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

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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.

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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 Rafserine-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 (Xi 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, G469 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).

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; Zhai 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; Paiak 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...
patients without this mutation (Chen et al., 2014; Litvak et al., 2014). However, the type of B-Raf mutation seems to be a prognostic factor. Litvak, et al. observed that among patients with advanced stage NSCLC harboring B-Raf mutations, those with V600 mutations had a longer 3-year overall survival rate compared with patients with non-V600 mutations (24% versus 0%; $p < 0.001$) (Litvak et al., 2014). On the contrary, the study published by Marchetti et al. involving 1046 patients (37 harboring B-Raf mutations) found the V600E mutation as a negative prognostic factor, significantly associated with shorter overall survival on multivariate analyses (HR for death: 2.18; P = 0.014) (Marchetti et al., 2011).

B-Raf mutation does not seem to predict different response rates to chemotherapy. Paik, et al. observed a 40% response rate to chemotherapy among 10 NSCLC patients harboring B-Raf mutation, similar from those observed at contemporary phase III trials evaluating chemotherapy (Paik et al., 2011; Schiller et al., 2002).

Experimental studies with mice harboring a knock-in allele of B-Raf mutant kinase revealed that Braf V600E was able to induce cell transformation and proliferation (Mercey et al., 2005). Hongbin et al. developed a BRF V600E mutant mice lineage, which presented lung adenocarcinomas, histologically resembling human adenocarcinomas (Jemal et al., 2009). 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 B-Raf V600E expression led to tumor shrinkage, accompanied by dephosphorylation of ERK 1 and 2. These findings bring forth the interest about the role of B-Raf in cancer induction and promotion, and also as a driver mutation, being a potential therapeutic target (Jemal et al., 2009).

3. B-Raf inhibitors

3.1. B-Raf mutation detection

Several techniques have been investigated for the detection of B-Raf mutations. Sanger sequencing consists of polymerase chain reaction (PCR) amplification of the DNA/R region of interest, limited by dideoxynucleotide end termination, followed by sequence reading. This technique has analytical sensitivity of 10–20% (Su et al., 2012; Lee et al., 2010; Morandi et al., 2012). The Cobas® is another available method, based on real time PCR, with DNA probes designed specifically to detect V600 mutations: V600E, V600K, and V600D. The main disadvantage of this method is not being capable of detecting mutations other than V600. Newer techniques, such as next generation sequencing (NGS), provide a faster and more effective way of sequencing DNA from biopsy samples (Jo et al., 2009). NGS has the advantage of providing information about other Braf mutation variants (non-V600). Since this technique decodes all DNA bases from a pre-determined genome region, it detects unusual or even unknown B-Raf mutations, unlike Cobas®. Although the costs involved in NGS have been decreasing over the last years, a potential limitation for this method is that it is not widely available, especially in developing countries. Also, NGS may detect rare or even new B-Raf mutations, which have unknown clinical significance. Now these and other new technologies are under development, with the perspective of detecting this and other mutations in blood and urine in the near future (Vibat et al., 2015).

3.2. First and second-generation B-Raf inhibitors

One of the first Braf inhibitors, sorafenib was developed as a targeted therapy against Braf mutant kinase. This drug failed to demonstrate activity in melanoma patients harboring Braf mutations, although positive results were observed in renal cell carcinoma and hepatocellular carcinoma (Llovet et al., 2008; Escudier et al., 2007). In fact, sorafenib was found to be a multi-targeted kinase inhibitor, which targets VEGFR, PDGFR, FGFR and other pathways. Its anti-angiogenic effect is the potential mechanism of action in renal cell carcinoma and hepatocellular carcinoma (Kudo and Ueshima, 2010; Stennert et al., 2012; Wu and Zhu, 2011).

Dabrafenib and vemurafenib are second-generation ATP-competitive inhibitors of BRAF kinase, developed to selectively target V600E mutants. As previously mentioned, B-Raf mutation prevalence in melanomas is between 40 and 60%, with V600E and V600K representing more than 90% of these mutations (Chapman et al., 2011). Both vemurafenib and dabrafenib have demonstrated efficacy results in trials involving metastatic melanoma patients harboring B-Raf mutations, with response rates ranging from 48 to 59% (Chapman et al., 2011; Hauschild et al., 2013). The scenario is different in NSCLC, where non-V600E mutations, such as G469A and D594G, represent about 40–50% of B-Raf mutations (Davies et al., 2002; Domingo et al., 2004). The activity of dabrafenib and vemurafenib against these mutations is unknown but recently, were well evaluated the effects of vemurafenib in multiple non-melanoma cancers with BRAF V600E mutations, including NSCLC (Hyman et al., 2015).

The use of MEK inhibitors concomitantly with BRAF inhibitors improved response and survival rates in melanoma patients harboring B-Raf mutations (Larkin et al., 2014; Long et al., 2014). As 40–50% of B-Raf mutations in lung cancer are non-V600, MEK inhibitors, which block MAPK pathway downstream to BRAF, may be active against non-V600 BRAF mutated tumors, as demonstrated in pre-clinical data (Jemal et al., 2009).

In a phase 2 trial with 17 BRAF V600E NSCLC patients who had progressed after being exposed to, at least, one line of chemotherapy, Planchard et al. demonstrated a 54% response rate with dabrafenib (Planchard et al., 2013). Case reports have also demonstrated the activity of vemurafenib in NSCLC patients harboring BRAF V600E mutations (Gautschi et al., 2012; Peters et al., 2013).

The most compelling data about toxicity of vemurafenib and dabrafenib comes from melanoma trials. Most frequent side effects observed with both drugs are fatigue, rash and nausea. Pyrexia (24–31%) and hyperglycemia (1–8%) are more frequent with dabrafenib, while arthralgias (53–68%) and photosensitivity reactions (33–53%) are more common with vemurafenib (Chapman et al., 2011; Hauschild et al., 2013). These are usually mild to moderate, manageable with symptomatic medications and dose reductions.

Another side effect observed with both drugs is the development of new cutaneous tumors, such as basal cell carcinoma (2%), squamous cell carcinoma (6–19%), and new melanomas (1–2%) (Chapman et al., 2011; Hauschild et al., 2013). Hypothetically, BRAF inhibitors exert a paradoxical activating effect over WT BRAF in keratinocytes, leading to cell proliferation and apoptosis inhibition (Su et al., 2012). Concomitant use of MEK and B-Raf inhibitors reduced dramatically the incidence of second cutaneous tumors in melanoma patients, by blocking MAPK pathway in a target downstream than B-Raf (Larkin et al., 2014; Long et al., 2014) (Fig. 2).

Interestingly, it has been Fig. 3 demonstrated that vemurafenib is a potent radiosensitizer, leading to an increase of skin and mucosal toxicity when used in combination with radiotherapy (Merten et al., 2014).

3.3. New drugs in clinical development

Ongoing clinical trials are evaluating new BRAF inhibitors (Table 1). LGX818, a mutant RAF kinase inhibitor, demonstrated no inhibitory effect on WT B-Raf cell lines, and also showed activity in
Fig. 2. By binding to BRAF or MEK, tyrosine kinase inhibitors generate a blockade point in MAPK pathway, eliminating the constant stimuli to cell growth and apoptosis inhibition caused by mutant RAF.

Fig. 3. Mechanisms of tumor cells resistance to BRAF inhibition: 1. RAS mutations, activating MAPK pathway independently of the mutant BRAF. 2. ARAF or CRAF overexpression. 3. Acquired new BRAF mutations, avoiding BRAF inhibitors to bind its site. 4. MEK mutations, activating MAPK downstream. 5. Parallel pathways, like COT, activating MAPK downstream. 6. Activation of alternative pathways involved in cell growth and proliferation, like PI3K, PDGF and IGF.

Table 2

<table>
<thead>
<tr>
<th>BRAF inhibitor</th>
<th>Phase of development</th>
<th>Mechanism of action</th>
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<tbody>
<tr>
<td>LGX818</td>
<td>Phase 1 trial currently recruiting patients (Wu and Zhu, 2011)</td>
<td>Mutant BRAF selective inhibitor</td>
</tr>
<tr>
<td>ARQ736</td>
<td>Phase 1 trial currently recruiting patients (Chapman et al., 2011; Hauschild et al., 2013)</td>
<td>Pan-RAF inhibitor</td>
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<tr>
<td>RAF265</td>
<td>Phase 1 trial presented in 2011; Phase 2 trial currently recruiting patients (Hyman et al., 2015; Larkin et al., 2014)</td>
<td>Multi-kinase inhibitor (BRAF, RET)</td>
</tr>
<tr>
<td>GDC0879</td>
<td>Pre-clinical data (Long et al., 2014)</td>
<td>Mutant BRAF selective inhibitor</td>
</tr>
<tr>
<td>XL281</td>
<td>Phase 1 trial presented in 2009 (Planchard et al., 2013)</td>
<td>Mutant BRAF selective inhibitor</td>
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reducing pMEK and blocking MAPK pathways activation in B-Raf V600E melanoma xenograft models (Stuart et al., 2012). LGX818 has proven in vitro to be a selective B-Raf inhibitor, only targeting mutated B-Raf kinase. Theoretically, this may reduce the incidence of side effects observed with previous B-Raf inhibitors, especially new cutaneous tumors, which have been associated to WT B-Raf activation in keratinocytes (Su et al., 2012). A phase I/II trial is currently recruiting colorectal and melanoma cancer patients to receive LGX818 (NCT01436656).

ARQ736 is a pan-RAF inhibitor, which targets A-Raf, B-Raf and C-Raf. The presumed advantage of the pan-RAF inhibitors is their effect on A-Raf and C-Raf, different than B-Raf selective inhibitors.
Although there is little evidence that these kinases are mutated in NSCLC, A-Raf and C-Raf may be a part of parallel pathways activating MAPK, PI3 K and Cancer osaka thyroid (COT) kinases pathways downstream, generating cell resistance to B-Raf inhibitors (Caronia et al., 2011; Yu et al., 2010). A phase I trial is ongoing to test this new compound (NCT01225536).

RAF265, a multi-kinase inhibitor which targets mutant B-Raf, RET and VEGFR2, has demonstrated an inhibitory effect on MAPK pathway in thyroid cancer cells (Jin et al., 2011). RAF265 may delay the development of tumor resistance to B-Raf inhibition and also have an increased anti-proliferative effect by blocking other driver pathways, such as VEGFR2 and RET. A phase I dose-escalation trial shown promising results, and phase II trials results are eagerly awaited (Sharifman et al., 2011).

GDC0879, a highly selective Raf inhibitor, was tested in mice harboring B-Raf mutant tumors, and consistently inhibited the activation of MAPK pathway, assessed through levels of p-MEK and p-ERK. Moreover, administration of GDC0879 significantly improved survival rates of mice harboring B-Raf mutant tumors in comparison with a control group of mice harboring Ras mutations (Hoelfich et al., 2009). GDC0879 inhibitory effect was strictly associated with V600E B-Raf mutations, which may limit its use for NSCLC, where V600E comprises only a minority of the B-Raf mutations.

In a phase I dose-escalation trial with XL281 (a selective BRAF-inhibitor), 30 patients with solid tumors (including NSCLC) harboring Ras and Raf mutations were included (Schwartz et al., 2009). Promising results were observed: 43% of the patients achieved clinical benefit (partial response or stable disease) and one patient had a complete response. Four patients were submitted to a re-biopsy, after treatment with XL281. These patients presented decreased expression levels of Ki-67 and p-MEK and p-ERK, corroborating the inhibitory effect exerted by XL281 over MAPK pathway and cell proliferation. Data about new B-Raf inhibitors under development is summarized in Table 2.

4. Perspectives: scenario for the next 5 years

4.1. Overcoming resistance

Several mechanisms of resistance to B-Raf inhibitors have been described in melanoma, such as activation of PI3 K and COT pathways, and N-Ras mutations (Villanueva et al., 2010; Nazarian et al., 2010; Johannessen et al., 2010). By activating parallel pathways involved in cell growth, cancer cells are able to overcome the blockade at MAPK pathway. Moreover, regarding to NSCLC, 40–50% of the B-Raf mutations are non-V600. As vemurafenib and dabrafenib specifically target V600 mutations, a significant proportion of NSCLC patients with B-Raf mutations (non-V600) may be insensitive to these drugs.

A possible way to overcome resistance is blocking MAPK pathway downstream to B-Raf. MEK inhibitors, such as trametinib, cobimetinib and selumetinib exert their inhibitory effect by targeting a different kinase located downstream at the same pathway. Trametinib increased response and overall survival rates when compared to chemotherapy in melanoma patients harboring B-Raf mutations (Flaherty et al., 2012). As MEK inhibitors theoretically can be effective in patients harboring B-Raf non-V600 mutations, this may be an interesting therapeutic option for NSCLC patients harboring non-V600 BRAF mutations.

Blocking MAPK pathway at two different levels (B-Raf + MEK) has the advantage of overcoming some of the resistance mechanisms observed with B-Raf inhibitors. Moreover, MEK inhibition counterbalances the effect that B-Raf inhibitors do exert on WT B-Raf keratinocytes, which is responsible for the secondary cutaneous tumors observed with these drugs. Dual blockade increased response and survival rates when compared to B-Raf inhibitors alone in melanoma patients harboring B-Raf mutations (Larkin et al., 2014; Long et al., 2014). More interestingly, patients receiving dual-blockade did not reach the median duration of response, confirming the hypothesis that dual blockade delays the development of tumor-resistance when compared to B-Raf inhibitors alone. Also, dual blockade was associated with less secondary cutaneous tumors (Larkin et al., 2014; Long et al., 2014).

The combination of B-Raf and MEK inhibitors dabrafenib + trametinib is under study in a phase II single arm trial involving 33 patients with B-Raf V600E mutant NSCLC who had failed to at least one line of chemotherapy (NCT01336634). The preliminary results were presented at ASCO 2015, overall response rate was 63%, and 88% of patients achieved disease control; 39% of the patients developed grade 3 or higher adverse events, the most common being hyponatremia (6%), dehydration (6%), neutropenia (6%) and pyrexia (18%) (Planchard et al., 2015). The efficacy data of the combination is promising, with higher response rates than those observed with single-agent B-Raf inhibitors. Dual blockade arises as a promising strategy for the treatment of mutant B-Raf NSCLC. Nonetheless, more clinical trials are necessary to confirm these results.

Moreover, a double-blind randomized phase III clinical trial, which compared a double treatment (dabrafenib plus trametinib) with dabrafenib monotherapy in metastatic melanoma patients has shown differences on adverse events/effects, such as decrease of malignant and skin lesions during this drug combination compared with dabrafenib alone treatment, with a incidence of 2 and 9%, respectively (Long et al., 2014).

Other strategies to overcome B-Raf inhibitors resistance are being evaluated in melanoma, such as the use of PI3 K inhibitors after dual-blockade progression and pan-Raf inhibitors, which were mentioned previously in this manuscript. These therapies may have a role in overcoming B-Raf inhibitors resistance in NSCLC, although better understanding of the mechanisms involved in B-Raf inhibitors resistance specifically for NSCLC is necessary. The advances achieved in the comprehension of MAPK pathway and B-Raf mutations over the last years derive mostly from melanoma studies since B-Raf mutations are more frequent in this population. Although this leads to increased knowledge about therapies targeting MAPK pathway, it is not known if the results observed in melanoma can be translated into therapeutic benefit for NSCLC patients.

4.2. BRAF inhibitors and immunotherapy

Another area of growing interest is immunotherapy in NSCLC. Therapies that target immune system check-points, such as CTLA-4 and PD-1, were designed to enhance host's immune system, oppose tumor immune evasion and generate an effective immune response against tumor cells. CTLA-4 is a transmembrane receptor expressed on T-cells that exerts an inhibitory effect over T-cell stimulation and activation (Parry et al., 2005). Ipilimumab is an anti-CTLA-4 fully human monoclonal antibody. By targeting CTLA-4, ipilimumab activates T-cells, leading to a more effective immune response against tumor cells.

In phase II trial published by Lynch et al., 204 NSCLC patients were randomly assigned 1:1:1 to receive first-line treatment with paclitaxel (175 mg/m²) and carboplatin (area under the curve, 6) with either placebo, or ipilimumab in one of the following regimens: concurrent (four doses of ipilimumab plus chemotherapy followed by two doses of placebo plus chemotherapy) or phased ipilimumab (two doses of placebo plus chemotherapy followed by four doses of ipilimumab plus chemotherapy). The phased ipilimumab arm demonstrated and improvement in progression-free-survival (accessed by immune-RECIST criteria) compared to
chemotherapy: 5.7 versus 4.6 months (HR, 0.72; P = 0.5) (Lynch et al., 2012). A phase III trial is currently ongoing to further access the role on ipilimumab for NSCLC. (NCT01285609)

PD-1 is a membrane receptor present on T lymphocytes. When activated by its ligands, PDL-1 and PDL-2, PD-1 exerts an inhibitory effect over T-cells (Parry et al., 2005). PD-1/PDL-1 pathway is also involved in tumor evasion and immune tolerance. Many agents are currently under development to target this pathway. Nivolumab, and pembrolizumab are monoclonal antibodies that target PD-1. By blocking the receptor and thus avoiding the negative feedback over T-cells, these drugs enhance host immune response. In a phase I trial with 129 advanced NSCLC patients, nivolumab has demonstrated and overall response rate of 17.2%, and the median duration of response was 18.5 months (Brahmer et al., 2013). These results are encouraging, especially because of the long-term responses observed among heavily pre-treated patients (Brahmer et al., 2012).

Phase III trials have demonstrated the efficacy of anti-PD1 compounds in the second line treatment of NSCLC, with overall survival improvements in comparison to Docetaxel for nivolumab and pembrolizumab, both for squamous and non-squamous NSCLC (Brahmer et al., 2015; Hossein et al., 2015; Herbst et al., 2015).

The pro-apoptotic and cytotoxic effect observed after chemotherapy and targeted therapies, such as B-Raf inhibitors, may expose intracellular antigens that were previously “hidden” by tumor immune evasion mechanisms. This leads to the interesting hypothesis of a synergistic effect: B-Raf inhibitors, probably together with the events of immune response at different levels, may expose tumor antigens through their pro-apoptotic and cytotoxic effects, enhancing the efficacy of immune-checkpoint targeted therapies. This hypothesis warrants further investigation in future clinical trials.

5. Conclusions

B-Raf mutations are involved in cancer induction and proliferation, and as driver mutations, represent a potential therapeutic target for NSCLC. Although B-Raf inhibitors have proven to be effective in melanoma, the role of these medications for the treatment of NSCLC is still investigational. Phase I and II clinical trials have shown encouraging results that need to be confirmed in larger studies. Since non-V600 mutations are more common in NSCLC than melanoma, the use of MEK inhibitors and dual MAPK pathway blockade (BRAF + MEK) arises as promising strategies, warranting further investigation.

As the interest on immunotherapy in NSCLC evolves, the potential synergistic effect between B-Raf and immune check-point inhibitors emerges as an interesting hypothesis to be investigated. As the access to NGS and other diagnostic methods increases, testing biopsy samples for B-Raf and other driver mutations is essential. Enrolment of NSCLC patients harboring B-Raf mutations in clinical trials involving targeted therapies is encouraged, in order to improve medical knowledge about these rare mutations, and also to offer potentially more effective and less toxic targeted therapies.

Conflict of interest

Edgardo S. Santos:
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sion for accreditation in Medical Oncology. Current Secretary of the Chilean Society of Medical Oncology. Leader of the Oncogeriatrics Society in Chile (under creation).

Member of ASCO, ESMO, IBOIG, Grupo Latinoamericano in Gastrointestinal tumors, SIoG, Sociedad Médica de Chile.

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Current Member of Multidisciplinary Cancer Management Course of ASCO. Director of MCMC(ASCO) held in Latinamerica. Board Member of Ecancer Medicine Science. Current Reviewer of oncology articles for Oncotarget, Ecancer Medical Science, and Revista Medica de Chile.

Director of the Latinamerican Symposium of Gastroenterological Cancer (SLAGO). Scientific Director of Latinamerican Pancreas Cancer Consensus held in Chile in 2015. Delegate of the Colegio Médico de Chile at Chilean Commission for accreditation in Medical Oncology. Current Secretary of the Chilean Society of Medical Oncology. Leader of the Oncogeriatrics Society in Chile (under creation). Member of ASCO, ESMO, IBOIG, Grupo Latinoamericano in Gastrointestinal tumors, SIoG, Sociedad Médica de Chile.

Maiaela Calogero got the degree in Biological Sciences in 1979. After a period spent at Max Plank Institute for Molekulare Genetics (Berlin, DE), in 1987, she moved back to Italy as researcher at SARIN Biomedica (I). Then in 1992 she became associated professor of Molecular Biology at University of Naples, where he set up a bioinformatics lab devoted to the analysis and data mining of microarrays. In 1998 he moved to University of Turin, where he consolidated his bioinformatics group (Bioinformatics & Genomics unit – B&Gu). The focus of B&Gu is the use of high-throughput OMICS technologies to identify biomarkers and to understand the molecular basis of cancer and multifactorial diseases.

Marco Galliambardo He has a bachelor degree in Biotecnology and a master degree in Medical Biotecnology and Molecular Medicine at the University of Palermo. He is currently an international joint PhD student in Oncology and Experimental Surgery at University of Palermo (Italy) jointed with the course in Medical Sciences of University of Antwerp (Belgium). The field of investigation of him the s is focused on exosomes released from chronic myeloid leukemia cells in the cross-talk with the tumor microenvironment.

Edgardo S. Santos Dr. Santos is the Medical Director of Cancer Research at the Lynn Cancer Institute in Boca Raton, Florida. He earned his M.D. in 1994 at the University of Panama, School of Medicine, Republic of Panama. Dr. Santos completed his internship and residency training in Internal Medicine at Jackson Memorial Medi cal Center, University of Miami School of Medicine, Miami, Florida. Then, he went on to complete his fellowship in Hematology/Oncology at the Sylvester Comprehensive Cancer Center, Miami, Florida. Dr. Santos is a former faculty member of University of Miami Miller School of Medicine, Miami, Florida where he hold an academic rank as an Associate Professor of Medicine (2008-2012) and Tulane University Health Sciences Center, New Orleans, Louisiana (2004-2008). He also was the Tulane University Principal Investigator at Southwest Oncology Group (SWOG), Associate Scientific Director of Tulane Cancer Center’s Office of Clinical Research, Associate Director of the Fellowship Programs (Tulane University and University of Miami), Chief of the Hematology/Oncology Section at the Southeast Louisiana Veterans Healthcare System, Chair of the Committee Research Advisory Board, Co-Leader of Clinical Research for the Louisiana Cancer Research Consortium, Co-Leader of the Head and Neck Cancer Program at Sylvester Cancer Center, and many others. He is an active member of the IASLC, AACR, ASCO, ESMO, ASH, ACP-ABIM, ALCCM, ECOG, ACCC, FLASCO among other organizations. Dr. Santos has authored or co-authored several manuscripts in peer-reviewed journals and also serves as reviewer for several scientific publications. Dr. Santos is a member of the Editorial Board of Expert Review series, Recent Patents on Biomarkers, and Clinical Practice. Dr. Santos has been the Founder/Chairman/Organizer/Director of the New Orleans Summer Cancer Meeting (NOSCM) since 2005, Co-Chair of Puerto Rico Fall Cancer Symposium (FCS) since 2010, and Co-Chair of Miami Cancer Meeting (MCM) starting in 2016. He has been appointed as Chair of the 2016 IASLC-Latin American Lung Cancer Congress (IALCA). Dr. Santos’ main interests are the conduction and development of early phases of clinical trials.

Luis E. Raez MD, FACP, FCCP is the Medical Director of Memorial Cancer Institute (MCI), he is also the Oncology Research Director of Memorial Health Care System (MHCS) and Director of the Thoracic Oncology Program. He is also Clinical Associate Professor of Medicine at Florida International University (FIU) and Visiting Professor of Medicine at Cayetano Heredia University in Peru. He was an Associate Professor of Medicine, Epidemiology and Public Health, and a Co-Director of Thoracic Oncology at Sylvester Cancer Center/University of Miami for 10 years (2001-2011). He has expertise in medical oncology in the areas of lung cancer, and head and neck cancer. He designs phase I-III clinical trials with new chemotherapeutic agents and combinations. Dr. Raez does translational research in the areas of cancer vaccines. He has been funded by NCI and the Pharma industry. He has given oral presentations and lectures in national and international meetings in the US, Europe, Latin America and Asia. He has been the International Chair of the 2014 IASLC-Latin-American Meeting (IALCA); Chairman for the Miami Best of ASCO 2014, Chair and Founder of the Miami Cancer Meeting (MCM) since 2002, Co-Chairman at the Puerto Rico Fall Cancer Symposia (FCS) since 2010. He is American Board Certified in Internal Medicine, Medical Oncology and Geriatric Medicine. He is board eligible in Hematology. He is a member of AACR, ESMO, ASCO, IASLC, ALLIANCE, NCTG, ACCP, ACP, ACG, FLASCO among other institutions.

Christian D. Rolfo MD, PhD, MBHA He was born in Córdoba, Argentina in 1972; studied at the National University of Córdoba, graduating from medical school in 1996. In 1998 he began his studies at the University of Milan, Italy. He got a scholarship for a project in Breast Cancer with the prestigious Dr. Luca Gianni, in one of the European reference centers for cancer, the National Cancer Institute of Milan. With him, he worked for more than six years, dealing with Breast Cancer, Head and Neck Tumors, Sarcomas and Rare Tumors. He trained with Drs. Lisa Licirata and Paolo Casali, international experts from both areas. During this period he dealt with cancer and Phase I Research Protocols, under the direction of Prof. Gianni. Obtained the European Oncology Board certification in 2003 with a thesis based on a Phase I trial with the combination of a new taxane and doxorubicin in Breast Cancer. Dr. Rolfo is also a Doctor of Medicine and Surgery at the University of Catania, Italy, with a thesis based on a Phase Ib trial and pharmokinetics of BMS 184476 and anthracyclines in solid tumors. In 2004 he moved to Palma de Mallorca, Spain, where he worked at the Oncology Unit of the Clinica Rotger until September 2012. It is here where he began his work in the Spanish Group for Lung Cancer, under the direction of Prof. Rafael Rosell. Actively involved in studies of molecular biology and clinical research in lung cancer. In 2009 obtained the PhD degree and Doctor Europaeus in Clinical and Experimental Oncology Research with cum laude from the University of Palermo, Italy, for the thesis: Relationship Between metabolic activity (SUV max) by 18-FDG PET and Histology, stage, EGFR mutations and survival in Patients with NSCLC, under the direction of Prof. Antonio Russo and Prof. Rafael Rosell. From October 2012 is Senior Staff Member in the Department of Oncology as Associate Professor at the University Hospital Antwerp, Antwerp University in Belgium, headed by Prof. Marc Peeters. Currently he is Head of Phase I – Early Clinical Trials Unit, Director of Clinical Trials Management Program as well. He is focus on Clinical Research, Drug Development and Resistance. He is actively working in a research program of Liquid Biopsies in Lung Cancer, specifically in exosomes isolation and circulating tumor DNA. He completed his training in organization of Phase I program at MD Anderson, Texas, USA with Prof. David Hong. Dr. Rolfo is the author of numerous papers published in various journals including New England Journal of Medicine, Translational Oncology, Journal of Thoracic Oncology, among others. It is also a speaker at national and international forums Lung Cancer. Dr. Rolfo is part of the working group of the ETOP mesothelioma (European Platform Thoracic Oncology), led by Prof. Rolf Stahel. He is also the member of the membership Board of IALSC (International Association for the Study of Lung Cancer). He is member of prestigious Societies including AACR, EACR, EACS, and ASCO and board member of Drug Development Group for ESMO from 2015. Prof. Rolfo also obtained the Master degree in Business Health Administration by Polytechnic University of Valencia, Spain in 2010. He was appointed in February 2011 as visiting professor in Medical Oncology by the Molecular and Clinical Genetic Oncology Unit at the Interdepartmental Center of Research in Clinical Oncology, School of Medicine, University of Palermo (Italy). In addition, he has teaching duties at the University of the Balearic Islands. From 2014, he is Guest Professor at Palermo University and Director of Investigational Cancer Therapeutics Fellowship in Drug Development: Clinical and Experimental at Antwerp University Hospital, Belgium.