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BRAF mutations in non-small cell lung cancer: has finally Janus opened the door?

Rafael Caparica[a,1], Gilberto de Castro Jr.[a,1], Ignacio Gil-Bazo[b], Christian Caglevic[e], Raffaele Calogero[f], Marco Giallombardo[g,h], Edgardo S. Santos[d], Luis E. Raez[c], Christian Rolfo[h,*]

[a] Instituto do Câncer do Estado de São Paulo, Faculdade de Medicina da USP, São Paulo, Brazil
[b] Oncology Department, Clínica Universidad de Navarra, Center for Applied Medical Research (CIMA), Pamplona, Spain
[c] Memorial Cancer Institute, Memorial Health Care System, Florida International University, Miami, FL, USA
[d] Lynn Cancer Institute, Thoracic and Head/Neck Cancer Programs, Florida Atlantic University, Boca Raton, FL, USA
[e] Oncology Department, Fundación Arturo Lopez Pérez, Santiago, Chile
[f] Department of Molecular Biotechnology and Health Sciences, University of Torino, Italy
[g] Biopathology and Medical Biotechnology Department, Biology section, University of Palermo, Italy
[h] Phase I – Early Clinical Trials Unit, Oncology Department, Antwerp University Hospital & Center for Oncological Research (CORE), Antwerp University, Belgium

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ABSTRACT

B-Raf mutations occur in about 1–2% of non-small cell lung cancers (NSCLC). These mutations generate a permanent activation of the mitogen activated protein kinase (MAPK) pathway, which promotes tumor growth and proliferation. In the present review, we discuss *B-Raf* mutation epidemiology, diagnostic methods to detect *B-Raf* mutations, the role of *B-Raf* as a driver mutation and a potential therapeutic target in NSCLC. The results of clinical trials involving *B-Raf* or MAPK pathway inhibitors for the treatment of NSCLC are also discussed. Clinical trials evaluating *B-Raf* inhibitors in BRAF mutated NSCLC patients have shown promising results, and larger prospective studies are warranted to validate these findings. Enrollment of these patients in clinical trials is an interesting strategy to offer a potentially more effective and less toxic targeted therapy.

* Corresponding author at: Head of Phase I– Early Clinical Trials Unit, Oncology Department & Center for Oncological Research (CORE), Antwerp University, Wilrijkstraat 10, 2650 Edegem, Belgium.
E-mail address: christian.rolfo@uza.be (C. Rolfo).
[1] Both authors collaborate equal.

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1. Introduction

The low survival rates observed in Non-Small cell lung cancer (NSCLC) patients occurs due to a dangerous association of late detection and limited efficacy of the available treatments (Jemal et al., 2009). The discovery of common oncogene drivers, such as epidermal growth factor receptor (EGFR) mutations, anaplastic lymphoma kinase fusion (EML-ALK) and proto-oncogene tyrosine-protein kinase ROS1 rearrangements, has led to the development of new accurate and efficient targeted therapies, radically improving the clinical outcomes of patients that harbor these mutations, opening the new era of targeted therapy in lung cancer (Solomon et al., 2014; Rosell et al., 2012).

Recently, through the development of the 'omics' sciences, genomic analysis has identified other potential targets in lung cancer treatment, including MET amplification and activating mutations in KRAS, HER2 and BRAF, among others (Cardarella and Johnson, 2013). Here, we describe the role of BRAF mutations in NSCLC, highlighting the attention on pre-clinical and clinical findings, BRAF inhibitors and immunotherapy in clinical development and on future perspectives.

2. BRAF mutations in NSCLC:

2.1. MAPK pathway overview

MAPK (mitogen activated protein kinase) pathway comprises several proteins with kinase domains involved in cellular growth and proliferation. After the extracellular binding of a growth factor (EGF, cKIT, FGF) to the respective tyrosine kinase transmembrane receptor, dimerization and auto-phosphorylation of these receptors occur, activating downstream the pathway through phosphorylation of RAS guanosine triphosphatases (GTPases): N-Ras, K-Ras, H-Ras. Other pathways, such as PI3 K/Akt/mTOR, are also activated in parallel.

The activation of Ras, through GTPases, leads to stimuli to the Raf serine-threonine kinases *A-Raf*, *B-Raf*, and *C-Raf*. Activated *A-Raf* and *C-Raf* are involved in several signaling pathways, whereas the exclusive targets of *B-Raf* are MEK-1 and MEK-2 kinases (mitogen-activated or extracellular signal-regulated protein kinase, or ERK). *B-Raf* phosphorylation leads to MEK and ERK activation. Activated ERK stimulates the transcription of genes involved in cell growth and proliferation, and apoptosis inhibition (Ji et al., 2007) (Fig. 1).

B-Raf mutations generate a constitutive activation of MAPK pathway, leading to constant stimuli to cell growth and proliferation, and resistance to negative modulatory feedback signals. In fact, *B-Raf* activating mutations are responsible for structural modifications at this protein, turning it into a permanent activated state, thereby generating continuous MEK and ERK activation. Not all *B-Raf* mutations promote MAPK pathway activation, with some mutations turning B-Raf kinase into an inactive or dysfunctional state. The most frequent activating *B-Raf* mutation is V600E, corresponding to a valine to glutamate substitution at codon 600, with 12.5 fold higher basal kinase activity in comparison to wild-type (*WT*) BRAF. Other mutations, such as V600 K, G469A, D469 V, D594G, V600 M have been described in NSCLC, although it is not known if all these mutations are actionable (Beeram et al., 2005). Some rare kinase-inactivating *B-Raf* mutations, like Y472C, have also been described in NSCLC (Sen et al., 2012).

Moreover, in preclinical models it has been described that MAPK and PI3 K/AKT/mTOR pathways may act together in order to overcome MAPK pathway inhibitors and induce oncogenic signals in several solid malignancies, suggesting that PI3 K/AKT/mTOR could be a pathway of resistance to the MAPK pathway inhibition for cancer therapy (Jokinen et al., 2012).

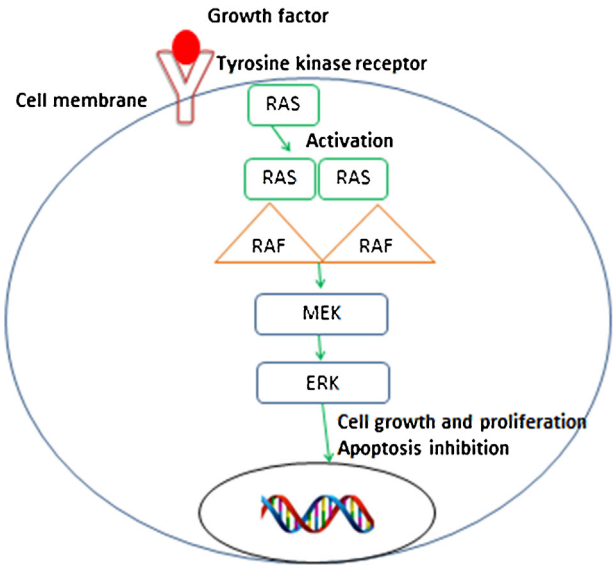

Fig. 1. MAPK pathway.

Table 1
BRAF mutations frequency in NSCLC (Data from Litvak, et al. (Davies et al., 2002)).

Mutation	Frequency in NSCLC
V600E	57%
G469A	22%
D469V	13%
D594G	6%
V600M	2%

2.2. Pre-clinical and clinical findings

B-Raf mutations have been identified in different cancers, such as melanoma (50–80%), colorectal (11%) and thyroid cancer (45%) (Davies et al., 2002; Domingo et al., 2004; Kebebew et al., 2007; Ziai and Hui, 2012). Regarding NSCLC, *B-Raf* mutations are detected in 1–2% of these patients, and they are more frequently observed in smokers, almost exclusive of the adenocarcinoma histologic subtype, and the presence of a *B-Raf* mutation virtually excludes other concomitant driver mutations, such as EGFR, *K-Ras* or EML4/ALK translocation (Chen et al., 2014; Litvak et al., 2014; Paik et al., 2011). In melanomas, the majority of *B-Raf* mutations occur at codon 600 (V600E and V600 K). However, in NSCLC approximately 50% of *B-Raf* mutations are V600 mutations, with the remaining cases harboring non-V600 mutations in exons 11 and 15 (Davies et al., 2002; Domingo et al., 2004). In a series with 63 patients, Litvak et al. identified five types of *B-Raf* mutations in NSCLC: V600E (57%), G469A (22%), D469 V (13%), D594 G (6%), and V600 M (2%) (Table 1) (Litvak et al., 2014).

In another series of 1046 NSCLC patients, Marchetti et al. had reported a prevalence of B-Raf mutations of 4.9% among adenocarcinomas, and 0.3%in squamous-cell carcinomas, with 56.8% of the mutations being V600E, and 43.2% non-V600E (Wan et al., 2004). In this study, the V600E mutation was significantly associated with unfavorable prognosis on multivariate analyses (HR for death: 2.18; P = .014). The fact that around 50% of BRAF mutations on NSCLC are non-V600 has direct therapeutic implications, since non-V600 mutant *B-Raf* kinases are resistant to *B-Raf* inhibitors, but they may be sensitive to MEK inhibitors, which block the pathway at a downstream level (Litvak et al., 2014; Wan et al., 2004).

The prognostic significance of *B-Raf* mutations is uncertain. At least two series have reported similar overall survival and outcomes for patients harboring *B-Raf* mutations in comparison to