Editorial

BRAF inhibitors in advanced BRAF-positive non-small cell lung cancer

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The importance of biological target-based studies is currently highlighted by impressive objective response rates (ORRs) and longer progression-free survivals (PFSs) provided by epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) compared with cytotoxic chemotherapies in the treatment of EGFR mutated non-small cell lung cancer (NSCLC) patients and, more recently, by anaplastic lymphoma kinase inhibitors (ALK-Is) in ALK-rearranged NSCLC ones (1-4). As a consequence, recent therapeutic research strategies in NSCLC, particularly in lung adenocarcinoma, focused on innovative potential molecular targets such as KRAS, BRAF, HER2, PIK3CA, and others in frequencies exceeding 1% (5).

Reports of lung cancers bearing *BRAF* gene mutations generated extensive interest since these alterations could potentially be associated with an increased sensitivity to those agents directly targeting BRAF or BRAF-mediated downstream signaling pathways (6).

BRAF (v-RAF murine sarcoma viral oncogene homolog B1) is a member of the RAF family of serine/threonine kinase which have roles in mediating proliferation and survival and lies downstream of RAS in the RAS-RAF-MEK-ERK signaling pathway: upon activation by RAS, BRAF phosphorylates a dual-specificity mitogen-activated protein kinase (MEK), this leads to the activation of an extracellular signal-regulated kinase (ERK) and finally ERK signaling pathway (7).

Mutations in BRAF are most commonly seen in melanoma (40% to 50% of cases) but they were also detected in 2–3% of lung adenocarcinomas (8). The most frequently observed mutation in BRAF is BRAF valine-to-glutamate amino acid substitution at codon 600 (V600E) which results in a constitutively active protein, since it no longer requires dimerization for its activity, it is transforming *in vitro* and stands for a driver mutation effectively targeted with selective BRAF and/or MEK inhibitors (9). BRAF-mutated melanomas harbor a V600E amino acid substitution in exon 15 in more than 80% of cases, but the actual prevalence, distribution, prognostic and predictive role of BRAF mutations and particularly $BRAF^{V600E}$ ones in patients with NSCLC is currently under investigation. According to Paik *et al*. the incidence of BRAF mutations in their series of lung adenocarcinomas was 3% [95% confidence interval (CI): 2% to 4%], similar to literature data, with a relative frequency of non-V600E mutations distributed in exons 11 and 15 in 39% and 11% of cases, respectively, while $BRAF^{V600E}$ mutations were reported in 50% of those patients (10). These data suggest that awareness about the exact type of *BRAF* mutation and the pathogenesis of such mutations could be critical in defining effective strategies for the targeted treatment of NSCLC with mutated BRAF. In fact, according to Cardarella *et al*., V600E, G469A, T599_V600insT, and V600_K601delinsE mutations showed increased BRAF kinase activity compared with wild-type BRAF; in contrast, the *G496del* mutation resulted in a reduced *in vitro* kinase activity (11).

In order to increase knowledge about this molecular subgroup of patients highlighting advances in therapeutic approach, the present editorial will discuss about *BRAF*

mutations, particularly BRAF^{V600E}-positive patients, and treatment with dabrafenib alone or in combination in the contest of the latest single-arm, multicentre, non-randomized, open-label, phase II trials conducted by Planchard *et al*. (12,13).

In the phase II study with dabrafenib alone, 84 previously treated (n=78) and untreated (n=6) patients with stage IV metastatic BRAF^{V600E}-positive NSCLC were enrolled, with the aim to investigate clinical activity and safety of dabrafenib in this specific setting. Of those patients 50% were females, 37% were never-smokers and 96% had adenocarcinoma histology (12).

BRAF mutations in lung cancer, as evidenced also by Planchard *et al*., are usually detected in adenocarcinoma histology and, according to previous reports, they were often recognized in smokers, although both V600E and non-V600E mutations were also identified in patients who had never smoked (8,11,12). The proportion of never and/or light smokers (≤10 pack-years) did not differ significantly according to *BRAF* mutation type (V600E or V600-like *vs*. other *BRAF* mutations) but Marchetti *et al*., in 37 of 1,046 screened lung cancers with a *BRAF* mutation, evidenced that all non-V600E mutations were detected in smokers, whereas BRAF^{V600E} mutation was significantly more frequent in never-smokers and in female patients (11,14). These data where described also by Planchard *et al*., suggesting that even if *BRAF* mutations were more frequently observed in smokers they could also be identified in patients irrespective of their smoking history, as opposed to *EGFR* mutations and ALK rearrangements, which are usually evidenced in patients with no-smoking history (12).

At present, considering the low amount of data, the prognostic significance of *BRAF* mutations in lung cancer is still uncertain even if the type of *BRAF* mutation seems to be a prognostic factor. About this issue, Marchetti *et al*. found that V600E mutation was a negative prognostic factor, significantly associated with shorter OS on multivariate analyses [hazard ratio (HR): 2.18; P=0.014); particularly, patients with BRAF^{V600E} mutations had shorter median disease free survival (DFS) and OS than patients without V600E mutations (15.2 *vs*. 52.1 months; P=0.001 and 29.3 *vs*. 72.4 months; P=0.001, respectively) (14).

Considering its predictive role, a strong correlation was observed between tumor initiation and expression/activation of MAPK pathway proteins, providing evidence that both tumor initiation and promotion were dependent on MAPK activation; conversely, suppression of BRAF^{V600E} expression led to tumor shrinkage, accompanied by dephosphorylation of ERK 1 and 2. These findings pointed the interest on the role of BRAF in cancer induction and promotion, also as a driver mutation and consequently as a potential therapeutic target (15).

Dabrafenib is a potent adenosine triphosphate (ATP)-competitive, reversible inhibitor of mutant BRAF kinase. It decreases phosphorylated ERK and causes cell cycle arrest (16). In preclinical studies it was almost 20 times more selective at inhibiting BRAF^{V600E} mutants than wild-type BRAF in multiple cancer cell lines and demonstrated activity in patients with NSCLC harboring BRAF^{V600E} mutation (16). However, despite the success of BRAF-directed treatment in cutaneous melanoma, only small numbers of NSCLC patients received a BRAF-directed therapy in prospective studies so far (16).

Planchard *et al*., in their study with dabrafenib alone, reported an overall response (OR) in 21 (33%; 95% CI: 22–46) with a disease control rate (DCR) in 34 patients (53%; 95% CI: 40–66), according to the independent review committee, and a median PFS of 5.5 months (95% CI: 3.4–7.3). Particularly, a post-hoc analysis of response based on detailed smoking history (Planchard *et al*. supplemental files) evidenced that 15 (52%) of 29 patients with no smoking history had a response rate, compared with 6 (24%) of 25 patients with a history of less than 30 pack-years and 5 (21%) of 24 patients with a history of 30 pack-years or more. However considering available literature data, it is still unclear if smoking habits have a predictive value or not in this particular population of patients (12).

Results from Planchard *et al*. study are encouraging steps towards validating the targeting of BRAF pathway in patients with lung adenocarcinoma harboring a BRAF^{V600E} mutation but, even considering response rates ranging around 60% in patients with melanoma treated with BRAF inhibitors, disease progression inevitably occurs (12,17,18). Several mechanisms of resistance to BRAF inhibitors were described in melanoma, such as activation of PIK3CA, new *BRAF* mutations, A-RAF and C-RAF increased expression (which can ultimately activate MAPK pathway downstream) and finally the activation of MAPK pathway at a downstream level (19,20).

A possible way to overcome resistance is blocking MAPK pathway downstream to BRAF. MEK inhibitors, such as trametinib which is an oral, reversible, highly selective allosteric inhibitor of MEK 1/2 activation, exert their inhibitory effect by targeting a different kinase located downstream at the same pathway (6,15). Blocking MAPK pathway at two different levels (BRAF in conjunction

with MEK) has the advantage of overcoming some of the resistance mechanisms observed with BRAF inhibitors alone (15).

BRAF and MEK inhibitors dabrafenib and trametinib, as a second line treatment, were tested by Planchard *et al*. in a prospective, single-arm, open-label, phase 2 study involving 57 NSCLC patients with $BRAF^{V600E}$ mutation, in order to improve efficacy over BRAF inhibitor monotherapy trough dual MAPK pathway inhibition (13). As already evidenced in melanoma patients harboring BRAF mutations, also in those with NSCLC, a double blockade increased response and DCR rates suggesting a delay in the development of tumor-resistance when compared to BRAF inhibitors alone. Particularly in Planchard *et al*. study on dabrafenib and trametinib combination, 36 of 57 patients achieved an OR of 63.2% (95% CI: 49.3–75.6); the independent review committee confirmed the investigator-assessed OR with a DCR in 43 patients (75.4%; 95% CI: 62.2–85.9) and a median PFS of 8.6 months (95% CI: 5.2–19.1) (13). Results of this study suggested that a combined approach could be preferable in BRAF-mutated NSCLC, just as it is in BRAF-mutated melanoma (21). Moreover MEK inhibition counterbalances the effect of BRAF inhibitors on keratinocytes, which is responsible for the secondary cutaneous tumors observed with these drugs. In fact in Planchard *et al*. study on dabrafenib alone, the development of cutaneous squamous-cell carcinomas (cuSCC) grade 3 was evidenced in 10 patients (12%), four cases had basal-cell carcinomas (5%) while one (1%) presented with lip squamous-cell carcinoma; the median time to development of cutaneous squamous-cell carcinoma was 13.1 weeks [interquartile range (IQR): 5.1–21.7], but none of these patients needed for a dose modification or interruption and any other squamous-cell carcinomas were evidenced in other organs. On the contrary, in Planchard *et al*. publication about dabrafenib and trametinib combination, a better cutaneous toxicity profile was evidenced considering that only two patients (4%) presented with basal cell carcinoma. This data confirmed that combination of MEK and BRAF inhibitors block a paradoxical activation of MAPK signaling in BRAF wild-type cells reducing the incidence of cuSCC compared with BRAF inhibitor monotherapy (1–3% *vs*. 9–18%) (12,13,22).

In addition to cutaneous toxicity, it is important to underline that both single agent treatment as well as combination therapy do have important, but manageable, toxicities in what remains a palliative situation. In BRAF inhibitor monotherapy study by Planchard *et al*., more than half of patients (45 of 84, 54%) had adverse events of grade 2 or worse. One patient died during the study from an intracranial hemorrhage judged to be related to the study drug. With dabrafenib and trametinib combination, Planchard *et al*. reported that nearly half of patients (28 of 57, 49%) had at least one grade 3–4 event. Dose reductions were needed for 33 patients (58%) who received at least 80% of the planned dose of dabrafenib, and 43 patients (75%) who received at least 80% of the planned dose of trametinib (12,13). Of potential concern were the cases of fatal hemorrhage (although anticoagulation was a risk factor in these cases) or haemoptysis which despite there being no strong signal of increased hemorrhagic risk in melanoma, is of particular importance in lung cancer and should be monitored closely in future trials (12,13,21).

If targeting multiple kinases at the same time is confirming to delay disease progression in this subgroup of patients, also alternative strategies are raising up to overcome BRAF inhibitors resistance, primarily in melanoma patients. LGX818 is a selective BRAF inhibitor which potently decreases ERK phosphorylation and inhibits proliferation in $BRAF^{V600E}$ mutant melanoma cell lines; it is currently under investigation in early phase trials, mostly in BRAF mutant melanoma patients (8,23). ARQ736 is a pan-RAF inhibitor, which targets A-RAF, B-RAF and C-RAF. It is has been studied in a phase I trial with the strategy of inhibiting all RAF kinases with a single drug to delay disease progression (8,24). Another compound, RAF265, a potent inhibitor of $BRAF^{V600E}$, wild-type-B-RAF, and C-RAF, is also under investigation on a phase II trial, after promising results demonstrated on the phase I trial (8,25). Finally another area of growing interest is immunotherapy: treatment targeting immune system check-points, such as CTLA-4 and PD-1, were designed to enhance host immune system, oppose tumor immune evasion and generate an effective immune response against tumor cells (15). As already evidenced in melanoma, the pro-apoptotic and cytotoxic effect evidenced after chemotherapy or targeted therapies, such as BRAF inhibitors, may expose intracellular antigens that were previously "hidden" by tumor immune evasion mechanisms (15). This leads to the exciting hypothesis of a synergistic effect: BRAF inhibitors, probably together with the events of immune response at different levels, may expose tumor antigens enhancing the efficacy of immune-checkpoint targeted therapies (15).

In conclusion, even if advances achieved in the comprehension of *BRAF* mutations and MAPK pathway, mostly in melanoma patients, are leading to an increased

knowledge in lung cancer research, it is still not clear if the results observed in melanoma can be undoubtedly translated into a therapeutic benefit for NSCLC patients. Previously described approaches have a role in lung cancer biology; although a better understanding of those mechanisms needs to be further investigated. For now, caution should be exercised in extrapolating definitive results from early-phase, single-arm studies without a comparator arm, but only with these trials intriguing hypothesis about new targeted agents or dual pathways blockade will emerge; the final aim is to optimize new sequencing strategies and stimulate research towards personalized therapy in NSCLC even warranting for additional investigation in future clinical trials.

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