 study of dabrafenib plus trametinib in previously untreated $BRAF^{V600E}$-mutant NSCLC has been completed, and $BRAF^{V600E}$ is expected to become the 4th practically treatable oncogenic mutation in NSCLC in the near future following *EGFR*, *ALK*, and *ROS1*; however, we know very little about resistance mechanisms in $BRAF^{V600E}$-mutant NSCLC treated with this combination, and, in addition, currently we have no effective treatment strategy for other *BRAF* mutation subtypes. Further studies are needed to resolve these difficult and pressing issues.

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Footnote

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