

B-RAF mutation in non-small cell lung cancer: the sleeping beauty is waking up

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Non-small cell lung cancer (NSCLC) is still a big problem in oncology and unfortunately is the major responsible of cancer deaths worldwide (1). Increasing efforts have been made over the last two decades, allowing a more precise comprehension of the unique characteristics of this disease. The development of next-generation sequencing techniques has opened a new era of possibilities, owing to the identification of many mutations present in NSCLC, and the characterization of its genomic profile. The description of the epidermal growth factor receptor (EGFR) mutation, the demonstration of its involvement in carcinogenesis process and its posterior validation as a targetable mutation has established a new era of precision medicine and targeted-guided treatment in NSCLC following for the discovery of other druggable targets like ALK, ROS1 and recently c-MET among others (2-4).

B-RAF is one of the last sleeping beauty targets in NSCLC and it seems to be waking up. It's a serine-threonine kinase, part of the mitogen-activated protein kinase (MAPK) pathway, involved in cellular growth, proliferation and angiogenesis. B-RAF mutations are present in 2% to 4% of NSCLC, being almost exclusive of the adenocarcinoma histology (5). Most of the B-RAF mutations generate a constitutively activated kinase protein, culminating in permanent stimuli to cellular growth and proliferation through MAPK pathway activation. The involvement of B-RAF mutations and MAPK pathway activation in NSCLC carcinogenesis process has been demonstrated on pre-clinical studies (6).

Targeting MAPK pathway activation by blocking B-RAF mutant kinases is arising as a promising strategy. In melanoma, B-RAF mutation is present in 50% to 60%

of the patients, with V600 representing 90% of these mutations. The scenario is different in NSCLC, where 50% of the mutations are V600 (5). The B-RAF inhibitors Vemurafenib and Dabrafenib, approved for the treatment of melanoma harboring B-RAF mutations, have been developed as B-RAF V600 mutation selective inhibitors, with their effect on other B-RAF mutations being unknown (7,8). In a phase 2 trial involving 78 patients with NSCLC harboring B-raf mutations, Planchard *et al.* have obtained a 53% response rate with Dabrafenib (independent review) with a median duration of response of 9.9 months and a median PFS of 5.5 months (9). There is also successful confirmed activity with Vemurafenib, another B-RAF inhibitor, in NSCLC patients harboring B-RAF mutations with an ORR of 42% in a cohort of patients with NSCLC and also confirmed efficacy in cases reports (10,11).

In melanoma patients treated with B-RAF inhibitors, despite the response rates ranging around 60%, disease progression invariably occurs (7,8). The main mechanisms underlying tumor resistance are: activation of other pathways (PI3K, PDGF, IGF), new B-RAF mutations (making the inhibitor incapable of binding to its target on the protein), A-RAF and C-RAF increased expression (which can ultimately activate MAPK pathway downstream) (12,13). However, the most frequent mechanism of resistance is the activation of MAPK pathway at a downstream level, mitogen-activated or extracellular signal-regulated protein kinase (MEK) (14). The concomitant blockade of B-RAF and MEK (two kinases at the same pathway) has demonstrated to be safe and effective in melanoma patients, with a favorable toxicity profile and significant delay in the development of progressive disease (15). The combined use

Table 1 Drugs targeting B-RAF in NSCLC

Compound	Mechanism of action	Development in NSCLC	Efficacy results available
LGX818	Mutant B-RAF selective inhibitor	Phase 2 NCT02109653	This study has been withdrawn prior to enrollment
GDC0879 (18)	Mutant B-RAF selective inhibitor	Pre-clinical	–
Vemurafenib (11)	Mutant B-RAF selective inhibitor	Cohort 19 pts in non melanoma cancers	42% ORR
Dabrafenib (9)	Mutant B-RAF selective inhibitor	Phase 2	53% ORR
XL281 (19)	Mutant B-RAF selective inhibitor	Phase 1	43% clinical benefit in all solid tumors population
RAF265	Multi-kinase inhibitor	Phase 1 In combination with MEK162 in solid tumors NCT01352273	Completed no results
Dabrafenib + Trametinib (16)	Mutant B-RAF selective inhibitor and MEK inhibitor	Phase 2 Completed	63% response rate

NSCLC, non-small cell lung cancer; ORR, overall response rate.

of B-RAF and MEK inhibitors Dabrafenib and Trametinib as a second line treatment was tested in a phase II single arm trial involving 57 patients with B-RAF V600E mutant NSCLC, and its final results were presented at ASCO 2016: the overall response rate was 63% of the 52 evaluable patients, disease control rate was 79% at 12 weeks and the median PFS was 9.7 months at the time of analysis (16). The efficacy data on the combination of a B-RAF and a MEK inhibitor is promising, and dual blockade arises as a potential strategy to improve outcomes of NSCLC patients harboring B-RAF mutations. Interestingly in both Dabrafenib trials, monotherapy and in combination with MEK inhibitor, the majority of the patients were former or current smokers and most common histology was adenocarcinoma.

As alternative strategies to improve outcomes and overcoming resistance, new drugs are arising, with interesting mechanisms of action, the pan-RAF (A-RAF, B-RAF, and C-RAF) inhibitor ARQ736 is currently being studied on a phase 1 trial, with the strategy of inhibiting all RAF kinases with a single drug to delay disease progression (NCT01225536). Another compound, RAF265 (multi-kinase inhibitor, targeting B-RAF and RET) is also under investigation on a phase 2 trial, after promising results have been demonstrated on the phase 1 trial (17). Targeting multiple kinases at the same time may delay resistance to treatment by avoiding activation of parallel pathways (other than B-RAF) involved in cellular growth. *Table 1* comprises the data on compounds that target B-RAF in NSCLC.

Genomic profiling of NSCLC, by the identification

of mutations that drive tumor growth and are suitable to treatment, has established a new paradigm on thoracic oncology: the era of personalized medicine. B-RAF mutations are arising as interesting targets in NSCLC, given the encouraging pre-clinical and clinical trial results that have been published recently. Testing NSCLC samples for the presence of B-RAF mutations should be encouraged, as well as the inclusion of these patients on clinical trials with B-RAF inhibitors whenever possible. The future for B-RAF in NSCLC is promising, with improved outcomes being expected as results of inhibiting this target and as far we know, the combination with a MEK inhibitor seems to be more effective than the monotherapy. B-RAF mutation definitely emerges as an oncogene of unique interest in NSCLC, which will certainly become more relevant in a near future, being part of the era of individual-guided treatment in NSCLC.

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Footnote

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