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

Biagio Ricciuti¹, Alessia Mira², Elisa Andrini³, Pietro Scaparone³, Sandra Vietti Michelina³, Federica Pecci¹, Luca Cantini², Andrea De Giglio³, Giuseppe Lamberti³, Chiara Ambrogio³, Giulio Metro⁶

¹Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; ²Department of Molecular Biotechnology and Health Sciences, Molecular Biotechnology Center, University of Torino, Torino, Italy; ³Department of Experimental, Diagnostic and Specialty Medicine, Sant’Orsola-Malpighi University Hospital, ENETS Center of Excellence, Bologna, Italy; ⁴Division of Medical Oncology, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy; ⁵Department of Pulmonary Medicine, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; ⁶Medical Oncology, Santa Maria Della Misericordia Hospital, Azienda Ospedaliera di Perugia, Perugia, Italy

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.

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.\(^{16}\)

**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 TGF\(_{\beta}\) 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 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 pembrolizumab (KEYNOTE-042, KEYNOTE-189) is currently the preferred 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.
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%). 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.

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.

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%. 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 KEYNOTE-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. Similarly, based on the IMpower110 trial, in which atezolizumab excelled over platinum doublet chemotherapy in terms of PFS and OS, 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...
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. 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. 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. 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. 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 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 IC1 monotherapy or chemo-immunotherapy, suggesting that these options are potentially equally effective for this subset of patients.

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.
alone in both PD-L1<sup>high</sup> and PD-L1<sup>low</sup> NSCLCs and decreased intratumoral 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 ICI. 55,48 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
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. 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. 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.

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.
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 N Ras and cell growth inhibition in NSCLC cells in vitro.28 In addition, 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

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.

Reference

Ricciuti B, Mira A, et al. Drugs Context. 2022;11:2022-7-4. https://doi.org/10.7573/dic.2022-7-4

ISSN: 1740-4398
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.
References

1. Soria J-C, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non–small-cell lung cancer. *N Engl J Med*. 2018;378(2):113–125. https://doi.org/10.1056/NEJMoa1713137

2. Peters S, Camidge DR, Shaw AT, et al. Alectinib versus crizotinib in untreated ALK-positive non–small-cell lung cancer. *N Engl J Med*. 2017;377(9):829–838. https://doi.org/10.1056/NEJMoa1704795

3. Planchard D, Smit EF, Green HJ, et al. Dabrafenib plus trametinib in patients with previously untreated BRAFV600E-mutant metastatic non–small-cell lung cancer: an open-label, phase 2 trial. *Lancet Oncol*. 2017;18(10):1307–1316. https://doi.org/10.1016/S1470-2045(17)30679-4

4. Wolf J, Seto T, Han JY, et al. Capmatinib in MET exon 14-mutated or MET-amplified non-small-cell lung cancer. *N Engl J Med*. 2020;383:944–957. https://doi.org/10.1056/NEJMoa2002787

5. Shaw AT, Ou SH, Bang Y-J, et al. Crizotinib in ALK-positive non–small-cell lung cancer. *N Engl J Med*. 2014;371(21):1963–1971. https://doi.org/10.1056/NEJMoa1406766

6. Drilon A, Siena S, Dziadziozszo R, et al. Entrectinib in ROS1 fusion-positive non–small-cell lung cancer: integrated analysis of three phase 1–2 trials. *Lancet Oncol*. 2020;21(2):P261–P270. https://doi.org/10.1016/S1470-2045(19)30690-4

7. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol*. 2020;21(4):P531–P540. https://doi.org/10.1016/S1470-2045(19)30856-3

8. Subbiah V, Yang D, Velcheti V, Drilon A, Meric-Bernstam F. State-of-the-art strategies for targeting RET-dependent cancers. *J Clin Oncol*. 2020;38(11):1209–1221. https://doi.org/10.1200/JCO.19.02551

9. Robichaux JP, Elamin YY, Tan Z, et al. Mechanisms and clinical activity of an EGFR and HER2 exon 20-selective kinase inhibitor in non-small cell lung cancer. *Nat Med*. 2018;24(5):638–646. https://doi.org/10.1038/s41591-018-0007-9

10. Reck M, Rodriguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med*. 2016;375(19):1823–1833. https://doi.org/10.1056/NEJMoa1606774

11. Hellmann MD, Paz-Ares L, Bernabe Caro R, et al. Nivolumab plus ipilimumab in advanced non–small-cell lung cancer. *N Engl J Med*. 2019;381:2020–2031. https://doi.org/10.1056/NEJMoa1910231

12. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al. Pembrolizumab in squamous-cell non–small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078–2092. https://doi.org/10.1056/NEJMoa1801005

13. Mok TSK, Wu YL, Kudaba I, et al. Pembrolizumab versus chemotherapy for previously untreated, PD-L1-expressing, locally advanced or metastatic non–small-cell lung cancer (KEYNOTE-042): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2019;393(10183):P1819–P1830. https://doi.org/10.1016/S0140-6736(18)32409-7

14. Socinski MA, Jotte RM, Cappuzzo F, et al. Atadrozib for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med*. 2018;378(24):2288–2301. https://doi.org/10.1056/NEJMoa1816948

15. The Cancer Genome Atlas Research Network. Comprehensive molecular profiling of lung adenocarcinoma. *Nature*. 2014;511(7511):543–550. https://doi.org/10.1038/nature13385

16. Ricciuti B, Son J, Okoro JJ, et al. Comparative analysis and isoform-specific therapeutic vulnerabilities of KRAS mutations in non-small cell lung cancer. *J Natl Cancer Inst*. 2022;114(3):228–239. https://doi.org/10.1093/jnci/djz523

17. Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non–small-cell lung cancer harboring a KRAS G12C mutation. *N Engl J Med*. 2021;384:2371–2381. https://doi.org/10.1056/NEJMoa2103695

18. Ihle NT, Byers LA, Kim ES, et al. Effect of KRAS oncogene substitutions on protein behavior: implications for signaling and clinical outcome. *J Natl Cancer Inst*. 2012;104(3):228–239. https://doi.org/10.1093/jnci/djr523

19. Salgia R, Pharaoh D, Mambetsariev I, et al. The improbable targeted therapy: KRAS as an emerging target in non-small cell lung cancer (NSCLC). *Cell Reports Med*. 2021;2(1):100186. https://doi.org/10.1016/j.xcrm.2020.100186

20. Skoulidis F, Byers LA, Diao L, et al. Co-occurring genomic alterations define major subsets of KRAS-mutant lung adenocarcinoma with distinct biology, immune profiles, and therapeutic vulnerabilities. *Cancer Discov*. 2015;5(8):860–877. https://doi.org/10.1158/2159-8290.CD-14-1236

21. Ihle NT, Byers LA, Kim ES, et al. Effect of KRAS oncogene substitutions on protein behavior: implications for signaling and clinical outcome. *J Natl Cancer Inst*. 2012;104(3):228–239. https://doi.org/10.1093/jnci/djr523

22. Uras IZ, Moll HP, Casanova E. Targeting KRAS mutant non–small-cell lung cancer: past, present and future. *Int J Mol Sci*. 2020;21(12):4325. https://doi.org/10.3390/ijms21124325

23. Singh H, Longo DL, Chabner BA. Improving prospects for targeting RAS. *J Clin Oncol*. 2015;33(31):3650–3659. https://doi.org/10.1200/JCO.2015.62.1052

24. Prior IA, Hood FE, Hartley JL. The frequency of ras mutations in cancer. *Cancer Res*. 2020;80(14):2969–2974. https://doi.org/10.1158/0008-5472.CAN-19-3682

25. Arbour KC, Rizvi H, Plodkowski AJ, et al. Treatment outcomes and clinical characteristics of patients with KRAS-G12C-mutant non–small cell lung cancer. *Clin Cancer Res*. 2021;27(8):2209–2215. https://doi.org/10.1158/1078-0432.CCR-20-4023
26. Ostrem JM, Peters U, Soo ML, Wells JA, Shokat KM. K-RAS(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature*. 2013;503(7477):548–551. https://doi.org/10.1038/nature12796

27. Ostrem JML, Shokat KM. Direct small-molecule inhibitors of KRAS: from structural insights to mechanism-based design. *Nat Rev Drug Discov*. 2016;15(11):771–785. https://doi.org/10.1038/nrd.2016.139

28. Nichols RJ, Cregg J, Schulze CJ, et al. Abstract 1261: a next generation tri-complex KRASG12C(ON) inhibitor directly targets the active, GTP-bound state of mutant RAS and may overcome resistance to KRASG12C(OFF) inhibition. *Cancer Res*. 2021;81(Suppl. 13):1261–1261. https://doi.org/10.1158/1538-7445.AM2021-1261

29. Chen N, Fang W, Lin Z, et al. KRAS mutation-induced upregulation of PD-L1 mediates immune escape in human lung adenocarcinoma. *Cancer Immunol Immunother*. 2017;66(9):1175–1187. https://doi.org/10.1007/s00262-017-2005-z

30. Lamberti G, Sisi M, Andrini E, et al. The mechanisms of PD-L1 regulation in Non-Small-Cell Lung Cancer (NSCLC): which are the involved players? *Cancers*. 2020;12(11):3129. https://doi.org/10.3390/cancers12113129

31. Coelho MA, de Carné Trécesson S, Rana S, et al. Oncogenic RAS signaling promotes tumor immunoresistance by stabilizing PD-L1 mRNA. *Immunity*. 2017;47(6):1083–1099.e6. https://doi.org/10.1016/j.immuni.2017.11.016

32. Testorelli C, Bussini S, De Filippi R, et al. Dacarbazine-induced immunogenicity of a murine leukemia is attenuated in cells transfected with mutated K-ras gene. *J Exp Clin Cancer Res*. 1997;16(1):15–22. http://www.ncbi.nlm.nih.gov/pubmed/9148855

33. Zdanov S, Mandapathil M, Abu Eid R, et al. Mutant KRAS conversion of conventional T cells into regulatory T cells. *Cancer Immunol Res*. 2016;4(4):354–365. https://doi.org/10.1158/2326-6066.CIR-15-0241

34. Ricciuti B, Awad MM. What is the standard first-line treatment for advanced non–small cell lung cancer? *Cancer J*. 2020;26(6):485–495. https://doi.org/10.1097/PPO.0000000000000489

35. Paz-Ares L, Luft A, Vicente D, et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med*. 2018;379(24):2288–2301. https://doi.org/10.1056/NEJMoa1817239

36. Herbst RS, Lopes G, Kowalski DM, et al. LBA4 association of KRAS mutational status with response to pembrolizumab. *J Thorac Oncol*. 2020;15(12):1583–1584. https://doi.org/10.1016/j.jtho.2020.12.013

37. Skoulidis F, Goldberg ME, Greenanwalt DM, et al. STK11/LKB1 mutations and PD-1 inhibitor resistance in KRAS-mutant lung adenocarcinoma. *Cancer Discov*. 2018;8(7):822–835. https://doi.org/10.1158/2326-6066.CD-18-0099

38. Hong DS, Fakhih MG, Strickler JH, et al. KRAS G12C inhibition with sotorasib in advanced solid tumors. *N Engl J Med*. 2020;383(13):1207–1217. https://doi.org/10.1056/NEJMoa1917239

39. Lamberti G, Spurr LFF, Li Y, et al. Clinicopathological and genomic correlates of programmed cell death ligand 1 (PD-L1) expression in nonsquamous non-small-cell lung cancer. *Ann Oncol*. 2020;31(6):807–814. https://doi.org/10.1016/j.annonc.2020.02.017
49. Johnson ML, de Langen AJ, Waterhouse JM, et al. Sotorasib versus docetaxel for previously treated non-small cell lung cancer with KRAS G12C mutation: CodeBreaK 200 phase III study. *Ann Oncol.* 2022;33:S808–S869. https://doi.org/10.1016/annonc/annonc1089

50. Ou S-HI, Jänne PA, Leal TA, et al. First-in-human phase I/IB dose-finding study of adagrasib (MRTX849) in patients with advanced KRAS G12C solid tumors (KRYSSTALL-1). *J Clin Oncol.* 2022;40(23):2530–2538. https://doi.org/10.1200/jco.21.02752

51. Jänne PA, Riely GJ, Gadgeel SM, et al. Adagrasib in non-small-cell lung cancer harboring a KRASG12C mutation. *N Engl J Med.* 2022;387:120–131. https://doi.org/10.1056/NEJMoa2204619

52. Reck M, Carbone DP, Garassino M, Barlesi F. Targeting KRAS in non-small-cell lung cancer: recent progress and new approaches. *Ann Oncol.* 2021;32(9):1101–1110. https://doi.org/10.1016/j.annonc.2021.06.001

53. Lindsay CR, Garassino MC, Nadal E, Öhrling K, Scheffler M, Mazières J. On target: rational approaches to KRAS inhibition for treatment of non-small cell lung carcinoma. *Lung Cancer.* 2021;160:152–165. https://doi.org/10.1016/j.lungcan.2021.07.005

54. Hofmann MH, Gerlach D, Misale S, Petronczki M, Kraut N. Expanding the reach of precision oncology by drugging all KRAS mutants. *Cancer Discov.* 2022;12(4):924–937. https://doi.org/10.1158/2159-8290.CD-21-1331

55. Zeng M, Xiong Y, Safaee N, et al. Exploring targeted degradation strategy for oncogenic KRASG12C. *Cell Chem Biol.* 2022;27(1):19–31.e6. https://doi.org/10.1016/j.chembiol.2019.12.006

56. Li X, Pu W, Zheng Q, Ai M, Chen S, Peng Y. Proteolysis-targeting chimeras (PROTACs) in cancer therapy. *Mol Cancer.* 2022;21(1):99. https://doi.org/10.1186/s12943-021-01434-3

57. Désage AL, Léonce C, Swalduz A, Ortiz-Cuarran S. Targeting KRAS mutant in non-small cell lung cancer: novel insights into therapeutic strategies. *Front Oncol.* 2022;12:796832. https://doi.org/10.3389/fonc.2022.796832

58. Luo J, Ostrem J, Pellini B, et al. Overcoming KRAS-mutant lung cancer. *Am Soc Clin Oncol Educ B.* 2022;42:700–710. https://doi.org/10.1200/EDBK_360354

59. Zhao Y, Murciano-Goroff YR, Xue JY, et al. Diverse alterations associated with resistance to KRAS(G12C) inhibition. *Nature.* 2021;599(7886):679–683. https://doi.org/10.1038/s41586-021-04065-2

60. Awad MM, Liu S, Rybkin II, et al. Acquired resistance to KRAS G12C inhibition in cancer. *N Engl J Med.* 2021;384(25):2382–2393. https://doi.org/10.1056/nejmoa2105281

61. Koga T, Suda K, Fujino T, et al. KRAS secondary mutations that confer acquired resistance to KRAS G12C inhibitors, sotorasib and adagrasib, and overcoming strategies: insights from in vitro experiments. *J Thorac Oncol.* 2021;16(8):1321–1332. https://doi.org/10.1016/j.jtho.2021.04.015

62. Xue JY, Zhao Y, Aronowitz J, et al. Rapid non-uniform adaptation to conformation-specific KRAS(G12C) inhibition. *Nature.* 2020;577(7790):421–425. https://doi.org/10.1038/s41586-019-1884-x

63. Hata AN, Shaw AT. Resistance looms for KRASG12C inhibitors. *Nat Med.* 2020;26(2):169–170. https://doi.org/10.1038/s41591-020-0765-z

64. Ryan MB, Fece de la Cruz F, Phat S, et al. Vertical pathway inhibition overcomes adaptive feedback resistance to KRASG12C inhibition. *Clin Cancer Res.* 2020;26(7):1633–1643. https://doi.org/10.1158/1078-0432.CCR-19-3523

65. Ambrogio C, Köhler J, Zhou Z-W, et al. KRAS dimerization impacts MEK inhibitor sensitivity and oncogenic activity of mutant KRAS. *Cell.* 2018;172(4):857–868.e15. https://doi.org/10.1016/j.cell.2017.12.020

66. Ramalingam S, Skoulidis F, Govindan R, et al. P52.03 efficacy of sotorasib in KRAS p.G12C-mutated NSCLC with stable brain metastases: a post-hoc analysis of CodeBreak 100. *J Thorac Oncol.* 2021;16(10):S1123. https://doi.org/10.1016/j.jtho.2021.08.547

67. Sabari JK, Spira AI, Heist RS, et al. Activity of adagrasib (MRTX849) in patients with KRAS G12C -mutated NSCLC and active, untreated CNS metastases in the KRYSSTALL-1 trial. *J Clin Oncol.* 2022;40(Suppl. 17):LBA9009–LBA9009. https://doi.org/10.1200/JCO.2022.40.17_suppl.LBA9009