KRAS oncogene in lung cancer: focus on molecularly driven clinical trials

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ABSTRACT *KRAS* mutations are the most frequent molecular abnormalities found in one out of four nonsmall cell lung cancers (NSCLC). Their incidence increases in cases of adenocarcinoma, smokers and Caucasian patients. Their negative value in terms of prognosis and responsiveness to both standard chemotherapy and targeted therapies remains under debate. Many drugs have been developed specifically for *KRAS*-mutated NSCLC patients. Direct inhibition of *RAS* activation failed to show any clinical efficacy. Inhibition of downstream targets of the mitogen-activated protein kinase (MEK) pathway is a promising strategy: phase II combinations of MEK 1/2 kinase inhibitors with chemotherapy doubled patients' clinical outcomes. One phase III trial in such a setting is ongoing. Double inhibition of MEK and epidermal growth factor receptor proteins is currently being assessed in early-phase trials. The association with mammalian target of rapamycin pathway inhibition leads to non-manageable toxicity. Other strategies, such as inhibition of molecular heat-shock proteins 90 or focal adhesion kinase are currently assessed. Abemaciclib, a cyclin-dependent kinase 4/6 inhibitor, showed promising results in a phase I trial, with a 54% disease control rate. Results of an ongoing phase III trial are warranted. Immunotherapy might be the next relevant step in *KRAS*-mutated NSCLC management due to the high burden of associated mutations and neo-antigens.

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KRAS mutations in lung cancer: epidemiology and clinical outcomes

Since the beginning of the 21st century, the paradigm of precision medicine has shaken up the landscape of lung cancer classification and treatment. The discovery of cancer-related driver molecular abnormalities led to the development of efficient targeted therapies. RAS proteins are GTP kinases, discovered in the 1960s, whose GTP-RAS active isoform stimulates several pathways involved in cellular growth. V-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue (*KRAS*) mutations are found in ~25–35% of newly diagnosed nonsmall cell lung cancer (NSCLC), with a higher proportion in the adenocarcinoma subtype [1, 2]. Figure 1 summarises the main amino acid substitutions and genomic features that are associated with *KRAS* mutations in NSCLC [3, 4]. Other molecular abnormalities related to RAS pathway activation are diagnosed in 25% of NSCLC cases, such as epidermal growth factor receptor (*EGFR*) (10–23%), *BRAF* mutations (2%), *MET* amplifications (2%), human epidermal growth factor (*HER*)*2* (1%) and *NRAS* (0.2%) mutations. Loss of the negative regulator neurofibromin is found in ~11% of other cases.

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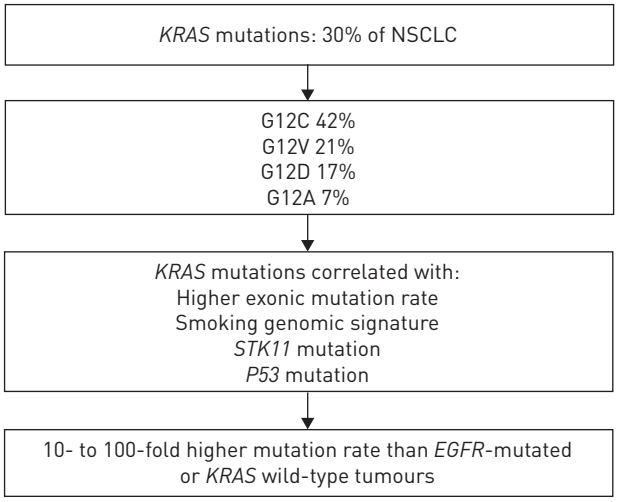

FIGURE 1 Main genomic features of V-Ki-ras2 Kirsten rat sarcoma viral oncogene homologue (*KRAS*)-mutated nonsmall cell lung cancer (NSCLC). EGFR: epidermal growth factor receptor.

Among *KRAS* mutations, G12C, G12V, G12D, G12A and other G12 and G13 mutations are diagnosed in approximately 40%, 21%, 17%, 10% and 12% of cases, respectively [3]. Patients' smoking history underlies the molecular profile of NSCLC, from the point of view of quantitative and qualitative molecular alterations. Incidence of *KRAS* mutations reaches 25–35% in smokers and only 5% in nonsmokers [5, 6]. Type of *KRAS* mutation is related to prior smoking history. In never-smokers, the most common *KRAS* mutation is *G12D* (56%), and *G12C* is the most frequent mutation among former and current smokers (41%). Never-smokers are more likely than former and current smokers to have *G>A* transition mutations, whereas *G>T* transversion mutations are the most common nucleotide change in former and current smokers [3, 7]. It is an early oncogenic event: patients harbouring such mutations have a significantly longer time since quitting smoking (9 *versus* 3 years, p=0.039), with no added difference regarding other tobacco consumption characteristics [8]. *KRAS* mutations are ethnicity driven, since they are found in only 10% of Asian patients [6]. They seem to be associated with poorer prognosis in NSCLC. In two meta-analyses, *KRAS* mutations led to a 30% relative mortality over-risk [9, 10]. Nevertheless, *EGFR* mutation status was not taken into account, which may have led to an overestimation of control arm outcomes: *KRAS* and *EGFR* mutations are exclusive from each other, and *EGFR*-mutated NSCLC has the better prognosis. A recent review confirmed the negative prognostic value of *KRAS* mutations. In this study, 265 *KRAS*-mutant NSCLC patients experienced shorter median overall survival compared to KRAS wild-type NSCLC, after excluding *EGFR*-mutant cases (43 *versus* 55 months, p<0.0001) [11]. Tumour stage might interfere with the prognostic interpretation of *KRAS* mutations [12]. Types of mutated codons seem to have a prognostic value [13]. Analysis was performed on 300 *KRAS*-mutant NSCLC from four randomised clinical trials in the postoperative setting by the Lung Adjuvant Cisplatin Evaluation (LACE)-BIO collaborative group. *KRAS*-mutant cases allocated to the observation arm were more likely to experience a second primary tumour occurrence (hazard ratio (HR) 2.76, 95% CI 1.34–5.70; p=0.005) [14]. In two studies, G12V codon 12 transversions were associated with worse survival [11, 15].

Some retrospective data suggest that *KRAS* mutations might present a negative predictive role of responsiveness to chemotherapy [16], especially when exploring types of *KRAS* molecular abnormalities. In the LACE-BIO collaborative group study, patients harbouring codon 13 mutations experienced much worse outcomes when allocated to the chemotherapy group compared to the observation arm (HR 5.78, 95% CI 2.06–16.22; p<0.001, interaction=0.002), suggesting a deleterious effect of adjuvant chemotherapy in this subgroup of patients [14]. In *KRAS*-mutant NSCLC, type of chemotherapy regimen seems to lead to similar clinical outcomes [17, 18]. Until 2010, *KRAS* mutations were considered negative predictive factors in advanced NSCLC patients treated by inhibitors of the tyrosine kinase domain (TKI) of the EGFR, according to the results of two meta-analyses evaluating both erlotinib and gefitinib [5, 19, 20]. When focusing exclusively on *EGFR* wild-type cases, *KRAS* mutations might not keep this negative predictive value [18, 21–23]. To the best of our knowledge, data related to clinical benefits of bevacizumab according to *KRAS* mutational status are lacking.

Molecularly driven trials: results and further directions in *KRAS*-mutated NSCLC

All the results of patients' clinical outcomes described are related to *KRAS*-mutated cases.

Pathways involved in RAS activation

The impaired GTPase activity related to *KRAS* mutations leads to higher cytoplasmic concentrations of pro-oncogenic GTP-KRAS compound. To directly inhibit RAS protein activity, three strategies were used (table 1).

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TABLE 1 Clinical outcomes related to evaluated drugs in *KRAS*-mutated nonsmall cell lung cancer patients

Trial arm [ref.]	Patients	Previous lines	ORR %	DCR %	Median PFS months	Median OS months
MAPK pathway						
Salirasib [24]	33	Any	0	33.3		
Sorafenib [25]	10	⩾1	33.3	60	3	
Sorafenib [26]	59	⩾1	8.5	50.8	2.3	5.3
Sorafenib	34	⩾2	2.9	44.1	2.6	6.4
versus placebo [27]	34	⩾2	0	7.6	1.7 (HR 0.46, 95% CI 0.25–0.82; p=0.007)	5.1 (HR 0.76, 95% CI 0.45–1.26; p=0.279)
Sorafenib	14	⩾1		79		
versus erlotinib	7	⩾1		14		
versus erlotinib + bexarotene	3	⩾1		33		
versus vandetanib [28]	14	⩾1		0		
Selumetinib	9	⩾1	0		3.9	
versus selumetinib + erlotinib [29]	30	⩾1	6.7		4.5	
Selumetinib + docetaxel	44	⩾1	36.4	80	5.3	9.4
versus docetaxel + placebo [30]	43	⩾1	0	46.5	2.1 (HR 0.58, 95% CI 0.42–0.79; p=0.014)	5.2 (HR 0.8, 95% CI 0.56–1.14; p=0.21)
Trametinib	86	1	11.6	90.7	3	8
versus docetaxel [31]	43	1	11.6	74.4	2.8 (HR 1.23, 95% CI 0.81–1.87; p=0.316)	Unreached (HR 0.97, 95% CI 0.52–1.83; p=0.934)
Trametinib + docetaxel [32]	22	⩾1	13.6	61		
Trametinib + pemetrexed [33]	20	⩾1	75	65		
mTOR inhibitors						
Ridaforolimus [34]	79	⩾1		35.4		
Ridaforolimus	14	⩾1 SD after 8 weeks ridaforolimus			4	18
versus placebo [34]	14	⩾1 SD after 8 weeks ridaforolimus			2 (HR 0.36, p=0.013)	5 (HR 0.46, p=0.09)
Hsp90 inhibitor						
Ganetespib [35]	17	⩾1	0	35	1.9	11.0

Data are presented as n, unless otherwise stated. ORR: objective response rate; DCR: disease control rate; PFS: progression-free survival; OS: overall survival; MAPK: mitogen-activated protein kinase; mTOR: mammalian target of rapamycin; Hsp90: heat shock protein 90; HR: hazard ratio.

First, targeting the nucleotide binding to RAS with a competitive inhibitor to prevent GTP-KRAS formation [36–39]. Second, improving GTPase activity of *KRAS*-mutated cells. High cytoplasmic guanine concentrations, very high affinity of the nucleotide and unknown KRAS binding sites hinder the clinical development of these options. Finally, RAS activation may be inhibited by targeting its endomembrane binding through phosphodiesterase-δ [40]. Yet a phase II trial testing salirasib, an inhibitor of such binding, failed to show any clinical benefit [24].

If direct blocking of RAS has not yet demonstrated its efficacy, inhibition of downstream targets of the mitogen-activated protein kinase (MAPK) cascade may be a more promising strategy. Sorafenib is an oral multitarget TKI which inhibits RAF and related transmembrane receptors. Phase II trials showed promising results with a disease control rate of ~50% [25, 26, 28]. Yet subgroup analyses performed in the *KRAS*-mutated group of the phase III MISSION trial did not reveal any specific efficacy of sorafenib in the third or fourth chemotherapy line [27].

Selumetinib is a non-ATP competitive oral inhibitor of mitogen-activated protein kinase kinase (MEK)1/2, which was combined with docetaxel in a second-line phase II trial. Compared to docetaxel monotherapy, progression-free survival and overall survival were doubled in the experimental arm with a good tolerance profile [30]. Yet the outcome in the control arm was poorer than expected, arm populations were unbalanced regarding prognostic factors and data regarding efficacy of the experimental combination in *KRAS* wild-type NSCLC patients are lacking. The SELECT-1 phase III trial is ongoing in this indication (clinicaltrials.gov: NCT01933932) (table 2). Trametinib belongs to the same molecular class as selumetinib and has been developed in *BRAF*-mutated metastatic melanoma. A second-line phase II trial comparing trametinib to docetaxel revealed similar survival outcomes, while grade 4 toxicity occurred only in the experimental arm [31]. Two phase I/Ib trials evaluating trametinib combinations with docetaxel

TABLE 2 Ongoing clinical trials performed in *KRAS*-mutated nonsmall cell lung (NSCLC) patients

	clinicaltrials.gov identifier	Phase	Tumour type
MEK inhibitors			
Selumetinib + docetaxel (*versus* docetaxel)	NCT01933932	III	NSCLC
Trametinib + chemoradiation	NCT01912625	I	Unresectable NSCLC
PD-0325901 + palbociclib	NCT02022982	I/II	NSCLC and other solid tumours
MEK162 + BYL719	NCT01449058	Ib	All solid tumours
MEK162	NCT01885195	II	All solid and haematological malignancies
MEK162 + RAF265	NCT01352273	I	All solid tumours
MEK162 + erlotinib	NCT01859026	I	NSCLC
PD-0325901 + dacomitinib	NCT02039336	I	NSCLC
Other			
BIND-014	NCT02283320	II	NSCLC
Bortezomib	NCT01833143	II	NSCLC
Retaspimycin HCl (IPI-504) + everolimus	NCT01427946	Ib/II	NSCLC
VS-6063 (defactinib)	NCT01951690	II	NSCLC
Wild-type reovirus + paclitaxel + carboplatin	NCT00861627	II	NSCLC
Abemaciclib (LY2835219)	NCT02152631	III	NSCLC

and pemetrexed, respectively, as a second line showed a disease control rate of ~60% [32, 33]. The radiosensitising effect of trametinib is currently being assessed in combination with a carboplatin–paclitaxel regimen (clinicaltrials.gov: NCT01912625). MEK162 and PD-0325901 are second-generation MEK1/2 inhibitors currently evaluated in molecularly driven phase I/II trials (clinicaltrials.gov: NCT02022982). Based on a genomic classification, the double inhibition of MEK and EGFR proteins is a promising therapeutic strategy [41]. Early-phase trials are assessing currently such associations: MEK162–erlotinib (clinicaltrials.gov: NCT01859026) or PD-0325901–dacomitinib (clinicaltrials.gov: NCT02039336).

The phosphatidylinositol-3-kinase (PI3K)–Akt–mammalian target of rapamycin (mTOR) pathway is a parallel signal transduction pathway. The single inhibition of mTOR by ridaforalimus led to disappointing results in *KRAS*-mutated NSCLC [34]. NVP-BEZ235, a dual PI3K–mTOR inhibitor, failed to demonstrate promising preclinical results in this context. PI3K–Akt–mTOR pathway inhibition may circumvent resistance to MEK inhibition in *KRAS*-mutated NSCLC. Yet the combination of both PI3K–Akt–mTOR and RAS–MEK–ERK inhibitors leads to nonmanageable toxicity [42, 43].

Other strategies

Bortezomib (Velcade) is a proteasome inhibitor which is currently evaluated in an ongoing molecularly driven phase II trial (NCT01833143). Molecular heat shock proteins (Hsp)90 are chaperones that assist proteins to fold properly, stabilising them against cellular stress and preventing their proteasomal degradation. Ganetespib and retaspimycin HCl (IPI-504) are Hsp90 inhibitors. A phase II study assessing ganetespib showed similar clinical outcomes according to the *KRAS* mutational status of patients [35]. Results of a phase Ib/II trial testing the association of retaspimycin with everolimus in *KRAS*-mutated advanced NSCLC patients are awaited (NCT01427946).

Focal adhesion kinase (FAK) is a nonreceptor tyrosine kinase involved in cellular matrix attachment, whose overexpression leads to tumoral growth. Defactinib (VS-6063) is a FAK inhibitor tested in a phase II trial among four cohorts of *KRAS*-mutated NSCLC patients (NCT01951690). The as-yet unpublished results were reported recently at the 16th World Conference on Lung Cancer and were negative.

Reovirus type 3 Dearing is a naturally occurring, nonpathogenic, double-stranded RNA virus isolated from 100% of the human respiratory and gastrointestinal tracts with some antitumoral activity among RAS pathway activation tumours. It has been tested in a phase II trial in association with a carboplatin/paclitaxel regimen in RAS pathway-activated NSCLC patients (NCT01951690).

BIND-014 is a drug made of docetaxel nanoparticles and is currently evaluated in a phase II trial among *KRAS*-mutated or squamous-cell NSCLC patients, as a second-line therapy (NCT02283320).

Abemaciclib (LY2835219) is a cell cycle inhibitor selective for the cyclin-dependent kinases CDK4 and CDK6. Promising results of a phase I trial were presented at the American Society of Clinical Oncology congress in 2014: in a relapse setting, disease control rate reached 54% in *KRAS*-mutated NSCLC and toxicity was manageable. The JUNIPER phase III clinical trial is currently ongoing (NCT02152631). *KRAS*-mutated NSCLC patients are randomised into the monotherapy experimental arm or into the erlotinib control arm, after failure of a platinum-based chemotherapy line.

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Discussion: is immunotherapy the next step in the treatment of *KRAS*-mutated NSCLC patients?

Treating *KRAS*-mutated NSCLC patients selectively remains a challenge in the era of precision medicine. Several reasons are involved: 1) the absence of oncogenic addiction leading to cancer primary resistance to MAPK pathway targeted therapies; 2) distinct patterns of *KRAS*-mutated NSCLC; 3) other forms of RAS pathway activation such as RAS overexpression or loss of RAS negative regulator (neurofibromin); 4) heterogeneity between the primary tumour site and metastases [44]; and 5) distinct methods of mutation assessment between solid and liquid biopsies [45]. MEK1/2 inhibitors are promising drugs in this setting. Yet, immunotherapy might be a relevant translational research option [46] since: 1) *KRAS*-mutated NSCLCs occur more frequently among smokers and tobacco-induced tumours present a higher burden of mutations and neo-antigens; 2) *KRAS* mutations are associated with a high number of mutations [47]; and 3) among responders to programmed cell death (PD)-1 inhibitor, 50% of cases harbour a *KRAS* mutation, while this concerns only one out of 17 nonreponders [48].

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