Editorial

BRAF inhibitors in metastatic non-small cell lung cancer

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Lung cancer is the first cause of death by cancer in men and the second in women worldwide (1). This huge mortality is explained by the presence of advanced disease at diagnosis of lung cancer (78% of patients present locoregional and/or distant metastasis). Non-small cell lung cancer (NSCLC) represents up to 85% of all lung cancers (2), with a 5-year overall survival about 17% (3).

Standard therapy for patients with NSCLC includes platinum based chemotherapy, with a median overall survival (OS) of 10–14 months approximately (4,5). In the last decade, important advances in the molecular profile of NSCLC have helped for the discovery of genetic driver alterations and development of targeted therapies. As a consequence, these advances have changed the therapeutics landscape of NSCLC and have also improved the outcomes of these patients. The majority of these alterations occur in lung adenocarcinoma.

Lung adenocarcinoma is the most frequent subtype in NSCLC. It is defined by abnormal growth of peripheral glandular epithelial tissue. Lung adenocarcinoma is tremendously heterogeneous, with a high proportion of somatic mutations and genomic rearrangements. The Cancer Genome Atlas (TCGA) reported the molecular profiling of 230 resected lung adenocarcinomas and identified genetic mutations in several genes: *KRAS* (32.2%), *BRAF* (7.0%), *EGFR* (11.3%), *ERBB2* (1.7%), *ALK* fusion (1.3%), *MET* exon14 (4.3%), *RET* fusion (0.9%), *ROS1* fusion (1.7%) and others (6). Interestingly, almost 50% of patients with lung adenocarcinoma present a genomic alteration that could be druggable.

Drugs targeting genetic driver mutations in epidermal growth factor receptor (EGFR) and rearrangement in anaplastic lymphoma kinase (ALK) are approved for patients with EGFR mutation or ALK translocation. As a result, to test for those genetic alterations upfront is mandatory in stage IV non-squamous NSCLC. EGFR inhibitors, ALK inhibitors and ROS1 inhibitors have dramatically improved the outcomes of NSCLC patients with activating mutations in terms of response rate, progression free survival and OS compared with standard platinum based chemotherapy and with a better toxicity profile (7-10). Also patients with ROS1 translocation benefit most from ROS1 inhibitors (11). As a result, it has been largely demonstrated that targeting driver mutations in NSCLC offers better outcomes compared to standard chemotherapy.

Mutations in V-raf murine sarcoma viral oncogene homolog B (BRAF) are identified in 2–4% of lung adenocarcinomas (12). BRAF mutation results in activation of the MAPK pathway that promotes cell growth, proliferation and survival. The clinical features of patients with BRAF mutated NSCLC were published for the first time in 2011 (13). They analyzed the presence of BRAF mutation in 1,046 samples from patients that underwent radical surgery of primary NSCLC (739 adenocarcinomas and 307 squamous). BRAF mutation was detected in 37 tumors (3.5%), 36 in adenocarcinomas and 1 in squamous NSCLC. The 56.7% of BRAF mutation was V660E. The association of BRAF mutation with clinicopathological parameters was evaluated, and only sex (female) was statistically significant in the multivariable

Table 1 Efficacy results of the BRF113928 trial

Patient cohort	ORR (%)	DCR (%)	PFS (months)	OS (months)
Cohort A dabrafenib (84 patients)	33 (95% CI, 25–45)	58 (95% CI, 46–67)	5.5 (95% CI, 3.4–7.3)	12.7 (95% CI, 7.3–16.9)
Cohort B dabrafenib + trametinib (59 patients)	63.2 (95% CI, 49.5–75.6)	78.9 (95% CI, 66.1–88.6)	9.7 (95% CI, 6.9–19.6)	NR
Cohort C dabrafenib + trametinib (36 patients)	64 (95% CI, 46–79)	75 (95% CI, 58–88)	10.9 (95% CI, 7–16.6)	24.6 (95% CI, 12.3–NR)

ORR, overall response rate; DCR, disease control rate; PFS, progression free survival; OS, overall survival; CI, confidence interval; NR, not reported.

analysis. However, later studies have not confirmed this data (14,15), and currently there are no clinical features that can help to identify which patients with NSCLC may present a BRAF mutation (16).

Although some reports have correlated BRAF mutation in NSCLC with a poorer outcome and reduced efficacy of platinum doublets, the prognostic implication of BRAF V600E mutated NSCLC remains unclear (17). Additionally, BRAF mutation is one of the mechanisms of resistance to EGFR-TKI that has been reported in 1–2% of cases (18).

Some case reports and retrospective case series have shown efficacy with BRAF inhibitors in BRAF V600 mutated NSCLC (12). The activity of vemurafenib in BRAF V600 mutated NSCLC patients BRAF was tested in an early phase II "basket" trial with patients with BRAF V600 mutated non-melanoma solid tumors (19). Nineteen patients with NSCLC and BRAF V600 mutation received vemurafenib 960 mg twice daily. The overall response rate (ORR) was 42% [95% confidence interval (CI), 20–67%] with a disease control rate (DCR) of 84% and a median progression-free survival (PFS) of 7.3 months (95% CI, 3.5–10.8).

The BRF113928 is a phase 2, multicenter, non-randomized, open label trial enrolling patients with advanced BRAF V600E mutant NSCLC in three cohorts. In the cohort A, 84 patients with previously treated or untreated stage IV metastatic BRAF V600E mutant NSCLC received dabrafenib 150 mg twice daily (12). The ORR was 33% (95% CI, 25–45%), the DCR 58% (95% CI, 46–67) and the duration of response (DOR) 9.6 months (95% CI, 5.4–15.2). The median PFS was 5.5 months (95% CI, 3.4–7.3) and the median OS 12.7 months (95% CI, 7.3–16.9). Almost all patients experienced minimum one adverse event; the 54% of them were grade 2 or worse. The 12% of patients experienced cutaneous squamous cell carcinoma and the 4% basal-cell carcinoma. These results were in concordance of data previously seen in advanced melanoma.

In the cohort B, 59 patients with BRAF V660E mutant metastatic NSCLC were treated with the combination of dabrafenib 150 mg twice daily and trametinib 2 mg per day (16). The ORR was 63.2% (95% CI, 49.5–75.6%), the DCR was 78.9% (95% CI, 66.1–88.6%) and the median DOR 9 months (95% CI, 6.9–18.3). The combined treatment achieved a PFS of 9.7 months (95% CI, 6.9–19.6) and results for OS were immature when this cohort was published. The majority of patients (98%) presented at least one adverse event, and a grade 3 or greater was seen in the half of patients. The presence of cutaneous squamous cell carcinoma decreased to 4% with the combination of MEK inhibitor to BRAF inhibitor and to 2% for basal cell carcinoma. The most common grade 3 or greater adverse events were neutropenia (9%), hyponatremia (7%) and anemia (5%).

Results of the cohort C of BRF113928 trial with patients with untreated metastatic BRAF V600E mutant NSCLC have been recently published by Planchard and colleagues (20). In this cohort, 36 patients with a stage IV previously untreated advanced NSCLC with BRAF V600E mutation received dabrafenib 150 mg twice daily and trametinib 2 mg daily. The ORR was 64% (95% CI, 46–79%), the DCR 75% (95% CI, 58–88%) and the DOR 10.4 months (95% CI, 8.3–17.9). The median PFS was 10.9 months (95% CI, 7–16.6) and the median OS 24.6 months [95% CI, 12.3– not estimable]. Almost all patients presented an adverse event, being the most frequent grade 3–4 adverse events pyrexia (11%), aspartate aminotransferase increase (8%) and decrease in the ejection fraction (8%). *Table 1* summarizes the efficacy results of the

BRF113928 trial in each cohort.

It is important to underline that the phase II BRF113928 trial with dabrafenib plus trametinib has shown excellent results that were similar in treated and untreated patients, with an average ORR of 64% and a median PFS of 10 months. The safety profile of dabrafenib-trametinib in the BRF113928 trial was predictable and manageable, and comparable to that previously reported in melanoma clinical trials.

The frequency of BRAF V600E mutation in NSCLC is low. In the cohort C of BRF113928 trial, screening of 2,000–4,000 patients was estimated to find 36 patients with BRAF V600E mutation. As a consequence, to conduct a randomized clinical trial comparing dabrafenib plus trametinib with platinum based chemotherapy would be very difficult to recruit. Of note, there is previous evidence of a targeted therapy for a very uncommon mutation that was approved with the results of a phase 1 trial (11).

Additionally, previous data indicates that BRAF V600E mutant metastatic NSCLC might have poor prognosis and lower response to platinum-based chemotherapy (16) so the results obtained with dabrafenib plus trametinib become more important.

Based on the efficacy of dabrafenib plus trametinib in NSCLC patients with BRAF V600E mutation, this combination has been recently included in the most important guidelines. The American Society of Clinical Oncology (ASCO) guidelines recommends to treat with dabrafenib plus trametinib those patients with previously treated BRAF V600 mutant NSCLC (21) and the National Comprehensive Cancer Network (NCCN) guideline recommends to test for BRAF mutation in patients with metastatic non-squamous NSCLC and offer dabrafenib plus trametinib in first line o beyond if positive (22). On 2015, the US Food and Drug Administration granted Breakthrough Therapy Designation for the combination of dabrafenib and trametinib for the treatment of pretreated patients with BRAF V600E mutant NSCLC. On June 22, 2017, the US Food and Drug Administration granted regular approval to the combination for the treatment of BRAF V600E mutant NSCLC patients detected by an FDA-approved test.

In summary, despite the low frequency of BRAF V600E mutation in non-squamous NSCLC, and given the meaningful antitumor efficacy of dabrafenib and trametinib in NSCLC patients with BRAF V600 mutation, all non-squamous NSCLC should be tested for BRAF V600E mutation. No clinical characteristics can guide us to select which patients might harbor a BRAF V600E mutation. For those NSCLC patients with BRAF V600 mutation, treatment with dabrafenib and trametinib should be consider the best treatment of choice when BRAF V600E mutation is detected irrespective of previous treatment history. Finally, the use of a next generation techniques to test for several genetic alterations in a single test using tumor tissue is highly recommended to easily test for all druggable mutations in NSCLC.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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