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REVIEW

How to manage *KRAS* G12C-mutated advanced non-small-cell lung cancer

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Abstract

Constitutive KRAS signalling drives tumorigenesis across several cancer types. In non-small-cell lung cancer (NSCLC) activating *KRAS* mutations occur in ~30% of cases, and the glycine to cysteine substitution at codon 12 (G12C) is the most common *KRAS* alteration. Although *KRAS* mutations have been considered undruggable for over 40 years, the recent discovery of allelic-specific KRAS inhibitors has paved the way to personalized cancer medicine for patients with tumours harbouring these mutations. Here, we review the current treatment landscape for patients with advanced NSCLCs harbouring a *KRAS* G12C mutation, including PD-(L)1-based therapies and direct KRAS inhibitors as well as sequential treatment options. We also explore the possible mechanisms of resistance to KRAS inhibition and strategies to overcome resistance in patients with *KRAS* G12C-mutant NSCLC.

Keywords: G12C, immunotherapy, KRAS, NSCLC, sotorasib.

Citation

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Introduction

The treatment landscape of patients with advanced non-small-cell lung cancer (NSCLC) has dramatically changed over the last 15 years due to improved tumour genomic sequencing technologies and the development of highly effective targeted therapies against cancer drivers such as *EGFR, HER2, BRAF, MET, RET, ALK, ROS1* and *NTRK*.[1–9] In addition, for lung cancers lacking targetable alterations, PD-1/PD-L1 immune-checkpoint inhibitors (ICIs), used alone or in combination with CTLA4 inhibitors and/or cytotoxic chemotherapy, have also led to significant improvements in clinical outcomes and unprecedented benefit in survival.[10–14]

KRAS represents the most commonly mutated oncogene in human cancers. *KRAS* mutations can be detected in up to 30% of lung adenocarcinoma, with the *KRAS* glycine to cysteine substitution (G12C) being the most frequent.[15] Evidence produced over the last decade has highlighted that, similarly to other oncogene-addicted NSCLCs, *KRAS* mutations define a unique subset of patients, with distinct clinicopathological and genomic characteristics.[16–19] *KRAS*-driven lung cancers are generally associated with a history of smoking, high tumour mutational burden, genomic signatures of tobacco smoke exposure with predominant C>A (G>T) transversion mutations, and distinct co-mutation and transcriptomic patterns.[16,17] Although *KRAS* mutations, including the most common *KRAS* G12C variant, have traditionally been considered undruggable, results from early phase clinical trials of direct *KRAS* G12C inhibitors have shown promising activity, with responses observed in 35–40% of NSCLCs harbouring this variant.[20,21]

As more therapeutic options are becoming available for patients with *KRAS*-mutant NSCLC, particularly for those with NSCLC harbouring the *KRAS* G12C variant, it is critical to generate novel therapeutic algorithms to optimize patient selection and inform treatment decisions. Here, we provide a comprehensive overview on the treatment landscape of *KRAS* G12C-mutant NSCLC.

Review

KRAS G12C mutation in lung cancer

KRAS activation is controlled by regulatory factors that promote GDP–GTP exchange (guanine nucleotide-exchange factors; GEFs) or influence GTPase activity (GTPase-activating proteins; GAPs) and its function is dependent on the ratio of GTP to GDP. GEFs and GAPs bind to one or two pockets on RAS proteins, termed Switch I and Switch II regions. Whilst GEFs increase the release of GDP from KRAS and leads to KRAS activation via GTP binding, GAPs enhance KRAS GTPase activity, which leads to a quick active–inactive KRAS state transition.[22,23]

Across tumour types, including in NSCLC, approximately 98% of oncogenic *RAS* mutations occur at either G12 or G13 codons in Switch I or at Q61 codon in Switch II regions.[24] The acquisition of these mutations results in altered KRAS activity that sustains uncontrolled KRAS signalling networks and promotes tumour formation and progression (Figure 1A,B). G12 mutations in *KRAS* are the most common alteration, accounting for nearly 90% of all *KRAS* mutations in lung cancer followed by mutations in codons 13 and 61.[24] Emerging evidence has shown that different KRAS isoforms are highly heterogeneous in terms of clinical features, concurrent genomic alterations and gene-expression profiles, highlighting potential isoform-dependent therapeutic vulnerabilities of different *KRAS* mutants.[16] *KRAS* G12C mutations are strongly associated with tobacco exposure and have been consistently reported to have a higher tumour mutational burden and a high rate of concurrent mutations in genes such as *STK11*, *KEAP1*, *SMARCA4* and *ATM* compared to other *KRAS* isoforms and *KRAS* wild-type NSCLCs.[16,17] In addition, NSCLCs with *KRAS* G12C mutations tend to upregulate markers of immune evasion such as PD-L1 and PD-L2, thus partly explaining the increased sensitivity to ICIs observed in this patient population.[16,25]

Despite the well-established role of KRAS in tumorigenesis, past efforts to develop targeted inhibitors have failed, until recently. In 2013, Ostrem et al. identified small-molecule inhibitors capable of irreversibly binding in the Switch II pocket, thereby locking the target in its inactive conformation[26] (Figure 2A). Two major features of *KRAS* G12C made direct targeting possible: first, the strong nucleophilicity of the acquired cysteine allowed the exploitation of covalent drug-discovery methods that were not applicable to the other common *KRAS* alleles, and second, the exquisite intrinsic GTPase activity uniquely maintained in this allele allowed successful targeting of KRAS in its GDP state (RAS [OFF] inhibitors)[27] (Figure 2A). Recently, the accelerated FDA approval of sotorasib (AMG 510), a *KRAS* G12C-selective inhibitor, for the treatment of patients with *KRAS* G12C lung adenocarcinoma and the breakthrough therapy designation for adagrasib (MRTX849) marked the first approved targeted therapy for tumours with *KRAS* mutation[20,21] (Figure 2B,C). Based on this success, several other direct KRAS inhibitors are being developed. Interestingly, another recent approach to target *KRAS* mutations, including the *KRAS* G12C variant recently disclosed by Revolution Medicine, relies on the so-called 'molecular glue' mechanism targeting the active GTP state of KRAS and involving the formation of a tri-complex with cyclophilin.[28] Due to their ability to target GTP-bound KRAS (G12C), these compounds are referred as to RAS (ON) inhibitors. Amongst these, RMC-6291 shows sustained pathway inhibition following RTK activation, consistent with targeting the active form of KRAS G12C.

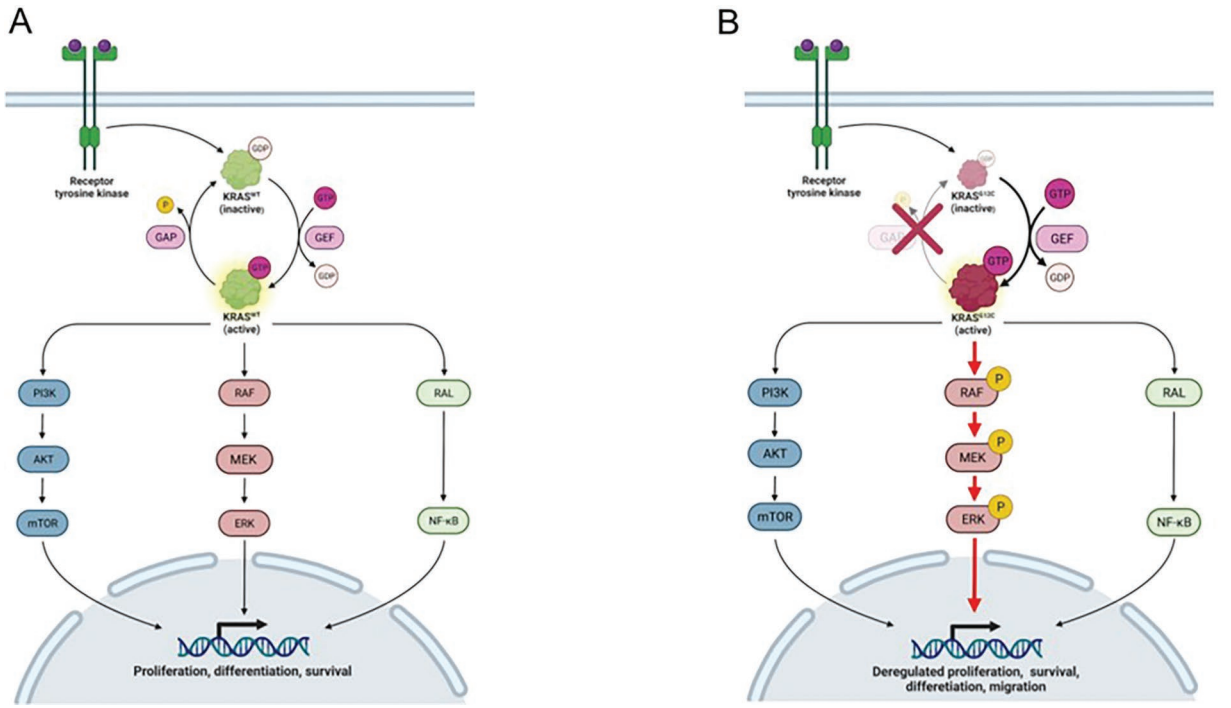
Therapeutic approach to *KRAS* G12C-mutant NSCLC

Immune-checkpoint inhibition with or without platinum-based chemotherapy for *KRAS* G12C-mutant NSCLC

Oncogenic *KRAS* mutations have diverse immunomodulatory effects in solid tumours, including NSCLC. Preclinical studies have shown that PD-L1 is up-regulated by *KRAS* mutation through sustained p-ERK activation. Furthermore, this upregulation induces $CD3^+$ T cell apoptosis, which can be reversed by anti-PD-1 antibody or ERK inhibitor treatment, suggesting that PD-1 blockade potentially restores the antitumour immunity of T cells in *KRAS*-mutated NSCLCs.[29,30] More recently, it was shown that KRAS increases PD-L1 expression via an increase in PD-L1 mRNA stability through the regulation of the AU-rich element-binding protein tristetraprolin (TTP), which is mediated by downstream MEK signalling pathways.[31] *KRAS* mutations have also been shown to be involved in the downregulation of major histocompatibility complex (MHC) class I molecules, leading to a reduced ability of $CD8^+$ cytotoxic T cells to recognize tumour antigens and elicit anti-tumour immune responses.[32] In addition, Zdanov et al. identified that mutant *KRAS* can induce the conversion of conventional $CD4^+$ T cells to regulatory T cells. Notably, this conversion is largely driven by the secretion of IL-10 and TGFβ1 via MEK–ERK–AP1 axis activation,[33] again highlighting the role of the constitutive activation of KRAS signalling in producing an immunosuppressive tumour microenvironment.

Against this preclinical background, and because *KRAS* mutations (especially the *KRAS* G12C variant) have also been associated with tobacco use and with an increased burden of non-synonymous mutations, it has been suggested that patients with *KRAS*-mutant NSCLC may have improved clinical outcomes with ICIs than patients with NSCLCs lacking *KRAS* alterations. PD-(L)1 inhibition with or without platinum-based chemotherapy has improved clinical outcomes and survival in patients with metastatic NSCLC[34] and currently represents the optimal first-line treatment for patients with NSCLC with no actionable drivers based on large randomized phase III clinical trials.[10,12–14,35] In such cases, the percentage of tumour cells that express PD-L1 (the tumour proportion score; TPS) is currently the most important factor determining the choice of first-line treatment and can guide treatment decisions. The combination of the PD-1 inhibitor pembrolizumab (KEYNOTE-189, KEYNOTE-407) or the PD-L1 inhibitor

Figure 1. Signalling pathways in wild-type and mutant *KRAS* cells. (A) KRAS plays a crucial role in signalling through the MAPK pathway, the PI3K–Akt–mTOR pathway and the NF-kB pathway. (B) Mutations in *KRAS* result in enhanced GTP-loading, causing aberrant activation of the MAPK pathway.

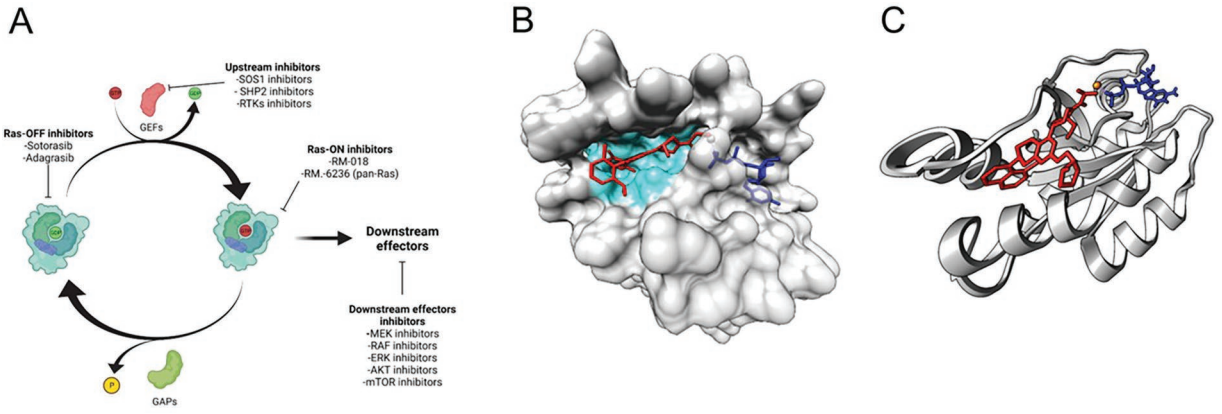


atezolizumab (IMpower150, IMpower 130) with platinum-based chemotherapy has improved the objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) compared to chemotherapy alone in NSCLC across all PD-L1 expression levels (from <1% to 100%).[12,35,36] Importantly, in each of these studies, increasing PD-L1 expression levels were associated with improved efficacy in the chemo-immunotherapy arm. Similarly, the combination of PD-1 (nivolumab) and CTLA4 (ipilimumab) inhibition with platinum-based chemotherapy also improved clinical outcomes compared to chemotherapy alone in the CheckMate 9LA study across all PD-L1 expression levels amongst patients with *EGFR/ALK* wild-type NSCLC.[37,38] When deciding between the various first-line chemo-immunotherapy options, the different safety profiles may help individualize treatment decisions. In general, the KEYNOTE-189 regimen is favoured because of the better safety profile of pemetrexed-based chemotherapy, whereas taxane-based strategies (Impower150/130) are associated with alopecia and peripheral neuropathy and may impact patients' quality of life. Nonetheless, taxanes are an appropriate alternative for patients with renal failure in whom other chemotherapies (e.g. pemetrexed) are contraindicated. Lastly, in the KEYNOTE-189 study, patients could receive maintenance pemetrexed, which was shown to extend OS compared with no maintenance therapy in the pre-ICI era PARAMOUNT study.[39]

The combination of PD-(L)1 blockade with chemotherapy is preferred for most of the patients with *KRAS* G12C mutation and negative or low PD-L1 expression. However, based on the KEYNOTE-042 study, which randomized patients with PD-L1 TPS ≥1% to receive pembrolizumab or platinum-based chemotherapy, the use of PD-1 inhibition as monotherapy has also been explored and approved as an alternative therapy for NSCLCs and a PD-L1 TPS ≥1%.[13] Although the study met its primary endpoint of OS, there was no difference between the treatment arms amongst patients with PD-L1 expression of 1–49%, suggesting that the benefit observed in all comers in the pembrolizumab treatment arm was driven by cases with high PD-L1 expression (TPS ≥50%). Moreover, no difference in PFS was observed between the two groups in this study, confirming the limited role for PD-1 monotherapy for NSCLC with low PD-L1 expression.

ICI monotherapies have also been investigated as therapeutic options for patients with advanced NSCLC and high PD-L1 expression (≥50%) regardless of *KRAS* mutation status. In the KENYNOTE-024 study, pembrolizumab monotherapy was superior to platinum doublet chemotherapy in patients with NSCLC and a PD-L1 TPS ≥50% in terms of ORR, PFS and OS.[10] Similarly, based on the IMpower110 trial, in which atezolizumab excelled over platinum doublet chemotherapy in terms of PFS and OS,[40] atezolizumab monotherapy has been approved as front-line treatment for patients with NSCLC and a high PD-L1 expression of ≥50% on tumour cells (TC3) or ≥10% on tumour-infiltrating immune cells (IC3). This study met its primary endpoint (OS) in patients whose tumours had high

Figure 2. **(A) KRAS GTPase cycle. GTP binding is induced by guanine nucleotide-exchange factors (GEFs) and GTP hydrolysis is catalysed by GTPase-activating proteins (GAPs) to cycle KRAS from the active form to the inactive form. (B) Sotorasib (red) binding GDP (blu)-KRAS G12C in Switch II pocket. (C) GDP (blu)-KRAS G12C binding with MRTX-849 (red) in Switch II pocket. (Molecular graphics and analyses performed with UCSF Chimera, developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco, with support from NIH P41-GM103311.)**

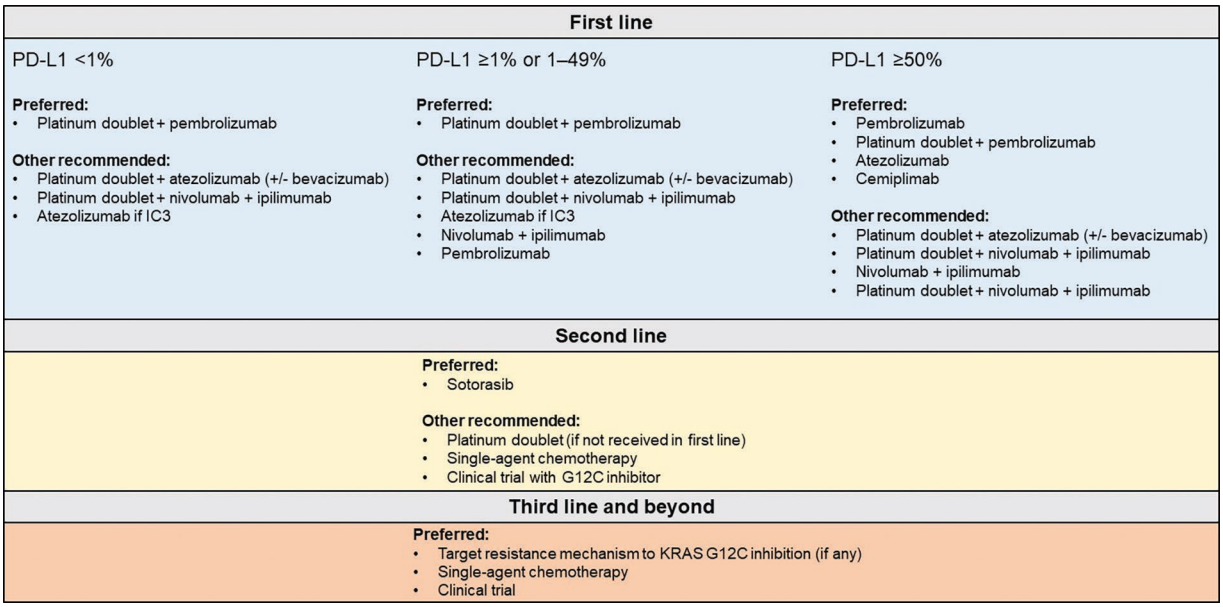


PD-L1 expression on either cancer cells or immune cells. However, whether this treatment strategy improves outcomes for tumours with PD-L1 expression restricted only to immune cells remains to be determined as the evidence supporting the predictive value of PD-L1 expression on immune cells in NSCLC is limited. Therefore, for patients with NSCLC and high levels of PD-L1 expression on immune cells but not on tumour cells, including *KRAS* G12C-mutant NSCLCs, a combination therapy of chemotherapy plus PD-(L)1 inhibition should be preferred (Figure 3).

Whether *KRAS* mutation is associated with distinct clinical outcomes to PD-(L)1-based therapies is still under investigation. A subgroup analysis of the KEYNOTE-042 study comparing pembrolizumab *versus* chemotherapy in advanced, PD-L1-positive (≥1%) NSCLC showed an ORR of 56.7% in patients with any *KRAS* mutation and of 66.7% in patients with a *KRAS* G12C mutation treated with pembrolizumab.[41] These response rates were significantly higher than the ORR in patients with any *KRAS* mutation or a *KRAS* G12C mutation (18% and 23.5%, respectively), treated with chemotherapy alone. Importantly, PFS and OS were also significantly improved amongst patients with any *KRAS* mutation, including *KRAS* G12C, who were allocated in the pembrolizumab arm compared to those who received chemotherapy.[41] In a similar *post hoc* analysis of the KEYNOTE-189 trial, patients whose NSCLC harboured any *KRAS* mutation, and specifically the *KRAS* G12C mutation, who received chemo-immunotherapy experienced improved outcomes compared to those who were randomized to chemotherapy alone. In another subgroup analysis of the IMpower150 study, patients with *KRAS*-mutant tumours demonstrated greater OS and PFS improvements with atezolizumab plus chemotherapy compared to those who received chemotherapy alone.[42] Although these results derive from a retrospective analysis of randomized clinical trials and are limited by the small sample size, they consistently suggest that PD-1 monotherapy and PD-(L)1 inhibition with platinum-based chemotherapy are effective for *KRAS*-mutant NSCLC and should be considered appropriate first-line options for these patients. At the present time, we favour using PD-(L)1 monotherapies or chemo-immunotherapy for *KRAS* G12C-mutant NSCLCs and a PD-L1 TPS ≥50%, and a combination of chemotherapy plus PD-(L)1 inhibition for patients with a PD-L1 TPS of 1–49%. However, for patients with low PD-L1 TPS (e.g. 1–49%) who are likely to not tolerate chemotherapy, pembrolizumab monotherapy is an acceptable alternative option. For patients with a PD-L1 TPS <1%, a combination approach with either PD-1 or PD-L1 inhibition plus chemotherapy represents the best first-line option. Although we do not have prospective data on whether patients with advanced NSCLC and PD-L1 expression ≥50% have different outcomes to PD-1 monotherapy *versus* chemo-immunotherapy, a recent retrospective analysis has identified that patients with PD-L1^{high} NSCLC with *KRAS* mutation had favourable survival (median OS ≥20 months) with either ICI monotherapy or chemo-immunotherapy, suggesting that these options are potentially equally effective for this subset of patients.[43]

Although PD-(L)1-based therapies are associated with better outcomes compared to chemotherapies in *KRAS*-mutant NSCLC, an important consideration when deciding the optimal first-line therapy is the mutation status of genes frequently co-mutated in *KRAS*-driven tumours, which may affect the efficacy of immunotherapies. In the context of *KRAS* mutation, loss-of-function mutations in *STK11*, *KEAP1* and *SMARCA4* have been associated with resistance to PD-(L)1 blockade

Figure 3. Proposed therapeutic algorithm for patients with *KRAS* G12C-mutant non-small-cell lung cancer.



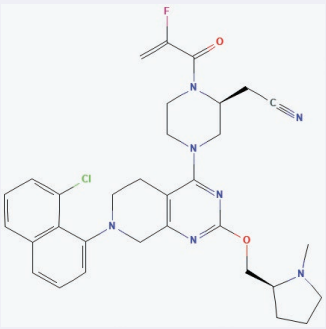
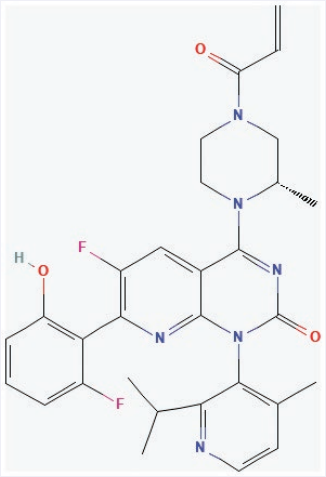
alone in both PD-L1^{high} and PD-L1^{low} NSCLCs and decreased intratumoural T cell density.[44–46] Specifically, amongst *KRAS* G12C-mutant NSCLC, concurrent *STK11* mutations are associated with significantly shorter PFS (2.3 *versus* 4.9 months; HR 1.91; $p<0.001$) and OS (6.2 *versus* 16.9 months; HR 1.91; $p<0.001$) to PD-1/PD-L1 inhibitors compared to cases with an *STK11* wild-type genotype. Similarly, loss-of-function mutations in *KEAP1* are also associated with worse PFS (23.3 *versus* 4.8 months; HR 1.70; $p<0.01$) and OS (6.2 *versus* 17.2 months; HR 1.87; $p<0.01$) to PD-1/PD-L1 inhibition amongst *KRAS* G12C-mutated NSCLC. In such cases, which are predicted not to respond to PD-(L)1 monotherapy, a combination of platinum-based chemotherapy with PD-(L)1 blockade can be considered as an appropriate first-line option regardless of PD-L1 status. Whether these alterations also affect outcomes to chemo-immunotherapy in *KRAS*-mutant NSCLC is currently under investigation.

Targeting *KRAS* G12C mutation with direct KRAS inhibition

Over the last decade, several potent small molecules that irreversibly bind to the mutant cysteine of *KRAS* G12C and lock KRAS G12C in the GDP-bound inactive state have been developed. To date, two highly specific, irreversible small-molecule inhibitors of KRAS G12C are in advanced clinical development either alone or in combination with other therapeutics, sotorasib and adagrasib (Table 1). Sotorasib was granted accelerated approval for adult patients with *KRAS* G12C-mutated locally advanced or metastatic NSCLC who have received at least one prior systemic therapy, whilst a new drug application for adagrasib was accepted by the FDA.

CodeBreaK 100 is a phase I trial that investigated the safety of sotorasib at doses ranging from 180 to 960 mg amongst 129 patients with advanced solid tumours harbouring *KRAS* G12C mutation.[47] The most common treatment-related adverse events (TRAEs) were diarrhoea (29.5%), fatigue (23.3%) and nausea (20.9%), whereas no dose-limiting toxicities were observed. In terms of activity, amongst 59 patients with NSCLC included in the study, 19 (32.2%) had a confirmed partial response (PR) and 33 had stable disease, with a disease control rate of 88.1%. The median time to response was 1.4 months, the median duration of response (mDOR) was 10.9 months, whereas median PFS (mPFS) was 6.3 months. Based on these encouraging results, a single-arm phase II trial evaluated the activity of sotorasib (at a dose of 960 mg once daily) in patients with previously treated KRAS G12C mutant advanced NSCLC.[20] Amongst 124 evaluable patients, the ORR was 37.1%, including 3.2% complete response and 33.9% PR. The mDOR was 11.1 months, the disease control rate was 80.6% whereas the mPFS and median OS were 6.8 and 12.5 months, respectively. The most reported TRAEs were diarrhoea (31.7%), nausea (19%), increased transaminase levels (15.1% for both AST and ALT) and fatigue (11.1%), leading to dose modification in 22.2% of cases and to therapy discontinuation in 7.1% of cases. Interestingly, responses were observed across all levels of PD-L1 expression, including tumours with low PD-L1 and *STK11* co-mutations, which identify patients less likely to benefit from ICIs.[45,48] More recently, the results of the phase III, randomized, open-label trial of sotorasib compared to docetaxel in patients with previously treated *KRAS* G12C-mutant advanced NSCLC (CodeBreaK 200) were reported. This study met its primary endpoint of improved PFS (5.6 *versus* 4.5 months; HR 0.66; $p=0.002$). Sotorasib was also associated with an improved ORR of 28.1% *versus* 13.2% as compared with docetaxel.[49] Of note, no difference in OS was

Table 1. Structure and ongoing clinical trials of sotorasib and adagrasib.

Compound	Structure	Target	Clinical trial and setting
Adagrasib (MRTX-849)		GDP-KRAS (OFF) G12C	**NCT04685135** (≥second line) **NCT04613596** (combination with pembrolizumab, first line) **NCT04975256** (combination with BI 1701963, any line) **NCT04330664** (combination with TNO155, any line)
Sotorasib (AMG-510)		GDP-KRAS (OFF) G12C	**NCT05118854** (combination with cisplatin/carboplatin and pemetrexed, neoadjuvant) **NCT04625647** (≥second line) **NCT04933695** (first line) **NCT05180422** (combination with MVASI, any line) **NCT05273047** (EAP) **NCT04667234** (EAP) **NCT04303780** (≥second line) **NCT05074810** (combination with VS-6766 MEK inhibitor, post G12C inhibition) **NCT04185883** (in combination with AMG 404, trametinib, RMC-4630, afatinib, pembrolizumab, panitumumab, carboplatin, pemetrexed, docetaxel, atezolizumab, everolimus, palbociclib, loperamide, TNO155, any line)

EAP, expanded access program.

reported between the treatment arms, possibly because of crossover. CodeBreaK 200 also confirmed the safety profile of sotorasib, with grade ≥3 adverse events occurring in 33.1% of patients receiving sotorasib.

The safety and activity of adagrasib (MRTX849) were evaluated in the phase I/Ib first-in-human KRYSTAL-1 trial amongst patients with solid tumours harbouring a *KRAS* G12C mutation.[50] Amongst 15 patients with NSCLC, 8 (53.3%) were treated with the recommended phase II dose (RP2D) of 600 mg twice daily and showed a PR; mDOR was 16.4 months and mPFS was 11.1 months. At the recommended phase 2 dose, the most common TRAEs of any grade were nausea (80%), diarrhoea (70%), vomiting (50%) and fatigue (45%), the latter being the most common grade 3–4 TRAE (15%).
A subsequent registrational phase II cohort investigated the activity of adagrasib amongst patients with *KRAS* G12C-mutated NSCLC previously treated with platinum-based chemotherapy and ICI.[51] Amongst 112 evaluable patients, 1 (0.9%) had a complete response, 47 (42.0%) had a PR and 41 (36.6%) had stable disease, with a confirmed ORR of 42.9%. Amongst 48 patients showing response to adagrasib, the median time to response was 1.4 months and mDOR was 8.5 months. mPFS was 6.5 months, and the updated median OS was 12.6 months.

Amongst 33 evaluable patients with previously treated, stable brain metastases, the intracranial ORR was 33.3% and the median duration of intracranial response was 11.2 months. The most common TRAEs were diarrhoea (62.9%), nausea (62.1%), vomiting (47.4%), fatigue (40.5%), transaminases elevation (27.6% for ALT, 25% for AST) and increased blood creatinine level (25.9%). The most common grade 3 TRAEs were fatigue, nausea and transaminases elevation (4.3% for each), whereas TRAEs leading to dose modification and to therapy discontinuation were observed in 51.7% and in 61.2% of cases, respectively. A phase III trial evaluating adagrasib compared to docetaxel in patients with previously treated *KRAS* G12C-mutated NSCLC is also currently underway (KRYSTAL-12, NCT04685135) and results are awaited.

Together, these data indicate that direct KRAS G12C inhibitors are safe and active in patients with advanced *KRAS* G12C-mutant NSCLC. As of today, sotorasib is the only agent approved for these patients and should be considered as the optimal second-line option for patients with NSCLC and a *KRAS* G12C mutation who progressed following a PD-(L)1-based regimen. Whether KRAS inhibition is non-inferior to immunotherapy as first-line treatment remains to be addressed prospectively.

Other KRAS inhibitors

In addition to sotorasib and adagrasib, a number of other inhibitors, including direct GDP-bound KRAS G12C (OFF) inhibitors, are in clinical development such as GDC-6036, D-1553, JDQ443 and LY3499446 (NCT04449874, NCT04585035, NCT04699188 and NCT04956640, respectively).[52,53] In addition to irreversible covalent inhibitors, a new class of tri-complex inhibitors of the active GTP-bound (ON) form of KRAS G12 or RAS (ON) inhibitors are in preclinical development. RMC-6291 is a first-in-class, orally available, potent and selective tri-complex RAS (ON) inhibitor, which showed sustained pathway and cell growth inhibition in NSCLC cells *in vitro*,[28] and is currently being evaluated in early phase clinical trials in patients with *KRAS* G12C-mutated tumours (NCT05462717). Additionally, pharmaceutical companies are developing pan-KRAS inhibitors that inhibit SRC homology region 2–containing protein tyrosine phosphatase 2 (SHP2) or Son of sevenless homolog 1 (SOS1), preventing KRAS nucleotide exchange and activation.[54] Currently, SOS1 inhibitors and SHP2 inhibitors are being investigated both as monotherapy (NCT03634982, NCT03114319, NCT04111458) and in the combination setting with MEK inhibitors (NCT04294160, NCT03989115, NCT04720976, NCT04111458, NCT048357), ERK inhibitors (NCT04916236) and EGFR inhibitors (NCT03989115, NCT03114319) for patients with *KRAS* mutation. Several other ongoing studies are investigating the combination of SOS1 and SHP2 inhibitors (which shift KRAS to GDP-bound state) with mutant-specific KRAS inhibitors that bind KRAS in its GDP-bound state (NCT04330664, NCT04185883, NCT04699188, NCT04973163, NCT04975256). More recently, preclinical studies of direct pan-KRAS inhibitors showed selective activity against *KRAS*-driven cell lines (e.g. *KRAS* G12C, *KRAS* G12D, *KRAS* G12V) and cell lines with *KRAS* amplifications but not against *HRAS*-mutated, *NRAS*-mutated or *KRAS* wild-type cell lines.[54] Another emerging pan-KRAS inhibition strategy is based on direct pan-KRAS proteolysis targeting chimeras,[55,56] which are bifunctional molecules that activate the cell protein degradation machinery by recruiting an E3 ligase, ultimately leading to proteasomal degradation of specific targeted proteins such as KRAS.

Resistance to KRAS inhibitors

The lower ORRs obtained with both sotorasib and adagrasib compared to other selective inhibitors, such as osimertinib and alectinib, in other NSCLC subtypes, suggest the presence of mechanisms of intrinsic resistance, such as the compensatory activation of RTKs (e.g. EGFR, HER2, FGFR and c-MET), resulting in rebound activation of wild-type *RAS* (*NRAS* and *HRAS*).[57,58] However, also amongst responders, acquired resistance invariably develops by either on-target or off-target mechanisms.

A recent study evaluating pre-treatment and post-treatment samples from 43 patients with *KRAS* G12C-mutant cancer treated with sotorasib showed that mechanisms of resistance can be identified in more than 50% of cases, including mutations in *KRAS*, *NRAS*, *BRAF*, *EGFR*, *FGFR2*, *MYC* and other genes.[59] Another recent study explored acquired resistance mechanisms amongst 38 patients with *KRAS* G12C-mutant cancer who had disease progression to adagrasib in the KRISTAL-1 study by analysing matched DNA sequencing on tissue samples or circulating tumour DNA.[60] The study detected putative mechanisms of resistance in 17 (45%) patients who were classified into three groups. The first included on-target *KRAS* alterations such as activating mutations in *KRAS* (G12D, G12V, G12V, G13D and Q61H), secondary *KRAS* mutations within the Switch II drug-binding pocket (R68S, H95D/Q/R and Y96C) or *KRAS* amplifications. In the second group, acquired bypass alterations activating the RTK–RAS signalling pathway, such as *MET* amplifications, were included, whilst the third group included histological transformation from adenocarcinoma to squamous-cell carcinoma. Importantly, *in vitro* studies showed that the spectrum of acquired resistance mechanisms was significantly different between sotorasib and adagrasib due to the distinct binding of the two drugs in the Switch II pocket, with potential implications for therapeutic sequencing. Specifically, whilst R68S and Y96C mutations conferred resistance to both drugs, H95D/Q/R mutations were associated with resistance to adagrasib but not to sotorasib, whereas G13D, R68M, A59S and A59T were highly resistant to sotorasib but retain sensitivity to adagrasib.[61]

Adaptive mechanisms of resistance may also contribute to the development of acquired resistance to KRAS inhibition. In preclinical models, Xue et al. identified that the overexpression of constitutively active KRAS mediated by EGFR-stimulated nucleotide can contribute to the development of resistance to RAS (OFF) inhibitors.[62] Increased expression of wild-type *RAS* isoforms (*KRAS*, *HRAS*, *NRAS*) can also sustain proliferation in the presence of RAS (OFF) inhibitors in *KRAS* G12C-mutated tumour cells,[63,64] highlighting the role of wild-type *KRAS* in response to targeted therapy.[65]

Conclusion

KRAS mutations define a distinct biological subtype of NSCLC that is associated with unique clinical, genomic and immunophenotypic features. Although *KRAS* variants have been traditionally grouped together as a single entity, emerging evidence indicates that each KRAS allele has different oncogenic properties and genomic correlates and potentially different outcomes to standard-of-care therapies.[16,25] Because *KRAS* G12C mutation is becoming an established therapeutic target in advanced NSCLC, it is critical to routinely assess *KRAS* mutation status in all patients with newly diagnosed NSCLC.

Currently, NSCLCs harbouring a *KRAS* G12C mutation are grouped with other types of NSCLC that are considered to lack a targetable oncogenic driver when deciding the most appropriate first-line therapy. For these patients, upfront PD-(L)1-based therapies with or without chemotherapy should be considered. Ultimately, whether to use PD-(L)1 monotherapy or chemo-immunotherapy will depend on PD-L1 expression

levels, patient performance status and other features such as age, tumour mutational burden and co-mutation status.

The development of an allosteric inhibitor of KRAS G12C represented a major advance in the field of precision medicine for patients with *KRAS* G12C-mutant NSCLC, and direct KRAS G12C inhibition should be considered as the optimal second-line therapy for patients with advanced NSCLC and a *KRAS* G12C mutation whose tumours have progressed on or following immune-checkpoint inhibition according to available evidence. Importantly, both sotorasib and adagrasib have shown promising activity in patients with central nervous system (CNS) metastasis, which is a common occurrence in this patient population. In a *post hoc* analysis of the CodeBreaK 100 trial, 16 of 174 (9.2%) patients had a baseline and at least one on-treatment evaluable brain scan. Amongst 3 patients with both target and non-target CNS lesions, 1 had a stable disease and 2 had progressive disease. Amongst 13 patients with only non-target CNS lesions, 2 had a complete response, 11 had stable disease and none had progressive disease.[66] Similarly, in the phase Ib cohort of the KRISTAL-1 study of adagrasib in patients with active, untreated CNS metastasis, the intracranial response rate per RANO criteria was 31.6% and the intracranial disease control rate was 84.2%.[67] Whilst *KRAS* G12C direct inhibitors have shown clinically meaningful activity, acquired resistance develops within the first 6–9 months of therapy, and treatment options upon progression to these inhibitors are limited. A number of mechanisms responsible for adaptation and resistance to sotorasib and adagrasib have been identified and are informing several strategies that are under preclinical and clinical development, including combination therapies targeting tyrosine kinase and nucleotide-exchange factors (e.g. EGFR, SHP2, SOS1) or other pathways (e.g. PI3K, mTOR). As more options will be available for these patients, an important question will be how to optimally sequence KRAS inhibition with PD-(L)1 blockade in patients with *KRAS* G12C-mutant NSCLC. Several studies have shown that PD-L1 expression, tumour mutational burden and co-mutation shape the likelihood of responding to PD-(L)1 blockade and KRAS inhibition in patients with *KRAS* G12C-mutant NSCLC. The development of novel biomarkers for ICI efficacy and a deeper understanding of the genomic correlates of sensitivity and resistance to KRAS-directed therapies will help optimize treatment sequences and critically inform the next generation of clinical trials for patients with *KRAS*-mutant NSCLC.

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