Review Article

The treatment of advanced non-small cell lung cancer harboring KRAS mutation: a new class of drugs for an old target—a narrative review

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Background and Objective: The genetic nature of cancer provides the rationale to support the need for molecular diagnosis and patient selection for individualised antineoplastic treatments that are the best in both tolerability and efficacy for each cancer patient, including non-small cell lung cancer (NSCLC) patients. Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations represent the prevalent oncogenic driver in NSCLC, being detected in roughly one-third of cases and KRAS G12C is the most frequent mutation found in approximately 13% of patients.

Methods: This paper gives an overview of the numerous scientific efforts in recent decades aimed at KRAS inhibition.

Key Content and Findings: Sotorasib is the first approved KRAS G12C inhibitor that has been shown to provide a durable clinical benefit in patients with pre-treated NSCLC with KRAS G12C mutation. Together with the development of new targeted drugs, the development of strategies to control resistance mechanisms is one of the major drivers of research that is exploring the use of KRAS inhibitors not only alone, but also in combination with other targeted therapies, chemotherapy and immunotherapy.

Conclusions: This review will describe the major therapeutic developments in KRAS mutation-dependent NSCLC and will analyse future perspectives to maximise benefits for this group of patients.

Keywords: Adagrasib; KRAS G12C; non-small cell lung cancer (NSCLC); resistance; sotorasib

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Introduction

In recent years, the management of patients with non-small cell lung cancer (NSCLC), about 85% of lung cancers, has changed considerably, mainly due to the introduction of new molecularly targeted drugs, immunotherapy and better integration of available treatments. An accurate histological diagnosis of the tumor and its biomolecular characterisation are therefore essential for the most appropriate choice of therapy, allowing the optimal treatment strategy to be assessed for each patient (1). These new treatment approaches have resulted in increased objective responses, increased patient survival and improved quality of life. Biomarkers that can be used in clinical practice today, representing targets for targeted therapies, also include Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation, but the panel of mutations useful for defining the therapeutic strategy is progressively increasing. KRAS mutations are the most common oncogenic driver in NSCLC, accounting for approximately 30% of cases (*Figure 1*) (2). In this article, we discuss the biology of KRAS in NSCLC and provide an update on emerging anti-KRAS therapies, among which sotorasib represents a first-in-class, selective, irreversible

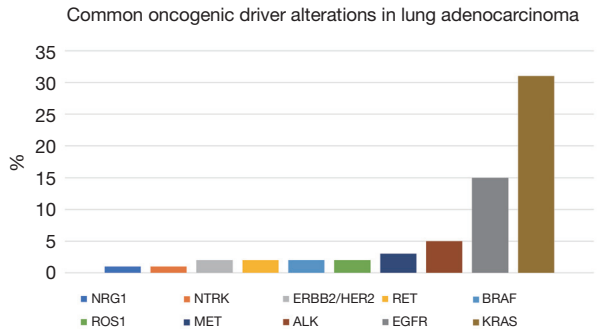

Figure 1 NSCLC adenocarcinoma molecular classification. NSCLC, non-small cell lung cancer; ALK, anaplastic lymphoma kinase; BRAF, v-raf murine sarcoma viral oncogene homolog B1; EGFR, epidermal growth factor receptor;ERBB2/HER2, erb-b2 receptor tyrosine kinase 2/human epidermal growth factor receptor 2; KRAS, Kirsten rat sarcoma viral oncogene; MET, mesenchymal-epithelial transition factor; NRG1, neuregulin 1; NTRK, neurotrophic tyrosine receptor kinase; RET, rearranged during transfection; ROS1, c-ros oncogene 1.

small molecule inhibitor of KRAS G12C that received accelerated approval from the Food and Drug Administration (FDA) on May 28, 2021 for the treatment of patients with locally advanced or metastatic NSCLC, with KRAS G12C mutation, who have received at least one prior systemic therapy. Here, we also discuss the mechanisms of resistance to these new therapies and future research perspectives. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-21-948/rc).

Methods

Published data useful for this review were identified by searching in PubMed Medline, until November 2021. Only articles English written studies were considered. The research was performed using the following search terms “KRAS NSCLC”, “KRAS G12C”, “KRAS inhibitor resistance”, “adagrasib”, “sotorasib”. Titles and abstracts presented at recent major international meetings also were screened to determine eligibility in the review (*Table 1*).

KRAS: from biology to therapeutic target

KRAS is the most frequently mutated oncogene in human cancers (approximately 85%) (3) and encodes for one of the proteins with GTPase activity in the RAS family. KRAS works as a cellular switch that is “switched on” by extracellular stimuli such as growth factors, leading to the activation of downstream signal transduction pathways that regulate the proliferation, migration, survival and differentiation of the cell (4). In its regulation of signal transduction, KRAS cyclically switches from the GDP-bound inactive state (KRAS-GDP) to the GTP-bound active state (KRAS-GTP). The latter directly activates downstream signalling pathways, in particular the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway and the phosphatidylinositol 3-kinase (PI3K) pathway (5,6). Gain-of-function missense mutations are mainly responsible for the transformation of KRAS from proto-oncogene to oncogene. The resulting mutated KRAS protein remains in the KRAS-GTP state, which constitutively activates downstream signal transduction pathways, leading to tumorigenesis (7,8). These mutations are mainly represented by nucleotide substitutions in codons 12, 13 and 61 of the gene (9,10). More than 80% of tumors with mutated KRAS have single nucleotide variations in codon 12. G12C (transversion with replacement of the glycine at codon 12 by a cysteine) is the prevalent KRAS mutation in NSCLC and is present in approximately 13 % of patients with NSCLC (2). Other KRAS mutations include those from amino acid glycine (Gly) to valine (Val) G12V (approximately 21%) and from amino acid Gly to aspartic acid (Asp) G12D (approximately 17%) but G12C remains the predominant mutation (around 40% of KRAS mutations) in lung adenocarcinoma (*Figure 2*) (11). Compared to other KRAS mutations, G12C is prevalent in women (P=0.007) (11). Similar to most driver mutations in NSCLC, KRAS alterations are almost uniquely present in adenocarcinoma histology (12) but, unlike most oncogenic driver alterations, are largely linked to smoking habits; only about 5% of KRAS mutations are detected in light- or non-smokers, in whom the KRAS G12D mutation is most often found (56%) (11). KRAS mutations are also more common in Western versus Asian populations (26% versus 11%) (13).

In prognostic terms, some studies have reported poorer survival outcomes in NSCLC patients with KRAS mutations compared to those with wild-type KRAS (14-17). A high frequency of liver (P=0.01) and brain (P=0.04) metastases at baseline has been reported in KRAS-mutant NSCLC patients, suggesting the greater aggressiveness of this type of disease (18). Other studies, however, have not found an effect on overall survival (OS) related to KRAS mutational status (19-23).

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	05 October 2021
Databases and other sources searched	PubMed Medline, ClinicalTrials.gov
Search terms used (including MeSH and free text search terms and filters)	"KRAS NSCLC", "KRAS G12C", "KRAS inhibitor resistance", "adagrasib", "sotorasib"
Timeframe	July 1998 to 30 November 2021
Inclusion and exclusion criteria (study type, language restrictions etc.)	It is a review: registration studies, reviews, ClinicalTrials.gov database, titles and abstracts presented at recent major international meetings. Only English-language studies were included
Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)	The authors conducted the research independently; consensus was not needed
Any additional considerations, if applicable	None

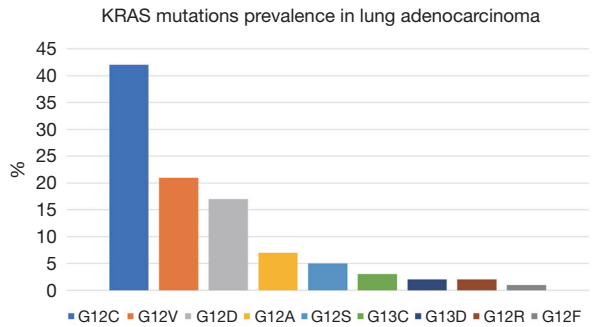

Figure 2 KRAS mutations in NSCLC adenocarcinoma. KRAS, Kirsten rat sarcoma viral oncogene; NSCLC, non-small cell lung cancer.

Co-occurring mutations observed with KRAS in NSCLC may influence prognosis: while KRAS mutations are often mutually exclusive of those in other oncogenic drivers (24,25), KRAS co-occurring mutations in non-oncogenic drivers are fairly ordinary (19) and may cooperate in influencing therapeutic responses, thus some of them [such as mutations in genes such as serine/threonine kinase 11 (STK11), Kelch-like ECH-associated protein 1 (KEAP1) and tumour protein 53 (TP53)] having a proposed negative impact on survival (26-30).

The central role of KRAS in cell growth has meant that for decades it has been the subject of extensive drug development efforts. However, KRAS has long been considered "undruggable" due to its high affinity for GTP, its limited number of active binding sites and the complexity of its downstream pathways (31,32). This led to unsuccessful research attempts (24) until advances in computational modelling and crystallography showed the complete structure of the KRAS G12C mutant protein, leading to the discovery of a small inhibitory molecule (ARS-1620) capable of binding to the switch-II pocket allosteric binding site near the effector region of mutant KRAS G12C (33). Since then, several small inhibitory molecules with enhanced potency have been discovered that selectively and irreversibly bind to cysteine in the KRAS G12C transversion and thereby block the mutated protein in its inactive KRAS-GDP state (34-36). The first KRAS G12C inhibitors to demonstrate efficacy in the clinical setting were sotorasib (AMG-510) and adagrasib (MRTX-849).

KRAS inhibitors

Sotorasib is the first oral KRAS G12C inhibitor that has demonstrated sustained clinical benefit in patients with pre-treated NSCLC with KRAS G12C mutation. Based on preclinical data, a phase I/II study assessed the safety, tolerability, pharmacokinetics and efficacy of sotorasib alone in heavily pretreated patients with locally advanced or metastatic KRAS G12C solid tumors (CodeBreak 100; NCT03600883) (37-39). In the phase II study, 126 patients with locally advanced or metastatic NSCLC with KRAS G12C mutation were enrolled to take 960 mg of oral sotorasib once a day until cancer progression. Patients with stable brain metastases were also included. The primary endpoint of the study was objective response rate (ORR), the secondary endpoints duration of response (DOR), disease control rate (DCR), time to response, progression-

free survival (PFS), overall survival (OS) and safety. Most patients (92.9%) were smokers or ex-smokers and had been pre-treated with 1 (42.9%), 2 (34.9%) or 3 (22.2%) previous lines of therapy. These previous treatments included platinum-based chemotherapy (89.7%), programmed cell death protein 1 (PD-1)/ programmed death ligand 1 (PD-L1) inhibitors (91.3%) or chemotherapy combined with PD-1/PD-L1 inhibitors (81.0%). The ORR of 37.1% [95%confidence interval (CI): 28.6–46.2%] included a complete response (CR) rate of 3.2% (n=4) and a partial response (PR) rate of 33.9% (n=42); the stable disease (SD) rate was 43.5% (n=54) and 16.1% (n=20) of patients experienced progressive disease (PD). The DCR achieved 80.6% (95% CI: 72.6–87.2%) with a median time to response of 1.35 months. Clinical activity was consistent between the pre-specified subgroups based on patient characteristics at baseline. Given a median follow-up of 15.3 months, sotorasib demonstrated a median OS of 12.5 months [95% CI: 10.0–not evaluable (NE)] and a median PFS of 6.8 months (95% CI: 5.1–8.2 months). The DOR resulted in 11.1 months (95% CI: 6.9–NE) (38,39). Efficacy was also assessed in exploratory analyses of subgroups defined at the molecular level. The probability of response to sotorasib was independent of allele frequency. Tumor mutational burden (TMB) failed to be predictive of response; additionally, responses were seen in patients with concomitant mutations: TP53 (wild-type: 40%; mutated: 39%), STK11 (wild-type: 39%; mutated: 40%) and KEAP1 (wild-type: 44%; mutated: 20%) (38,40). With regard to safety, mainly grade 1/2 treatment-related adverse events (TRAEs) were reported. TRAEs of all grades involved 69.8% of patients and those of grade 3 19.8% of patients (37,39). Among the most recurrent grade 3 TRAEs were diarrhoea (4.0%), ALT increase (6.3%) and AST increase (5.6%). TRAEs leading to dose reductions were observed in 22.2% (n=28) of patients and therapy discontinuation because of TRAEs was reported in 7.1% (n=9) of patients. Patients who discontinued treatment due to TRAEs had: drug-induced liver damage (n=3), increased liver function tests (n=1), elevated ALT levels (n=2), elevated AST levels (n=2), elevated alkaline phosphatase (n=1), hypertransaminasemia (n=1), pneumonia (n=2) and dyspnoea (n=1). Based on the described results obtained in a CodeBreak 100 patient cohort, the FDA approved sotorasib on 28 May as a treatment for patients with NSCLC with KRAS G12C mutation who have received at least one prior systemic therapy (41).

The confirmatory phase III CodeBreak 200 study (NCT04303780), which is investigating sotorasib versus docetaxel in pretreated NSCLC patients harbouring KRAS G12C mutation, is currently in progress (42). Sotorasib is now also undergoing evaluation in association with other anticancer therapies (including epidermal growth factor receptor (EGFR), mitogen-activated protein kinase (MEK), src homology region 2 domain phosphatase (SHP2), pan-epidermal growth factor (ErbB), mammalian target of rapamycin (mTOR) and cyclin-dependent kinases (CDK) inhibitors as well as immunotherapy and chemotherapy) in the phase Ib/II CodeBreak 101 trial (NCT04185883) in patients with advanced solid cancers (43). The latter study included patients with active untreated brain metastases. However, sotorasib showed intracranial activity in KRAS G12C-mutated NSCLC brain metastases (44). According to findings from a post-hoc analysis of the CodeBreak 100 trial, at a median follow-up of 12 months, sotorasib resulted in an ORR of 25% in patients with NSCLC and brain metastases at baseline compared with 42% in patients with NSCLC without brain metastases at baseline. The median PFS was 5.3 months (95% CI: 2.7–9.3 months) versus 6.7 months (95% CI: 5.3–8.2 months) in patients with and without brain metastases, respectively. The median OS was 8.3 months (95% CI: 7.3–12.5 months) in patients with brain metastases compared to 13.6 months (95% CI: 10.0–NE) in patients without brain metastases. Intracranial DCR was 88% (n=14) among 16 patients with evaluable brain metastases. Responses to sotorasib in target and non-target stable brain metastases were retrospectively assessed by the investigators in the post-hoc analysis. Patients with brain metastases were 40 at baseline. None of the 3 patients with target and non-target brain lesions achieved a CR, 1 patient (33%) achieved a SD and 2 (67%) a PD. Of the 13 patients with only non-target brain metastases, 2 (15%) achieved a CR, 11 (85%) a SD and none a PD. Of the 16 evaluable patients with central nervous system (CNS) lesions, 2 (13%) achieved a CR, 12 (75%) a SD and 2 (13%) a PD. With regard to safety, 8 patients (20%) with brain metastases at baseline had grade 3 TRAEs compared to 26 patients (19%) without brain metastases. In zero and 2 patients (1.5%), respectively, grade 4 TRAEs were reported (44).

Adagrasib is the second oral small molecule inhibitor of KRAS G12C to move into clinical trials. It has a common mechanism of action with sotorasib, from which it differs in pharmacokinetics (PK) properties including oral bioavailability, long half-life (approximately 24 hours) and extensive tissue distribution (45,46). On 24 June, adagrasib received the breakthrough therapy designation

from the FDA for the potential treatment of patients with NSCLC positive for the KRAS G12C mutation, who have received at least one previous systemic therapy (47). The designation is supported by preliminary results from the phase I/II registration study KRYSTAL-1 (NCT03785249) in patients with NSCLC whose tumor carried the KRAS G12C mutation and progressed after treatment with immunotherapy and chemotherapy. Seventy-nine patients were given adagrasib 600 mg two times a day and of the 51 evaluable patients, 45% had an objective response and 96% disease control (median follow-up 3.6 months) (48). Grade 3 or 4 TRAEs were observed in 30% of patients and those commonly found (>5%) were fatigue (6%) and high levels of AST/ALT (5%). TRAEs resulted in discontinuation of treatment in 4.5% of patients and 2 patients died from TRAEs (one pneumonitis and one cardiac failure) (49). KRYSTAL-12 (NCT04685135) is a phase III study of adagrasib versus docetaxel that is recruiting pretreated patients with KRAS G12C-mutated NSCLC while a number of other studies are combination clinical trials in NSCLC with afatinib (NCT03785249), pembrolizumab (NCT04613596), TNO155 (SHP2 inhibitor; NCT04330664).

GDC-6036/RG6330, D-1553, JDQ443 and JNJ-74699157 are among the other KRAS G12C inhibitors in development, which have reached the trial clinical phase (NCT04449874, NCT04585035, NCT04699188 and NCT04006301, respectively).

A phase I study of mRNA-5671/V941 as a monotherapy and in combination with pembrolizumab in KRAS mutant advanced NSCLC, colorectal cancer or pancreatic adenocarcinoma is now ongoing (NCT03948763) and uses the mRNA-derived KRAS-targeted vaccine V941 that targets certain KRAS mutations (G12D, G12V, G13D and G12C).

Interestingly, indirect inhibitors of KRAS are in development and could be useful against multiple KRAS mutations. BI-1701963 is a selective oral son of sevenless homolog 1 (SOS1): KRAS inhibitor that binds the nucleotide exchange factor SOS1, impeding it from binding to KRAS-GDP (50). A phase I study of BI-1701963 in KRAS-positive advanced cancers is being conducted (NCT04111458) but preliminary results are available and of 31 patients treated with monotherapy, 7 (22.58%) experienced SD lasting up to 18 weeks. Three grade ≥3 TRAEs were observed: hypertension, congestive cardiomyopathy and decreased platelet count. The maximum tolerated dose of BI-1701963 was reached at 800 mg once daily; two dose-limiting toxicities were reported: grade 3 congestive cardiomyopathy and grade 4 decreased platelet count.

RMC-4630 is an inhibitor of SHP2 which is necessary for complete RAS-MAPK activation and is critical for KRAS-mutant carcinogenesis (51). RMC-4630 showed clinical activity in patients with KRAS-mutant NSCLC, with a DCR of 67% for all KRAS mutations and 75% for the KRAS G12C mutation in a phase I trial (NCT03989115) (52). TNO155 is a further SHP2 inhibitor in a phase I study in patients with advanced solid cancers in selected indications (also patients with KRAS G12C-mutated NSCLC) (NCT03114319). Initial results indicate favourable pharmacokinetic properties, with mainly grade 1 and 2 adverse events and among grade ≥3 adverse events in particular thrombocytopenia, increased AST, diarrhoea and neutropenia (53). *Table 2* lists the clinical trials described with direct and indirect inhibitors of KRAS.

Resistance to KRAS G12C inhibitors

The development of resistance hinders the efficacy of therapy. More precisely, resistance to cancer therapies can be intrinsic or acquired. Among the causal mechanisms implicated in KRAS G12C inhibitor resistance, intrinsic resistance to these drugs could result from a low dependency on KRAS signalling (54,55). Specifically, PI3K activation is not exclusively controlled by RAS and KRAS G12C inhibitors may act primarily by the target of MAPK/ERK (56-58). Resistance may occur when parallel redundant signalling pathways may bypass the need for KRAS activity and in turn activate cell proliferation (59). In addition, secondary KRAS mutations can still cause intrinsic resistance to KRAS G12C inhibitors (60) for example by enhancing nucleotide exchange (Y40A, N116H or A146V mutations) or by impairing the GTPase activity (A59G, Q61L or Y64A mutations) (58). The intratumoral heterogeneity of KRAS mutational status itself in the same patient may lead to variable responses to KRAS G12C inhibitors (61).

With regard to secondary resistance, all tyrosine kinase inhibitors (TKIs) induce the development of acquired resistance mechanisms. Among them, new production of KRAS G12C, resulting from reduced MAPK signalling, may reactivate overall RAS activity by increasing activation of receptor tyrosine kinase (RTK)-SHP2. SHP2 is activated in mutant cell lines after TKI therapy and SHP2 inhibition notably suppresses stemness of KRAS-mutant NSCLC cells thereby indirectly inhibiting KRAS (62). Indeed, one possible mechanism by which neoplastic cells become resistant to therapy with KRAS G12C inhibitors assumes

Table 2 Direct and indirect inhibitors of KRAS in selected clinical trials

NCT number	Phase	KRAS inhibitor	Molecules tested	Indication	Status/outcomes
NCT03600883	I/II	Sotorasib	Anti PD-1/L1	Monotherapy for AST with KRAS G12C mutation; Combination therapy for advanced NSCLC with KRAS G12C mutation	For monotherapy in pretreated NSCLC: ORR: 37.1% (95% CI: 28.6 to 46.2); DCR: 80.6% (95% CI: 72.6 to 87.2); mOS: 12.5 months (95% CI: 10.0 to NE); mPFS: 6.8 months (95% CI: 5.1 to 8.2)
NCT04303780	III	Sotorasib	Docetaxel	Sotorasib versus docetaxel for pretreated advanced NSCLC with KRAS G12C mutation	Ongoing
NCT04185883	I/II	Sotorasib	SHP2, EGFR, pan-ErbB, mTOR, CDK and MEK inhibitors; PD-1/L1 inhibitors; chemotherapy	Monotherapy and combination therapy for AST with KRAS G12C mutation	Ongoing
NCT05074810	I/II	Sotorasib	Anti-RAF-MEK	Combination therapy for NSCLC with KRAS G12C mutation	Ongoing
NCT03785249	I/II	Adagrasib	Anti PD-1; Anti-ErbB	Monotherapy for AST with KRAS G12C mutation; Combination therapy for advanced NSCLC with KRAS G12C mutation	For monotherapy in pretreated NSCLC: ORR: 45% (23/51 pts); DCR: 96% (49/51 pts)
NCT04685135	III	Adagrasib	Docetaxel	Adagrasib versus docetaxel for pretreated advanced NSCLC with KRAS G12C mutation	Ongoing
NCT04613596	II	Adagrasib	Anti PD-1	Monotherapy and combination therapy for advanced NSCLC with KRAS G12C mutation	Ongoing
NCT04330664	I/II	Adagrasib	Anti-SHP2	Combination therapy for AST with KRAS G12C mutation	Ongoing
NCT04449874	I	GDC-6036	PD-L1, VEGF and EGFR inhibitors	Monotherapy and combination therapy for AST with KRAS G12C mutation	Ongoing
NCT04585035	I/II	D-1553	Other	Monotherapy and combination therapy for AST with KRAS G12C mutation	Ongoing
NCT04699188	I/II	JDQ443	SHP2 and PD-1 inhibitors	Monotherapy and combination therapy for AST with KRAS G12C mutation	Ongoing
NCT04006301	I	JNJ-74699157	–	Monotherapy for AST with KRAS G12C mutation	Completed
NCT04111458	I	BI-1701963 (pan-KRAS SOS1 inhibitor)	Anti-MEK	Monotherapy and combination therapy for AST with KRAS mutation	Ongoing
NCT03989115	I/II	RMC-4630 (SHP2 inhibitor)	Anti-MEK Anti-EGFR	Combination therapy for AST with specific genomic aberrations Combination therapy for advanced NSCLC with EGFR mutation	Ongoing

Table 2 (*continued*)

Table 2 (*continued*)

NCT number	Phase	KRAS inhibitor	Molecules tested	Indication	Status/outcomes
NCT03114319	I	TNO155 (SHP2 inhibitor)	Anti-EGFR	Monotherapy and combination therapy for AST in selected indications	Ongoing
NCT03948763	I	mRNA-5671/ V941 (KRAS vaccine)	Anti PD-1	Monotherapy and combination therapy for AST in selected indications	Ongoing

KRAS, Kirsten rat sarcoma viral oncogene; AST, advanced solid tumors; DCR, disease control rate; mOS, median overall survival; mPFS, median progression-free survival; NCT, national clinical trial; NSCLC, non-small cell lung cancer; ORR, objective response rate.

that the cells, adapting to the oncogenic shock, select other proliferation mechanisms including activation of Harvey rat sarcoma viral oncogene (HRAS) and neuroblastoma rat sarcoma viral oncogene (NRAS) with subsequent restoration of MAPK activation despite KRAS being maintained in its inactive state. Furthermore, MEK mediates the proliferative signal between RTKs and the RAS pathway as well as CDK4/6 but also PI3K, AKT (protein kinase B, PKB), mTOR constitute the downstream KRAS pathway and represent an attractive target for combining therapies with KRAS inhibitors. Similarly, agents acting upstream of the KRAS pathway (EGFR/ErbB inhibitors) are under investigation (63,64).

New approaches and combination strategies for KRAS-mutant NSCLC

The development of resistance to TKIs therapy leads to the continuous expansion of alternative strategies to target KRAS. Hence the attempt to combine drugs active on different levels of the cellular signal in the therapeutic scheme (*Figure 3*).

Use of inhibitors of the downstream signal pathway of KRAS

Table 3 shows clinical trials with KRAS downstream effector molecule inhibitors. Rapidly accelerated fibrosarcoma (RAF) is a kinase involved in the MAPK signal transmission pathway: the MAPK signal starts with activation of the RAS protein followed by membrane recruitment and activation of RAF, which phosphorylates MEK, which in turn phosphorylates ERK, a terminal kinase that can directly or indirectly activate transcription factors (65-68). RAF inhibitors exhibit some efficacy in KRAS-mutant tumors (69). Belvarafenib is undergoing a phase I clinical study (NCT03284502). Similarly, several MEK inhibitors are being studied in ongoing phase I clinical trials for KRAS-mutant NSCLC: HL-085 (NCT03990077), binimetinib (NCT01859026; NCT02964689 now completed), cobimetinib in combination with the dual EGFR/HER3 inhibitor MEHD7945A in the completed NCT01986166 trial. RAS-GTP levels, RAF dimerisation and RAF kinase activity are induced by MEK inhibition in mechanistic studies and combined RAF-MEK inhibition exhibits synergy in RAS mutant cancers (69). The combination of the RAF inhibitor LXH254 and the MEK inhibitor trametinib is being evaluated in the phase I clinical trial NCT02974725. Another phase I clinical trial (NCT03284502) of the combination of belvarafenib with cobimetinib is in progress, while NCT04620330 is a phase Ib/II study evaluating the RAF-MEK inhibitor VS-6766 versus VS-6766 in combination with the focal adhesion kinase (FAK) inhibitor defactinib in patients with KRAS-mutant NSCLC. Additionally, an arm evaluating the combination of sotorasib and a MEK inhibitor is included in CodeBreak 101. NCT 05074810 is a phase I/II study of VS-6766 plus sotorasib in G12C NSCLC patients and adagrasib is also close to being evaluated in combination with VS-6766 for NSCLC patients with KRAS G12C mutation. ERK feedback activation is commonly behind the resistance of KRAS mutated cancers to RAF or MEK inhibitors. ERK inhibitors such as JSI-1187-01 (NCT04418167), ASN007 (NCT03415126, completed) and KO-947 (NCT03051035, completed) are undergoing phase I clinical research. Another KRAS downstream effector molecule is PI3K and PI3K inhibitors BKM120, GDC0941 and XL147 showed some positive results in phase I clinical studies (70-72). Serabelisib is a PI3Kα inhibitor being investigated in a phase I/II clinical trial in patients with

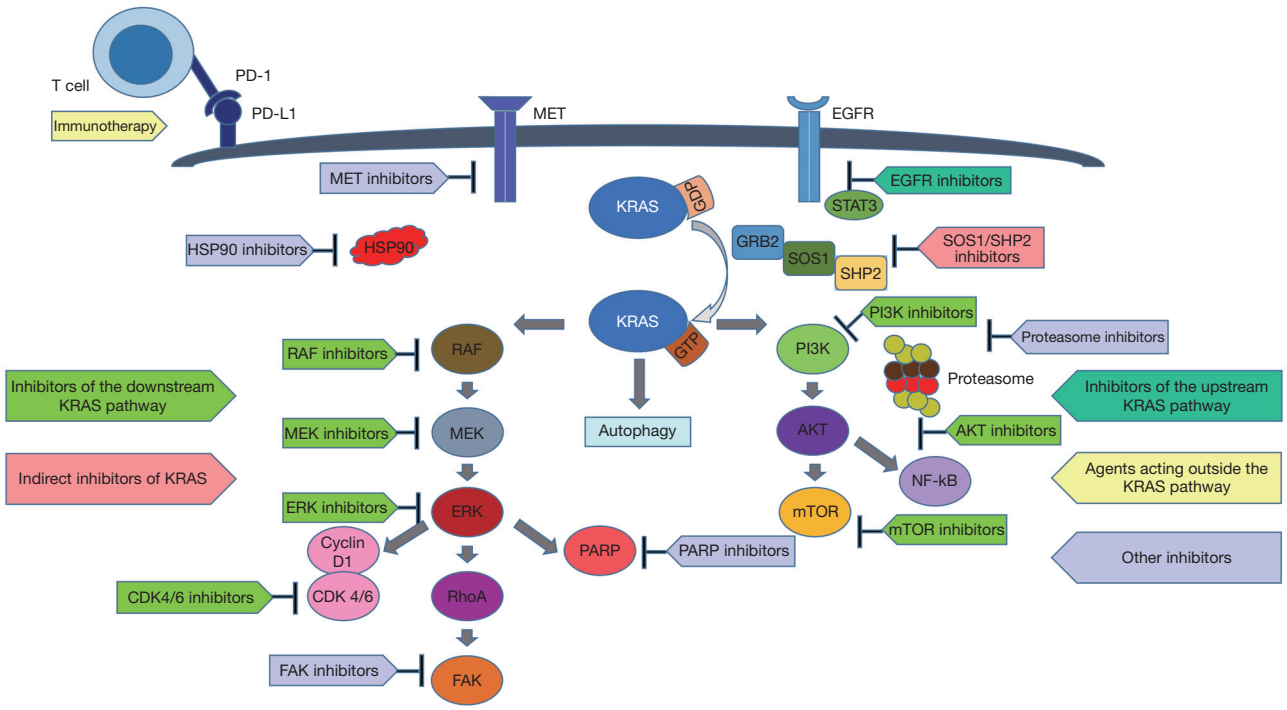

Figure 3 Therapeutic strategies aimed at multiple targets and their associated signalling pathways for KRAS-mutant NSCLC. AKT, protein kinase B, PKB; CDK 4/6, cyclin-dependent kinases 4/6; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; GRB2, growth factor receptor-bound protein 2; HSP90, heat shock protein 90; KRAS, Kirsten rat sarcoma viral oncogene; MEK, mitogen-activated protein kinase; MET, mesenchymal-epithelial transition factor; mTOR, mammalian target of rapamycin; NF-kB, nuclear factor kB; PARP, poly (ADP-ribose) polymerases; PD-(L)1, programmed cell death (ligand) protein 1; PI3K, phosphatidylinositol 3-kinase; RAF, rapidly accelerated fibrosarcoma; RhoA, ras homolog gene family, member A; SHP2, src homology region 2 domain phosphatase; SOS1, son of sevenless homolog 1; STAT3, signal transducer and activator of transcription 3; NSCLC, non-small cell lung cancer.

advanced solid tumors with PIK3CA or KRAS mutations (NCT04073680). A phase I study of TAS0612, AKT inhibitor, is also ongoing (NCT04586270) as well as a phase I/II trial evaluating AZD2014, an inhibitor of mTOR, serine/threonine protein kinase downstream of PI3K in the PI3K-AKT-mTOR pathway (NCT02583542). Again, it has been observed that in KRAS-mutant NSCLC, MEK inhibition leads to autocrine activation of signal transducer and activator of transcription 3 (STAT3) via the fibroblast growth factor (FGF) receptor and Janus (JAK) kinases, and pharmacological inhibition of MEK together with JAK and FGFR can enhance tumor regression (73).

Adagrasib in combination with palbociclib, a CDK4/6 inhibitor, showed antiproliferative effects in adagrasib-resistant models. KRAS mediates, in part, cellular proliferation through regulation of the cyclin D family and triggering Rb/E2F dependent entry of cells into cell cycle (45). Consequently, potential combination options to KRAS inhibition include a CDK4/6 inhibitor (NCT04185883).

Use of indirect inhibitors of KRAS

The combination of KRAS G12C and SHP2 inhibitors showed higher efficacy in preclinical and animal models (74,45). Phase I/II ongoing clinical trials are exploring the association of a KRAS G12C inhibitor and a SHP2 inhibitor (NCT04330664, NCT04185883, NCT04699188) (*Table 2*). SOS1 is another possible target protein (75). The SOS1 inhibitor BAY-29 exhibited efficacy in combination with ARS-853, a KRAS G12C inhibitor (76). BI-3406 is a selective SOS1-KRAS interaction inhibitor, effective in KRAS-driven tumors through combined MEK inhibition (77).

Table 3 Inhibitors of the downstream signal pathway of KRAS in selected clinical trials

NCT number	Phase	Compound	Other molecules tested	Indication	Status/outcomes
NCT03284502	I	Belvarafenib (pan-RAF inhibitor)	Anti-MEK; anti-EGFR	Combination therapy for AST with RAS or RAF mutation	Ongoing
NCT03990077	I	HL-085 (MEK inhibitor)	Docetaxel	Combination therapy for NSCLC with KRAS mutation	Ongoing
NCT01859026	I	Binimetinib (MEK inhibitor)	Anti-EGFR	Combination therapy for NSCLC with KRAS or EGFR mutation	Ongoing
NCT02964689	I	Binimetinib (MEK inhibitor)	Chemotherapy	Combination therapy for advanced NSCLC with KRAS mutation	Completed
NCT01986166	I	Cobimetinib (MEK inhibitor)	EGFR/HER3 inhibitor	Combination therapy for AST with KRAS mutation	Completed
NCT02974725	I	LXH254 (RAF inhibitor)	RAF/ERK, MEK and CDK inhibitors	Combination therapy for advanced KRAS or BRAF mutant NSCLC or NRAS mutant melanoma	Ongoing
NCT04620330	II	VS-6766 (RAF/MEK inhibitor)	Anti-FAK	Monotherapy and combination therapy for NSCLC with KRAS mutation	Ongoing
NCT04418167	I	JSI-1187 (ERK inhibitor)	Anti-BRAF	Monotherapy and combination therapy for AST with MAPK pathway mutations	Ongoing
NCT03415126	I	ASN007 (ERK inhibitor)	–	Monotherapy for AST in selected indications	Completed
NCT03051035	I	KO-947 (ERK inhibitor)	–	Monotherapy for AST in selected indications	Terminated
NCT04073680	I/II	Serabelisib (PI3K inhibitor)	SGLT2 inhibitor	Combination therapy for AST with PIK3CA or KRAS mutation	Ongoing
NCT04586270	I	TAS0612 (multikinase inhibitor)	–	Monotherapy for AST in selected indications	Ongoing
NCT02583542	I/II	AZD2014 (mTOR inhibitor)	Anti-MEK	Combination therapy for AST in selected indications	Ongoing

KRAS, Kirsten rat sarcoma viral oncogene; AST, advanced solid tumors; NCT, national clinical trial; NSCLC, non-small cell lung cancer.

Use of inhibitors of the upstream signal pathway of KRAS

The therapeutic addition of EGFR inhibitors counteracts the activation feedback of the EGFR signalling pathway induced by KRAS inhibitors. NCT01859026 is a phase I trial of MEK162, a MEK inhibitor, in combination with erlotinib, an EGFR inhibitor, in NSCLC harbouring KRAS or EGFR mutations (*Table 3*). The KRYSTAL-1 study consists of an arm with adagrasib together with afatinib, an ErbB family inhibitor, in KRAS-mutant NSCLC. CodeBreak 101 also combines, in one arm, sotorasib with a pan-ErbB inhibitor. NCT04449874, Phase I, studies GDC-6036 with erlotinib. These mentioned clinical trials are summarised in *Table 2*.

Use of agents acting outside KRAS

Since in NSCLC chemotherapy is now routinely combined with first-line immunotherapy (78), it is of particular interest to understand whether the addition of a KRAS G12C inhibitor to standard therapy may be synergistic. Although chemotherapy is standard-of-care for patients with KRAS-mutant NSCLC, response rates are in many cases low and outcomes poor (79). Promising evidence from preclinical studies came from the combination of carboplatin with sotorasib, which was shown to significantly increase tumor cell killing (80). Sotorasib is presently under study in combination with chemotherapy in the CodeBreak 101 trial. Certainly, the choice of chemotherapy regimen is important,

as subtypes of KRAS-mutant NSCLC may respond differently to different regimens (81). A phase III clinical trial of cisplatin-pemetrexed compared with carboplatin-paclitaxel-bevacizumab as first-line therapy in patients with NSCLC and KRAS mutation is ongoing (NCT02743923). *In vitro*, data indicates that KRAS-mutant cancers are immunosuppressive and induce the formation of regulatory T cells (82,83). PD-L1 expression is also higher in KRAS-mutant tumors such as lung adenocarcinoma where KRAS mutations are linked to tobacco smoke, high TMB and an inflammatory tumor microenvironment (84-88). In addition, oncogenic RAS signalling increases PD-L1 expression by activating various KRAS downstream pathways and increases PD-L1 mRNA stability (89,90). All this evidence is suggestive that KRAS-mutant NSCLC may respond positively to immunotherapy. However, co-occurring mutations may influence the response to immunotherapy. In a paper by Skoulidis *et al.*, in KRAS-mutant lung adenocarcinoma, the ORR of immunotherapy was approximately 28.6%, 7.4% and 35.7% in the groups with KRAS mutations alone, KRAS co-mutations with STK11/liver kinase B1 (LKB1) and TP53, respectively (91). This is likely related to the high levels of tumor-infiltrating $CD8^+$ cytotoxic cells, the high overall mutation load and the high expression of PD-L1 in the TP53-mutated subgroup (92,93). Patients with co-mutations in KEAP1/nuclear factor (erythroid-derived 2)-like 2 (NFE2L2) have significantly lower survival [hazard ratio (HR) =1.96, 95% CI: 1.33–2.92, P≤0.001] (91). In an exploratory analysis on STK11 and KEAP1 mutational status and efficacy in KEYNOTE-042, ORR, PFS and OS with pembrolizumab were similar in patients with versus without STK11 or KEAP1 mutation. The efficacy of chemotherapy was lower in patients with versus without STK11 mutation. Better outcomes were observed with pembrolizumab compared to chemotherapy, regardless of STK11 or KEAP1 status (94). In another exploratory analysis of KEYNOTE-189 by STK11 and KEAP1 status, lower ORR and shorter PFS and OS were obtained with pembrolizumab plus chemotherapy in patients with versus without STK11 and KEAP1 mutations. However, pembrolizumab plus chemotherapy was associated with better outcomes than placebo plus chemotherapy regardless of mutational status (95). These data suggest a prognostic and non-predictive value of response to immune checkpoint inhibitors (ICIs) by STK11 and KEAP1 mutations (96).

Compared to KRAS wild-type patients, heavily pretreated patients with KRAS-mutant NSCLC had better responses to immunotherapy. A meta-analysis of three studies showed extended OS in KRAS-positive pretreated patients who received nivolumab or atezolizumab (97). In a retrospective study of patients treated with immunotherapy for oncogene-addicted NSCLC, KRAS mutated patients achieved a better ORR (26%) than those with different mutations such as EGFR (12%) and anaplastic lymphoma kinase (ALK) (0%) (98). In addition, patients with the KRAS G12C mutation appear to gain a greater benefit from immunotherapeutic agents than patients with other mutations (99). In a retrospective study, the KRAS G12D mutation was associated with poor OS (HR =2.43, 95% CI: 1.15–5.16, P=0.021) (92). A further retrospective study of patients with KRAS-mutant NSCLC treated with ICIs, did not detect relevant differences in OS or PFS between the major KRAS mutations (G12A, G12C, G12D, G12V and G13C) (100). The majority of data to date supports the benefit on ICIs in KRAS-mutant NSCLC. In a retrospective analysis of the first-line KEYNOTE-042 trial of pembrolizumab versus chemotherapy in advanced, non-squamous NSCLC with PD-L1 Tumor Proportion Score (TPS) ≥1%, 69 (23%) patients had KRAS mutations and 29 (10%) of them had G12C mutation (88). In both these subgroups, a better OS was found with pembrolizumab compared to chemotherapy, with HR 0.42 (95% CI: 0.22–0.81) and 0.28 (95% CI: 0.09–0.86) respectively. First-line therapy with ICIs in patients with advanced NSCLC and PD-L1 TPS ≥50% was evaluated in a retrospective analysis in which KRAS mutations were found in 573 patients (50.8%) out of 1127 evaluated (101). Monoimmunotherapy resulted in a better median OS in the KRAS mutated group than in the KRAS wild-type group (mOS 21.1 versus 13.6 months, P=0.03). No differences were observed for OS with chemoimmunotherapy in KRAS mutated and wild-type patients nor between ICI monotherapy and chemoimmunotherapy in the KRAS-mutant NSCLC patients. The efficacy of chemoimmunotherapy in KRAS-mutant NSCLC was also retrospectively studied in the KEYNOTE-189 trial of pembrolizumab plus chemotherapy versus placebo plus chemotherapy as first-line therapy for advanced non-squamous NSCLC (85). 89 (31%) patients were KRAS mutated and 37 (13%) had the G12C mutation. Immunotherapy-associated OS benefit was observed in KRAS wild-type patients while immunotherapy-associated improved PFS was seen in both KRAS mutated and wild-type patients. Regarding the therapy setting after first-line, in a systematic review and meta-analysis of five randomised clinical trials and over 3000 patients, ICIs were associated with a longer OS (HR 0.69, 95% CI: 0.63–0.75, P<0.001). The survival benefit was not observed in 371 KRAS wild-

type patients (HR 0.86, 95% CI: 0.67–1.11, P=0.24) but in 148 KRAS mutated patients (HR 0.65, 95% CI: 0.44–0.97, P=0.03) (102).

A recent meta-analysis considered randomised-trial data comparing first- or second-line anti-PD-(L)1 with or without chemotherapy versus chemotherapy alone for KRAS-mutant advanced NSCLC (103). The authors analysed three first-line clinical trials (IMpower-150, KEYNOTE-189 and KEYNOTE-042) and three second-line trials (Oak, Poplar and CheckMate-057) that involved 1, 313 NSCLCs (386 with the KRAS mutation and 927 without this mutation). Immunotherapy with or without chemotherapy was significantly associated with prolonged OS (HR 0.59, 95% CI: 0.49–0.72, P<0.00001) and PFS (HR 0.58, 95% CI: 0.43–0.78, P=0.0003) compared to chemotherapy alone in patients with KRAS-mutant NSCLC. Survival for KRAS mutated patients was longer than for KRAS wild-type patients (P=0.001) (103).

Blocking the PD-1/PD-L1 pathway is a promising therapeutic option for the management of KRAS-mutant NSCLC. To date, several studies have suggested a synergistic effect between KRAS G12C inhibitors and immunotherapeutic agents. In a KRAS G12C syngeneic tumor model, sotorasib combined with an anti-PD-1 agent resulted in complete remission in 9/10 mice bearing KRAS G12C-mutated tumors. In contrast, responses appeared in only 1/10 mice with both treatments alone (80). The use of sotorasib in mice with an efficient immune system resulted in increased tumor infiltration by T cells, especially $CD8^+$ T cells, inducing a pro-inflammatory tumor microenvironment (45,80). Therefore, combination therapies are a rational field of research. Phase I studies of sotorasib combined with PD-1 and PD-L1 inhibitors are ongoing (CodeBreak 100 and 101 trials). Also, it has been shown that the immune system is activated by adagrasib (104). In the phase Ib trial NCT03785249, adagrasib is being studied in combination with pembrolizumab as well as in the phase II trial NCT04613596 for NSCLC with KRAS G12C mutation. Finally, GDC-6036 plus atezolizumab and JDQ443 plus spartalizumab are being tested in phase I studies NCT04449874 and phase I/II NCT04699188, respectively (*Table 2*).

Use of inhibitors of KRAS synergetic genes

Bortezomib is a proteasome inhibitor. Specifically, it inhibits the chymotrypsin-like activity of the 26S proteasome, which is a polypeptide complex responsible for the degradation of ubiquitinated proteins. Proteasome inhibition mediated by bortezomib has several effects on cancer cells, including alteration of regulatory proteins controlling cell cycle progression and activation of nuclear factor kB (NF-kB). The result is cell cycle arrest and apoptosis (105). In addition, selinexor is a selective nuclear export inhibitor that blocks exportin 1, the main mediator of nuclear export of many cargo proteins, including tumor suppressor proteins, growth regulators and oncoprotein mRNAs (106). Selinexor administered with docetaxel is being evaluated for pretreated, advanced KRAS-mutant NSCLC in a phase I/II study (NCT03095612).

Ganetespib is a small molecule capable of inhibiting heat shock protein 90 (HSP90), which is responsible for the activation of several protein systems that in turn determine neoplastic growth and progression. Sos *et al.* found tumor regression after treatment with HSP90 inhibitors in a mouse model of lung adenocarcinoma with KRAS mutation (107). Ganetespib showed efficacy in KRAS-mutant NSCLC in a phase II study (108) but not in another phase II study combined with docetaxel (109). Puyol *et al.* found CDK4 to have a synthetic effect on KRAS-mutant NSCLC (110). Palbociclib and abemaciclib are CDK4/6 inhibitors being tested in clinical trials.

Other treatment options

Mesenchymal-epithelial transition factor (MET) is a transmembrane tyrosine kinase receptor that plays a key role in cell growth, survival, angiogenesis, invasion and can also activate the KRAS pathway. Onartuzumab and tivantinib are MET inhibitors: the former did not lead to a response in KRAS-driven NSCLC in a phase II study (111), the latter showed a significantly improved PFS in patients with KRAS-mutant NSCLC in an exploratory analysis in a phase II study (HR =0.18, 95% CI: 0.05–0.70, P=0.006) (112).

Inhibition of FAK can remodel multiple aspects of the tumor microenvironment and induce KRAS-mutant cell death (113). In a phase II study of the FAK inhibitor defactinib as a treatment in patients with KRAS-mutant NSCLC, the drug showed some clinical activity (NCT01778803) (114).

Poly (ADP-ribose) polymerases (PARP) enzymes, such as PARP-1, are involved in DNA damage repair, cell cycle regulation and cell death, and the combination with Wee1-like protein kinase (WEE1) (G2 checkpoint regulatory kinase of the cell cycle) inhibitors kills 25–40% of KRAS-mutant NSCLC cells (115). Further potential synergistic interactions

include WEE1 and mTOR inhibition, combined inhibition of checkpoint kinase 1 (Chk1) and MAPK-activated protein kinase 2 (MK2) and combined bromodomain and extraterminal (BET)/MEK inhibitors (116-118).

Conclusions

G12C is the prevalent KRAS mutation in NSCLC and is present in an estimated 13% of lung adenocarcinomas. KRAS has always been one of the most challenging therapeutic targets in cancer research; the results with sotorasib change clinical practice by providing a new therapeutic opportunity to patients who previously had no targeted treatment options available. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) also recently adopted a positive opinion recommending conditional marketing authorisation of sotorasib for the treatment of patients with KRAS G12C-mutant NSCLC and who have progressed after at least one prior line of systemic therapy (119). However, there are co-mutations of special interest and it is hypothesised that baseline tumor genomic profiles may affect clinical response in patterns of resistance to sotorasib (44,92). Co-mutations or alterations were detected in TP53 (39–42%), STK11 (20–29%), KEAP1 (13–27%), ataxia telangiectasia mutated (ATM) (13%), MET receptor (15.4%) and ERBB2 (13.8%) (19,26). TP53 inactivating mutations occur in more than 50% of NSCLC (120) and are associated with active inflammation and adaptive immune resistance that may induce PD-L1 expression (121). Inactivating STK11 mutations, on the other hand, affect approximately one-third of KRAS-mutant NSCLC (26) and correlate with neutrophil recruitment and proinflammatory cytokine release to suppress T cell activity (122). An exploratory analysis from KRYSTAL-1 proved a better efficacy of adagrasib in patients with KRAS G12C and STK11 co-mutations compared to those with KRAS G12C mutation alone (46) and tumors with STK11 co-mutation showed an increase in immune response transcripts after adagrasib treatment (123). In addition, researchers performed tissue analysis from CodeBreak 100 and looked at the ensuing genomic profiles in 65 patients at 3 months of follow-up: KEAP1 (n=11), STK11 (n=13), cell cycle genes (n=27), DNA damage response (DDR) genes (n=50), RAS/MAPK pathway (n=23), PI3K-AKT-mTOR pathway genes (n=24), RTK genes (n=39), wingless-related integration site (WNT) pathway genes (n=24). Twenty-two patients (33.8%) presented disease progression before 3 months; 23 patients (35.4%) were late progressors with disease progression at or after 3 months and 20 (30.8%) had disease control. KEAP1 mutational status was associated with early progression (n=7; 63.6%) (44). However, strong conclusions cannot be drawn due to the small number of patients in each subgroup and additional investigation into co-mutational status and sotorasib response is required. In fact, multiple, frequently co-existing resistance mechanisms are possible with KRAS G12C inhibitors and include secondary alterations in KRAS itself, as well as other components of the MAPK pathway and acquired genomic rearrangements and histologic transformation. Direct inhibitors of KRAS G12C have been tested in preclinical trials combined with downstream, upstream and parallel inhibitors of KRAS signalling. For example, sotorasib has been tested *In vitro* in combination with inhibitors of HER kinases, EGFR, SHP2, MEK, PI3K and AKT (80) and synergy has been found with multiple agents, but varying in magnitude between cell lines and xenograft models (32,80). Similar for adagrasib, which showed maximum synergy with the ErbB inhibitor afatinib, followed by mTOR inhibitors such as vistusertib, the CDK4/6 inhibitor palbociclib and the SHP2 inhibitor RMC-4550 (45). Several additional anti-KRAS approaches have shown promise. These include vaccines or tumor-infiltrating lymphocytes (TILs), designed ankyrin repeat proteins (DARPins) that specifically inhibit KRAS/effector interactions, proteolysis targeting chimeras (PROTACs) that induce oncogenic KRAS degradation, unc-51 like autophagy activating kinase (ULK) inhibitors for blocking increased autophagy by MAPK pathway inhibitors and inhibitors of Aurora kinase A (AURKA) that belong to the family of serine/threonine kinases required for cell division processes (74,124-127).

Toxicity remains a key area of research when considering combined treatments, whether with chemotherapy, molecularly targeted drugs or immunotherapy. The latter has the potential to cause serious toxicities with unpredictable timing (128) and to impact subsequent lines of therapy (129). The IMMUNOTARGET registry in NSCLC and oncogenic driver alterations suggests that these patients should receive targeted therapies and chemotherapy before being considered for immunotherapy (98) but in the case of the KRAS mutation, predominantly associated with smoking, it may not be the best decision and additional investigation, especially to understand whether KRAS inhibition before immunotherapy could improve efficacy and safety, is needed.

The approval of sotorasib underlines the critical

importance of offering molecular profiling to each patient with advanced non-squamous NSCLC. The advent of targeted therapy has radically changed the treatment algorithm and the prognosis of patients with NSCLC and driver mutations. Therefore, in this panorama, broad molecular profiling plays a key role by offering the advantage of simultaneously screening for multiple oncogenic drivers as well as emerging biomarkers and providing valuable information for treatment choice at diagnosis but also at disease progression. The confirmatory phase III randomized CodeBreak 200 clinical trial of sotorasib versus docetaxel for the treatment of previously treated advanced NSCLC patients with KRAS G12C mutation is ongoing and, in this context, a comprehensive molecular characterisation of response determinants and mechanisms of innate and acquired resistance to sotorasib is a priority to optimally tailor combination therapies.

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Footnote

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