



Dabrafenib in patients with *BRAF*-mutated non-small cell lung cancer

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Lung cancer is the leading cause of cancer death worldwide and non-small cell lung cancer (NSCLC) accounts for more than 85% of all cases of lung cancer. Molecular targeted drugs, which specifically inhibit a particular molecular target, have been developed actively and have contributed to improved outcomes of advanced NSCLC patients. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) (e.g., gefitinib, erlotinib, icotinib, afatinib, olmutinib and osimertinib) and anaplastic lymphoma kinase (ALK) TKIs (e.g., crizotinib, ceritinib and alectinib) have been reported to demonstrate dramatic efficacy in patients with *EGFR* mutation-positive and *ALK*-rearranged advanced NSCLC, respectively. However, other targeted treatment options for patients with advanced NSCLC have so far been limited.

RAF kinases have been associated with cancer since their discovery in 1983 (1). The *BRAF* gene makes serine/threonine-protein kinase B-Raf, one of the RAF kinase families of growth signal transduction protein kinases, and activating mutations in the *BRAF* gene result in a constitutively activated kinase that drives the growth and survival of cancer cells. *BRAF*^{V600E}, an amino acid substitution from a valine (V) to a glutamine (E) at codon 600 in *BRAF*, is the most common *BRAF* mutation, and has been widely observed in melanoma, papillary thyroid carcinoma, colorectal cancer and NSCLC.

Dabrafenib, an adenosine triphosphate-competitive *BRAF* inhibitor, is approved for the treatment of unresectable or metastatic *BRAF*^{V600E}-positive melanoma as a monotherapy and in combination with trametinib, an allosteric MEK inhibitor, based on the results of randomized

phase III trials (2,3). Dabrafenib significantly improved progression-free survival compared with dacarbazine, and dabrafenib plus trametinib, as compared with dabrafenib plus placebo, significantly improved overall survival in patients with *BRAF*-mutated melanoma. *BRAF* mutation is a targetable oncogene in melanoma, but not in all non-melanoma cancers. The therapeutic efficacy of vemurafenib, an adenosine triphosphate-competitive *BRAF* inhibitor, in *BRAF*-mutated colorectal cancer was disappointing (4). *BRAF* mutations are rare in NSCLC, and the frequency of *BRAF*^{V600E} mutation in lung adenocarcinoma is only 1–2% (5–7). There were no studies of targeted *BRAF*-inhibitor therapy exclusively in patients with *BRAF*^{V600E}-positive NSCLC.

Recently, Planchard *et al.* reported the results of a prospective phase 2 trial that included only patients with *BRAF*^{V600E}-positive NSCLC (8,9). They recruited patients from 34 centers in ten countries, and 78 previously treated and six untreated patients with *BRAF*^{V600E}-positive NSCLC were enrolled in the first cohort of this trial. Patients received dabrafenib 150 mg twice daily until disease progression, unacceptable adverse events, withdrawal of consent, or death. The primary analyses of clinical activity were done in previously treated patients who received at least one dose of dabrafenib. Among the 78 previously treated patients who received at least one dose of dabrafenib, investigator-confirmed overall response was reported in 26 patients (33%; 95% CI, 23–45%), all of whom had partial responses. Investigator-assessed median duration of response and progression-free survival in those patients were 9.6 (95% CI, 5.4–15.2) and 5.5 (95% CI, 3.4–7.3) months, respectively. In this study, 29 patients

(37%) were never smokers and 49 (63%) were current or former smokers. Overall responses were observed in 15 (52%) of 29 never smokers and 11 (22%) of 49 smokers. Regarding safety profiles, the most frequent grade 3 or worse adverse event was cutaneous squamous-cell carcinoma in 10 (12%) of 84 patients, which was similar to a previously reported trial of dabrafenib monotherapy (2). In the second cohort of this trial, 59 patients with *BRAF*^{V600E}-positive NSCLC were enrolled. Patients received dabrafenib 150 mg twice daily, plus trametinib 2 mg once daily, until disease progression, unacceptable adverse events, withdrawal of consent, or death. The primary endpoint was investigator-assessed overall response. Among 57 eligible patients with previously treated *BRAF*^{V600E}-positive metastatic NSCLC, investigator-confirmed overall response was reported in 36 patients (63.2%; 95% CI, 49.3–75.6%), including 2 patients (4%) with complete response and 34 (60%) with partial response. Investigator-assessed median duration of response and progression-free survival in those patients were 9.0 (95% CI, 6.9–18.3) and 9.7 (95% CI, 6.9–19.6) months, respectively. Regarding safety profiles, the most frequent grade 3 or worse adverse event was neutropenia in five patients (9%). Cutaneous squamous-cell carcinoma was reported in two patients (4%).

The therapeutic efficacy of dabrafenib monotherapy for *BRAF*^{V600E}-positive NSCLC seems to be better than that of docetaxel monotherapy for unselected NSCLC, but it is not as promising as either EGFR TKIs for *EGFR* mutation-positive or ALK TKIs for *ALK*-rearranged NSCLC. As for safety, proper monitoring and treatment for secondary skin cancer is necessary. Combination therapy with dabrafenib and trametinib demonstrated more favorable overall response and progression-free survival, and reduced the risk of cutaneous squamous-cell carcinoma, in patients with *BRAF*^{V600E}-positive NSCLC compared with dabrafenib monotherapy, which was consistent with previously reported results in patients with *BRAF*^{V600E}-positive melanoma. Although these findings are based on results from a non-randomized study with a relatively small sample size, the overall response rate of 63.2% and median progression-free survival of 9.7 months are extremely impressive. These results will encourage further investigation of the dabrafenib and trametinib combination in the third cohort of the trial which will assess its use as a first line therapy in previously untreated patients with *BRAF*^{V600E}-positive NSCLC. In addition to the combination of *BRAF* and MEK inhibitors, studies of the combination of *BRAF* inhibitors with immune checkpoint inhibitors have been reported in patients

with melanoma (10,11). Active development of immune checkpoint inhibitors has contributed to improved overall survival in patient with NSCLC (12). Combination therapy with dabrafenib and immune checkpoint inhibitors will be investigated in patients with *BRAF*^{V600E}-positive NSCLC in the future.

Unfortunately, patients with *BRAF*^{V600E}-positive NSCLC develop disease progression after a median of 9.7 months on the combination of *BRAF* and MEK inhibitors, which is similar to that in patients with *EGFR* mutation-positive NSCLC on EGFR TKIs. The *EGFR* T790M mutation is the most common mechanism of drug resistance to first-generation EGFR TKIs. Rebiopsy to identify T790M mutation is increasingly important in patients with *EGFR* mutation-positive NSCLC, because third-generation EGFR TKI osimertinib has activity against *EGFR* T790M resistant mutation (13). In *BRAF* mutation-positive colorectal cancer, there is a report of the emergence of a *KRAS* G12C mutation, and an increase in mutant *BRAF*^{V600E} allele frequency, in the circulating tumor DNA of a patient at relapse from combined treatment with *BRAF* and MEK inhibitors (14). It is essential to explore the mechanism of drug resistance to *BRAF* and MEK inhibitors in patients with *BRAF*^{V600E}-positive NSCLC.

A variety of targetable gene alterations (e.g., *EGFR*, *ALK*, *ROS1*, *RET*, *BRAF*, *KRAS*, *MET*, *ERBB2*, *PIK3CA*, *AKT* and *NTRK1*) have been identified in NSCLC. However, most of them are found only in 1–5% of patients with NSCLC. Indeed, it would have been necessary to screen 6,000 patients to recruit 59 patients with *BRAF*^{V600E}-positive NSCLC to the study. For the successful development of molecular targeted therapy in patients with rare gene alterations, large scale screening systems are essential. A nationwide lung cancer genomic screening project for individualized medicine in Japan (LC-SCRUM-Japan) was established in February 2013. This project has successfully detected various targetable gene alterations in NSCLC, thereby contributing to the establishment of precision medicine in Japan (15). A worldwide lung cancer genomic screening project for individualized medicine is warranted.

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Footnote

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