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Review

Immunotherapy in advanced, *KRAS* G12C-mutant non-small-cell lung cancer: current strategies and future directions

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***Abstract*:** Kirsten rat sarcoma (*KRAS*) mutations are present in up to 25% of non-small-cell lung cancer (NSCLC). *KRAS* G12C is the most common type of mutation, representing approximately half of the cases in *KRAS*-mutant NSCLC. Mutations in *KRAS* activate the RAF-MEK-ERK pathway, leading to increased cell proliferation and survival. Recent advances in drug development have led to the approval of KRAS G12C inhibitors sotorasib and adagrasib. This review explores the emerging therapeutic strategies in *KRAS* G12C-mutant NSCLC, including dual checkpoint blockade and combinations with checkpoint inhibitors, with a focus on the setting of advanced disease.

Plain language summary

Review on the use of immunotherapy in lung cancer harboring KRAS G12C mutation

In lung cancer, certain genes drive the growth of the disease. One common mutation is in the KRAS gene, specifically the KRAS G12C mutation, which occurs in about half of KRAS lung cancer. This mutation is particularly important because there are treatments that target this mutation. Immunotherapy, a treatment that boosts the immune system to help it recognize and attack cancer cells, has shown to be effective in this type of cancer. This review focuses on the latest treatment options for KRAS G12C, including immunotherapy and targeted KRAS G12C inhibitors.

Keywords: chemoimmunotherapy, immunotherapy, *KRAS* G12C, KRAS G12C inhibitors, non-small cell lung cancer

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Introduction

Kirsten rat sarcoma (*KRAS*) oncogene is the most common oncogene driver mutation in cancer and is found in approximately 25% of non-small-cell lung cancers (NSCLC). In the year 1982, it was the first human oncogene to be discovered.[1] Despite its early identification, KRAS is known as the "undruggable target" due to the lack of classic drug target sites, its high affinity for GTP, and its unusual shape. Recent progress in drug development led to the design of small-molecule inhibitors that target *KRAS* G12C mutations. This game-changer has opened the door for new treatment options with recent approvals of AMG510 (sotorasib) and MRTX849 (adagrasib).[2,3] This review will focus on *KRAS* G12C-mutated NSCLC, exploring its role in tumor growth as an oncogene driver mutation, as well as current and future therapeutic strategies that involve immunotherapy.

KRAS is a RAS protein that is part of the small GTPase family.[4] These proteins are intracellular guanine nucleotide-binding proteins (G proteins)

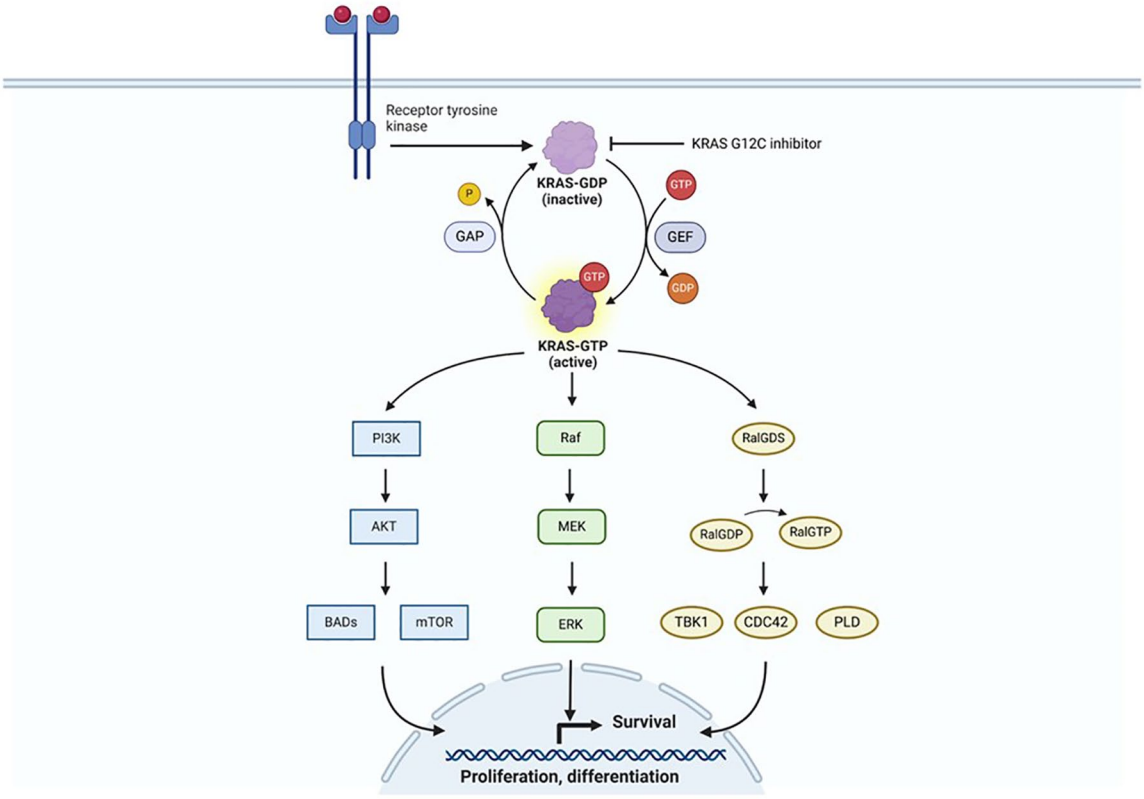

Figure 1. Schematic illustration of the KRAS signaling pathway. KRAS activation leads to downstream signaling through the RAF-MEK-ERK, PI3K-AKT-mTOR, and RalGDS pathways.
Source: Created in Biorender.com.
KRAS, Kirsten rat sarcoma; RalGDS, RAL guanine nucleotide dissociation stimulator.

that regulate cell growth and survival.[4] It shifts cyclically between an active GTP-bound state and an inactive GDP-bound state. Two important regulatory proteins control this shifting process: guanine nucleotide exchange factors (GEFs) and GTPase-activating proteins (GAPs).[5] When the GEFs interact with the KRAS-GDP complex, the KRAS-GDP complex has decreased affinity to GDP and GDP is replaced with GTP. GTP has higher affinity and concentration than GDP. The KRAS-GTP complex acquires a change in conformation in switches I and II of the G domain leading to *KRAS* activation.[6] On the other hand, GAPs promote binding between KRAS and GDP by promoting the GTPase activity of KRAS to maintain the inactive GDP-bound state.

When KRAS is activated, it triggers multiple downstream signaling pathways that drive cancer growth. The RAF-MEK-ERK pathway is the main downstream pathway of KRAS signaling. Activated KRAS-GTP leads to phosphorylation events involving MEK1/2 and ERK1/2. These events regulate the transcription and translation of specific genes, subsequently influencing cell proliferation and survival.[7]

Another pathway involved is the PI3K-AKT-mTOR pathway which is crucial for cellular growth, metabolism with glucose transportation, and apoptosis.[8] KRAS can activate PI3K which leads to downstream activation of AKT and mTOR proteins. Activation of mTOR proteins leads to cell proliferation and survival. AKT phosphorylates and activates Bcl-XL/Bcl-2-associated death promoters, eventually inhibiting apoptosis.[9]

RAL guanine nucleotide dissociation stimulator is another downstream signaling KRAS protein. It functions as a GTP/GDP exchange factor to promote conversion from RAL GDP to RAL GTP.[10,11] The downstream factors from RAL proteins include Rac/cell division cycle 42 (CDC42) for cell migration, TANK-binding kinase 1 associated with viral immunity, and

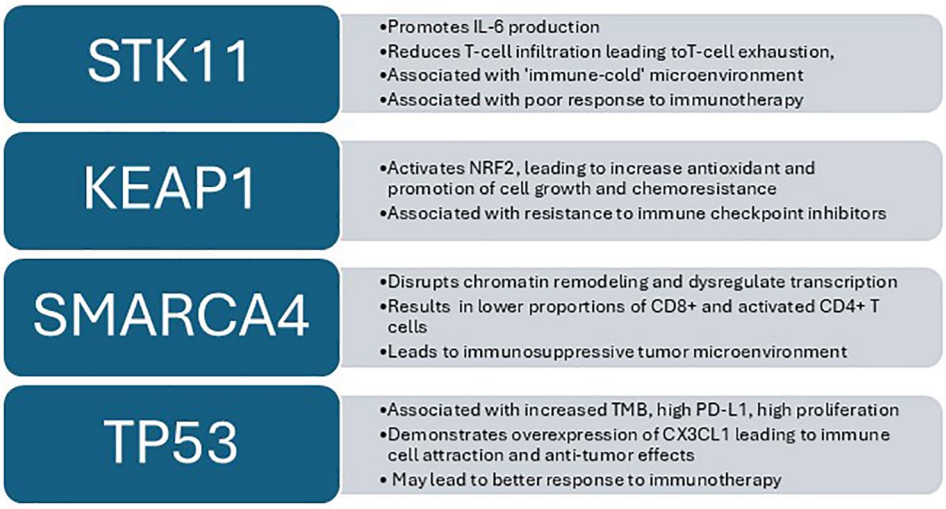

Figure 2. Summary of the effects of co-mutations on the tumor microenvironment in *KRAS*-mutant NSCLC.
KRAS, Kirsten rat sarcoma; NSCLC, non-small-cell lung cancer.

phospholipase D involved with endocytosis[10,11] (Figure 1).

Mutations in *KRAS*, particularly at codons 12 (G12), 13 (G13), and 61 (Q61), affect the protein's GTPase activity. As mentioned above, these mutations lead to continuous activation of the signaling pathways.[12] *KRAS* mutations are common in NSCLC, pancreatic adenocarcinoma, and colorectal cancer. The *KRAS* G12C mutation is the most common type of *KRAS*-mutated lung cancer.[13] Up to 80% of patients with *KRAS*-mutant NSCLC have a smoking history, in comparison to *KRAS* G12D, which is more frequent in non-smokers. *KRAS* G12C is more common in women who are often younger with less smoking history than men.[14]

Rationale for immunotherapy in *KRAS*-mutated NSCLC

The use of immunotherapy with immune checkpoint inhibitors such as pembrolizumab, nivolumab, cemiplimab, and atezolizumab has transformed the treatment landscape in lung cancer, improving survival in patients with advanced and now early-stage disease.[15–21]

The presence of a *KRAS* mutation is associated with an inflamed tumor microenvironment (TME) and increased tumor immunogenicity.[22] *KRAS*-mutant tumors have greater T-cell infiltration compared to *KRAS*-wild-type tumors.[22] This contributes to enhanced response to immunotherapy. *KRAS*-mutant tumors have an increased proportion of programmed death-ligand 1+ (PD-L1+)/TIL+ suggesting an inflammatory phenotype and adaptive immune resistance.[22] A study has shown *KRAS* mutation leads to upregulation of PD-L1 through the p-ERK signaling pathway.[23] Mutation profile analysis showed that *KRAS* mutations are associated with increased tumor mutational burden (TMB) and immunogenicity.[22] High TMB reflects genomic instability leading to increased neoantigen production that can attract immune cells.[24] In addition, high TMB has been linked to smoking and alteration in DNA replication and damage repair genes in *KRAS*-mutant NSCLC.[24–26]

KRAS mutations are typically mutually exclusive of other actionable alterations such as *EGFR* and ALK. There is heterogeneity in clinical outcomes of patients with *KRAS*-mutant NSCLC based on co-occurring alterations. The most common co-mutations in *KRAS*-mutant NSCLC are *STK11* (serine/threonine kinase 11), *KEAP1* (Kelch-like ECH-associated), *TP53*, *SMARCA4*, and *CDKN2A*/*CDKN2B*.[27] Each of these co-mutations can influence the biology and immune microenvironment of the cancer (Figure 2).

STK11, also known as *LKB1*, acts as a tumor suppressor gene that regulates cell metabolism and growth by phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) and 12 *AMPK*-related kinases.[28,29] Loss of *STK11* in *KRAS*-mutant tumors promotes

interleukin-6 (IL-6) production which attracts neutrophils, decreases T-cell infiltration, and leads to higher T-cell exhaustion.[30] NSCLCs with *STK11*-loss also express low levels of PD-L1.[31] The inactivation of *STK11* leads to an "immune-cold" TME and is associated with poor response to immunotherapy.[28,30,32] *STK11* co-mutation occurs in approximately 10%–28% of *KRAS* G12C-mutant NSCLC.[33]

KEAP1 protein is a negative regulator of the NRF2 pathway, which is involved in the oxidative stress response by triggering antioxidant and anti-inflammatory effects.[34] Mutations in *KEAP1* lead to NRF2 activation, promoting cell growth and chemoresistance. *KEAP1* mutations occur in about 11% of NSCLC.[35] *KRAS*-mutant NSCLC with concurrent *KEAP1* and/or *STK11* mutations had worse outcomes compared to those without *KEAP1* and *STK11* mutations. The presence of *KEAP1* mutations alone or in combination with *STK11* mutations is associated with worse progression-free survival (PFS) and overall survival (OS), even with the use of chemo-immunotherapy. A study showed that the median OS for patients with *KRAS*/*STK11* double-mutant NSCLC was 12 months compared to *KRAS*-mutant only NSCLC was 21 months (hazard ratio (HR) 1.7, 95% confidence interval (CI): 1.1–2.4, $p = 0.002$).[27] In the same study, *KEAP1* co-mutation had a median OS of 10 months (HR 2.1, 95% CI: 1.4–3.1, $p < 0.0001$).[27]

KRAS mutations influence the TME, leading to immune evasion and reduced effectiveness of therapies especially immunotherapy.[36,37] *KRAS* mutations promote immune escape by producing pro-inflammatory cytokines and chemokines, such as IL-6, IL-8, and GM-CSF.[38] These factors attract immunosuppressive cells like myeloid-derived suppressor cells (MDSCs) and regulatory T cells (Tregs) into the TME. This inhibits the immune response against the tumor. *KRAS*-mutant tumors have increased expression of PD-L1, which interacts with the PD-1 receptor on T cells to suppress their antitumor activity.[39] These tumors typically have reduced infiltration of cytotoxic T lymphocytes (CTLs) essential for effective antitumor response and have increased infiltration by immunosuppressive cells such as MDSCs and Tregs.[37,40]

KEAP1 and *STK11* mutations are associated with an adverse immunosuppressive microenvironment, creating resistance to immune checkpoint inhibitors. This microenvironment is characterized by the depletion of $CD8^+$ cytotoxic T cells while preserving the $CD4^+$ effector subsets.[41] Adding CTLA4 blockade to PD-(L)1 inhibition might mitigate this resistance. The combination of PD-(L)1 and CTLA4 inhibition utilizes two critical aspects of the suppressive *STK11MUT* and/or *KEAP1MUT* NSCLC tumor immune microenvironment. The first is the retention of anti-CTLA4-responsive CD4+ T cells, including TH1 T cells. The second is the reprogramming of myeloid-cell-rich tumor ecosystem to inducible nitric oxide synthase (iNOS)-expressing tumors in response to dual immune checkpoint blockade (ICB).[41]

Emerging evidence suggests that *STK11* and *KEAP1* mutations are not equivalent in effect and that predicting immunotherapy outcomes solely based on the presence or absence of these mutations may be insufficient.[42] For example, truncating mutations in *STK11* are more frequent in exons 1 and 2 which are associated with a worse prognosis compared to mutations in exons 3–9.[43] *KEAP1* mutations are distributed throughout the gene and less clustered in specific hotspot regions.[35] The functional impact of these missense mutations remains unknown and suggests the need for more accurate classification based on pathogenicity, protein expression, and downstream effector activity.[42] Mutation clonality can also impact immunotherapy efficacy. Clonal mutations with loss of heterozygosity in *KEAP1*, unlike subclonal mutations, are associated with resistance to PD-(L)1 monotherapy and a T-cell-excluded microenvironment.[44] The observation that some *STK11* and *KEAP1*-mutated tumors may still respond to ICI highlights the importance of identifying factors that can guide clinical decisions. For example, for those without concurrent *KRAS* mutations with subclonal *STK11* or *KEAP1* mutations and high PD-L1 expression levels, PD-(L)1 monotherapy may be sufficient. Alternatively, those with low or negative PD-L1 expression, concurrent *KRAS* mutation, truncating mutations, or clonal mutation may require PD-(L)1 inhibitor combination therapies with chemotherapy or CTLA4 inhibitor.[42]

A *SMARCA4* co-mutation occurs in nearly 6% of *KRAS*-mutant lung cancers.[45] *SMARCA4* encodes the SWItch/Sucrose NonFermentable complex, which controls gene expression by altering chromatin structure.[46,47] The loss or mutation of *SMARCA4* disrupts chromatin remodeling and may dysregulate transcription

programming.[48] Lung adenocarcinomas with *KRAS-SMARCA4* co-mutations, treated with or without immunotherapy, have poor survival outcomes.[45,49] These co-mutations were found to have lower proportions of CD8 and activated CD4+ T cells than those found in *KRAS*-mutant only and *KRAS-TP53*-mutant lung cancers, indicating an immunosuppressive TME.[45]

Tumors with both *KRAS* and *TP53* co-mutations in NSCLC have demonstrated high TMB, high PD-L1, and high tumor cell proliferation.[50] Genome-wide expression analysis showed that *KRAS*mut/*TP53*mut overexpress the *CX3CL1* gene. In its soluble form, the CX3CL1 chemokine (additionally termed fractalkine) can attract immune effector cells such as tumor-infiltrating CD8+ T cells, natural killer cells, and dendritic cells to the tumor leading to anti-tumor immune effect.[51,52] In lung adenocarcinoma, increased mRNA expression of CX3CL1 was associated with improved OS.[52] This gene is also associated with increased myeloid diversity and improved response to immunotherapy; thus, it could potentially be a biomarker of response in lung cancer.[53]

Testing for *KRAS* mutations by genomic profiling is recommended in NSCLC.[54] Liquid biopsy for plasma NGS testing can provide a noninvasive option for detecting these mutations. Routine testing for co-alterations such as *STK11*, *KEAP1*, and *TP53* mutations is not yet recommended by clinical guidelines, though many NGS vendors already include this information in their NGS profile reports. While not yet standard in clinical practice, these mutations are increasingly being recognized as prognostic biomarkers and may eventually guide treatment decisions.

KRAS inhibition

AMG-510 and MRTX849 are the two pioneers of allosteric inhibitors for KRAS G12C. These inhibitors can form covalent bonds with the mutant cysteine in codon 12 to inhibit GDP-GTP exchange and maintain the KRAS protein in its inactive state, preventing downstream signaling pathways.[55,56] The drugs not only have direct anticancer activity but they also exhibit immune-modulatory effects that contribute to their efficacy. Preclinical studies of AMG-510 demonstrated that this drug increases the infiltration of T cells, mainly CD8+ T cells, into the tumor. It induces a pro-inflammatory microenvironment marked by increased interferon signaling, chemokine production, antigen processing, cytotoxic and natural killer cell activity, along with markers of innate immune system activation. The inflamed TME renders the tumor more responsive to immune checkpoint inhibition.[57]

Resistance to KRAS inhibitors represents a challenge in the treatment of *KRAS*-mutant NSCLC. Many patients demonstrate primary resistance and never respond to the molecules, while other patients may initially respond but subsequently develop resistance leading to treatment failure and disease progression. The mechanisms of resistance to KRAS inhibition are multifaceted. Studies have shown that co-occurring mutations in *KEAP1*, *SMARCA4*, and *CDKN2A* are associated with poor OS in those with NSCLC treated with sotorasib or adagrasib.[58,59] Regarding secondary resistance, in one study by Awad et al.,[60] genomic and histologic analyses were performed using tumor biopsy samples of those who developed resistance after treatment with adagrasib monotherapy in *KRAS* G12C-mutant cancer. In 45% (17/38) of patients, a possible mechanism of resistance was identified such as a secondary *KRAS* mutation including $KRAS^{R68S}$, $KRAS^{H95D/G/N/R}$, and $KRAS^{Y96C/D/H/N}$ or amplifications in *KRAS*. Alternative oncogenic alterations that activate the RTK-RAS signaling pathway, without affecting KRAS, were seen, as were two cases of histologic transformation from lung adenocarcinoma to squamous-cell carcinoma. However, in the majority of patients, no new genomic event was detected to explain the pattern of resistance.[60]

Current strategies: Immunotherapy for *KRAS* G12C NSCLC

As of the writing of this article, patients with *KRAS* G12C mutations are treated in the front-line with non-selected, immunotherapy-based treatments, with or without chemotherapy.[61] KRAS G12C inhibitors are currently used in the second line as monotherapy after both demonstrated an improvement in PFS over docetaxel in randomized clinical trials.[62,63] Many retrospective studies have examined the efficacy of currently available immunotherapy-based regimens specifically in the *KRAS*-mutated patient population.

Single-agent immunotherapy

For patients with metastatic NSCLC with PD-L1 $\geqslant$50%, regardless of squamous or

non-squamous histology, there are currently three available single-agent immunotherapies that are approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA): pembrolizumab, atezolizumab, and cemiplimab.[15,16,18,64–66]

Regarding the efficacy of immunotherapy specifically in the *KRAS*-mutated NSCLC, a subgroup analysis of patients enrolled on KEYNOTE-042 has been performed.[67] KEYNOTE-042 randomized patients with PD-L1 expression ⩾1% to either single-agent pembrolizumab or chemotherapy.[68] A subgroup analysis of outcomes by *KRAS* mutational status included only 12 patients with a *KRAS* G12C mutation.[67] While this group was small, the ORR was 66.7% (95% CI: 34.9–90.1), mPFS 15 months (95% CI: 10–NR), and mOS not reached (95% CI: 23–NR), suggesting these patients did not perform worse than those without *KRAS* G12C mutations.[67] Additional retrospective data have suggested that PD-L1 expression, both >1% and ⩾50%, is particularly predictive for ICI efficacy in patients with *KRAS* mutations.[69]

Several groups have published conflicting results regarding the efficacy of immunotherapy for *KRAS* G12C versus *KRAS* non-G12C. One single-center retrospective analysis performed at Memorial Sloan Kettering indicated that patients treated with first-line immunotherapy may have worse outcomes for those with *KRAS* G12C when compared with those with *KRAS* non-G12C mutations.[33] Landmark 12-month PFS was 59% (22/37) in patients with non-G12C subtypes, compared with only 29% (11/38) with G12C mutations.[33] This analysis was not designed to compare outcomes with patients without *KRAS* mutations.

However, additional data have suggested that for patients with a PD-L1 expression ⩾50%, *KRAS* G12C mutations were associated with improved outcomes with first-line single-agent immunotherapy when compared to either patient with *KRAS* non-G12C mutations or *KRAS* wild-type tumors.[70–72] Among 696 patients from the German National Network Genomic Medicine Lung Cancer who were PD-L1 ⩾50%, patients with a *KRAS* G12C mutation demonstrated a longer PFS (25.3 (14.3–36.2) months) compared with non-G12Cmut *KRAS* (9.6 (7.1–12.1)) and *KRAS*wt patients (10.3 (8.0 = 12.5) months). For patients with a *KRAS* G12C mutation, a *TP53* co-mutation predicted an increased response rate (69.7% vs 46.5%) for *TP53*-mutated (*TP53mut*) versus wild-type as well as PFS (HR = 0.59, $p = 0.009$), with a trend toward improvement in OS (HR = 0.72, $p = 0.16$).[19] For patients with *KRAS* G12C/*TP53* co-mutations with a PD-L1 ⩾50%, there was an impressive mPFS and mOS (33.7 and 65.3 months, respectively).[19] An additional data set demonstrated that *TP53*/*KRAS* co-altered NSCLC derived significant clinical benefit from PD-1 inhibitors, more than either the *KRAS*-mutated/*TP53* wild-type or *KRAS* wild-type groups. However, this analysis was not restricted to *KRAS* G12C specifically.[73] A similar multicenter study from France of 681 non-squamous patients with PD-L1 ⩾50%, which included 86 patients with *KRAS* G12C mutations, demonstrated a mPFS of 7.0 months (3.7–14) for *KRAS* G12C with a mOS of 18.4 (12.6–NR) months, with similar results seen in both *KRAS* non-G12C and wild-type *KRAS*.[74]

We anticipate future data will more accurately describe efficacy outcomes in this patient population, given there are a number of prospectively enrolling clinical trials detailed below of frontline treatment of patients with *KRAS* G12C with single-agent immunotherapy control arms. In the interim, however, these data cumulatively show that frontline immunotherapy is efficacious for patients with *KRAS* G12C mutations and that alterations such as *TP53* can potentially predict patient outcomes.

Single-agent immunotherapy in combination with chemotherapy

For patients with PD-L1 0%–49%, there are multiple combinations of chemotherapy plus single-agent immunotherapy that have demonstrated significant clinical benefit and are FDA- and EMA-approved. Pembrolizumab plus chemotherapy, cemiplimab plus chemotherapy, and atezolizumab plus chemotherapy with or without bevacizumab all have demonstrated improvements in patient outcomes over chemotherapy alone.[75–79] The majority of patients with *KRAS* G12C mutations with PD-L1 0%–49% will be treated with one of these regimens, similar to those patients without *KRAS* G12C mutations. Understanding how patients with *KRAS* G12C mutations specifically perform using these regimens has never been prospectively studied. However, similar to single-agent immunotherapy, multiple retrospective analyses have

been conducted that were either subgroup analyses of clinical trials or multicenter retrospective cohort studies to better inform both our prognostic and predictive understanding of these patients.

A subgroup analysis of KEYNOTE-189 of patients treated with pembrolizumab plus chemotherapy included 26 patients with a *KRAS* G12C mutation, who demonstrated an ORR of 50% versus 47.5% in patients without any *KRAS* mutation.[80] Progression-free survival was 11 months (95% CI: 6–18), while it was 9 months (95% CI: 7–14) for those without *KRAS* mutations.[80] Median OS was 18 months (95% CI: 11–NR) with *KRAS* G12C, while it was 23 months in those without *KRAS* mutations.[80]

In a multicenter study of 138 patients with *KRAS* G12C treated with first-line chemo-immunotherapy, ORR was 41% (95% CI: 32–41), mPFS was 6.8 months (95% CI: 5.5–10), and mOS was 15 months (95% CI: 11–28).[81] When compared with patients with non-G12C *KRAS* mutations, in an adjusted analysis, there was not a statistically significant difference in PFS (HR 0.82, 95% CI: 0.61–1.11, $p = 0.2$) or OS (HR 0.55, 95% CI: 0.30–1.01, $p = 0.053$).[81] These data demonstrate that patients with *KRAS* G12C mutations can derive significant benefits from treatment with combination chemo-immunotherapy. We will obtain prospective data on the effectiveness of chemoimmunotherapy for patients with *KRAS* G12C mutations from the control arms of the upcoming phase III, randomized, first-line trials investing novel agents in the previously untreated setting, such as the CodeBreak202 trial.[82]

Doublet immunotherapy with or without chemotherapy

Doublet immunotherapy combinations currently available include nivolumab plus ipilimumab with or without chemotherapy, as well as tremelimumab plus durvalumab with chemotherapy.[83,84] Subgroup efficacy analysis has been performed for patients with *KRAS* mutations for CheckMate 227, CheckMate 9LA, and POSEIDON, though none of these analyses differentiate between *KRAS* G12C and non-G12C.[83,85–87]

The CheckMate-227 trial compared ipilimumab plus nivolumab to chemotherapy.[84] In the *KRAS* mutant population, ipilimumab/nivolumab outperformed chemotherapy with a mOS of 17.5 versus 15.7 months (HR 0.79, 95% CI: 0.55–1.12).[85] With the addition of two cycles of chemotherapy in CheckMate 9LA, at the 3-year update, patients with a *KRAS* mutation demonstrated an improvement in mOS at 19.2 versus 13.5 months (HR 0.72, 95% CI: 0.48–1.08).[87]

POSEIDON was a three-arm randomized trial of tremelimumab plus durvalumab plus chemotherapy, durvalumab plus chemotherapy, or platinum chemotherapy alone. In the *KRAS*-mutated subgroup, tremelimumab, durvalumab, and chemotherapy demonstrated an impressive mOS of 25.7 months compared with 10.4 months with chemotherapy (HR 0.56, 95% CI: 0.36–0.88).[86] Similarly in the durvalumab, tremelimumab, and chemotherapy arm, mPFS was 8.5 versus 4.7 months with chemotherapy alone (HR 0.57, 95% CI: 0.35–0.92).[86] Based on the results of these three trials of dual checkpoint blockade, the combination of doublet immunotherapy plus chemotherapy could be considered for patients with *KRAS* G12C mutations, though with the disclaimer that none of these data sets differentiated between *KRAS* G12C and *KRAS* non-G12C.

One of the biggest limitations of using dual checkpoint blockade is the increased risk of immune-related adverse events (irAEs) over single-agent immunotherapy regimens. However, as the science of predicting which patients are at higher risk for adverse events evolves, dual checkpoint blockade may be able to be used with decreased toxicity. As an example, germline single-nucleotide polymorphism data were used in a cohort of patients to develop and validate polygenic risk scores for hypothyroidism, which could predict the development of thyroid irAEs (HR per SD = 1.34; 95% CI: 1.08–1.66; AUROC = 0.6).[88] In a separate study, distinct human lymphocyte antigen-DR alleles were associated with specific immunotherapy-related adverse events, such as type 1 diabetes or hypophysitis.[89] Utilizing genetic biomarkers to better understand toxicity risks will allow for informed patient discussions and shared decision-making regarding the optimal treatment strategy.

Effect of co-mutations on immunotherapy efficacy

STK11 or *KEAP1*, occurring either independently or as co-mutations concurrent with *KRAS*, is increasingly being recognized as both

prognostic and perhaps also predictive.[90] *STK11* co-mutations occur in 28% of patients with *KRAS* G12C mutations, and *KEAP1* occurs in 23%.[33] Co-mutations in *STK11* or *KEAP1* have both been demonstrated to be associated with inferior outcomes with immunotherapy in patients with *KRAS* G12C.[27,32,44,58]

As a specific example, in a combined cohort from four medical centers of 1261 patients, *STK11* was associated with significantly worse PFS (HR 2.04, $p < 0.0001$) and OS (HR 2.09, $p < 0.0001$).[31] Similarly, *KEAP1* demonstrated inferior outcomes both of PFS (HR = 2.05, $p < 0.0001$) and OS (HR 2.24, $p < 0.0001$).[31] Interestingly, the inferior outcomes of *STK11* and *KEAP1* were observed only in patients with co-mutations in *KRAS*, but not in patients who had *KRAS* wildtype.[31] Similar results were found also for patients treated with chemotherapy alone.[91]

In KEYNOTE-189, whole-exome sequencing data from both tumor and normal DNA were evaluable for 289 (47%) of 616 patients, of whom 54 (19%) had an *STK11* mutation and 68 (24%) had a *KEAP1* mutation; 29 (10%) had both *STK11* and *KEAP1* mutations. PD-L1 Tumor Proportion Score (TPS) tended to be lower in patients with versus without *STK11* mutation (median (IQR) 0% (0–16) vs 15% (0–75)), whereas TMB score tended to be higher in patients with mutation (209 (132–265) vs 146 (89–264)). Similar patterns were seen for patients with or without *KEAP1* mutation (PD-L1 TPS: 1% (0–13) vs 20% (0–75); TMB: 173 (124–267) vs 147 (89–263)). Although the ORR of pembrolizumab plus chemotherapy was lower and PFS and OS shorter in patients with versus without *STK11* and *KEAP1* mutation, pembrolizumab plus chemotherapy was associated with numerically better outcomes than placebo plus chemotherapy regardless of mutation status, and the 95% CIs were wide given the modest mutation frequency and the 2:1 randomization in favor of pembrolizumab plus chemotherapy for patients with metastatic nonsquamous NSCLC, regardless of *STK11* or *KEAP1* status.[92]

A recent publication from Skoulidis et al.[41] demonstrated that for patients with *STK11* and/or *KEAP1*, the addition of a PD-L1 inhibitor durvalumab did not improve outcomes over chemotherapy; however, dual checkpoint blockade with the addition of tremelimumab, a CTLA4 inhibitor, to the PD-L1 and chemotherapy combination showed clinical benefit.

This strategy will be studied prospectively with the TRITON study, which is enrolling patients with metastatic non-squamous NSCLC with *KRAS* mutations and/or *STK11* and/or *KEAP1*.[93] Patients will be randomized to either tremelimumab, durvalumab, and chemotherapy versus pembrolizumab plus chemotherapy.[93]

Moving forward, as the next wave of clinical trials is designed for patients with *KRAS* mutations, consideration should be given to the stratification of patients by specific allele or co-mutation status. Stratifying based on *STK11* or *KEAP1* co-mutations may allow for a more nuanced understanding of treatment efficacy, as well as a more personalized treatment approach. Prospectively designing trials that are statistically powered to understand the effect of these co-mutations will allow for a greater understanding of small, unplanned, retrospective analyses, to guide future clinical decision-making and design more effective treatment paradigms.

Combining KRAS G12C inhibition with immunotherapy

KRAS G12C inhibitors including sotorasib and adagrasib have demonstrated clinical activity in the second line, with an improvement in response rate and PFS over docetaxel.[62,63] However, sotorasib did not demonstrate a statistically significant improvement in OS over docetaxel.[63] Monotherapy use of a KRAS G12C inhibitor is unlikely to provide robust benefit in front line setting due to the resistance mechanism from KRAS G12C inhibition.[60] Therefore, multiple clinical trials were designed to assess the safety and efficacy of immunotherapy in combination with KRAS G12C inhibitors. As detailed above, there is additionally a strong preclinical rationale for combining a KRAS G12C inhibitor with immunotherapy.[94]

Second line and beyond

Sotorasib is a small-molecule inhibitor of KRAS G12C that binds specifically and irreversibly.[63] In the second line, sotorasib demonstrated a response rate of 28.1% (95% CI: 21.5–35.4) and a mPFS of 5.6 months (95% CI: 4.3–7.8).[63] The first data presented the combination of immunotherapy with a KRAS inhibitor for patients with

Table 1. KRAS G12C inhibitors in combination with immunotherapy.

Study	Drug combination	Indication, sample size	ORR (%)	Safety profile (common AEs with %)
Treatment naïve				
KRYSTAL-7 Garassino et al.[100]	Adagrasib + pembrolizumab	Treatment-naïve; any PD-L1 enrolled ($n = 148$); efficacy data restricted to PD-L1 ⩾50% ($n = 54$)	RR: 63% (32/51, PD-L1 ⩾50%)	Nausea (51%), diarrhea (44%), ALT increase (38%), AST increase (32%)
NCT05067283 Rojas et al.[102]	MK-1084 + pembrolizumab	Treatment naïve; PD-L1 ⩾1% $n = 31$	RR 70% (19/27)	ALT increase (26%); AST increase (23%); pruritis (23%); diarrhea (23%)
LOXO-RAS-20001 Burns et al.[97]	Olomorasib + pembrolizumab	Treatment naïve; any PD-L1 expression $n = 17$	RR: 77% (13/17)	Diarrhea 23%, ALT increase 20%; AST 16%
LOXO-RAS-20001 Fujiwara et al.[104]	Olomorasib + pembrolizumab + chemotherapy	Treatment naïve; any PD-L1 expression $n = 21$	RR: 50% (10/20)	Anemia (43%), nausea (38%), ALT increase (29%), AST increase (24%)
Second line and beyond				
LOXO-RAS-20001 Burns et al.[97]	Olomorasib + pembrolizumab	Prior chemotherapy, anti-PD-(L)1, and KRAS G12C inhibitor therapy allowed; any PD-L1 expression; $n = 48$	RR: 40% (17/43)	Diarrhea 23%, ALT increase 20%; AST 16%
CodeBreaK 100/101 Li et al.[95]	Sotorasib + pembrolizumab or atezolizumab; administered concurrent or with sotorasib lead-in	Received (or refused) prior standard therapies; no prior KRAS G12Ci; $n = 58$	RR: 29% (17/58)	Any ⩾Grade 3 TRAE: 55% (32/58); hepatotoxicity 53% (10/19) in concurrent arm; 47% (9/19) in lead-in arm
NCT04449874 Sacher et al.[99]	Divarasib ± atezolizumab	At least 1 prior treatment; prior KRAS G12Ci allowed; any PD-L1; $n = 39$	All patients: 42.1% (16/38); No prior KRAS G12Ci: RR: 55.6% (15/27)	Nausea (64%); diarrhea (62%); vomiting (49%); AST increase (26%); ALT increase (26%)

AE, adverse event; KRAS G12Ci, Kirsten rat sarcoma G12C inhibitor; ORR, overall response rate; PD-L1, programmed death-ligand 1; RR, response rate; TRAE, treatment-related adverse event.

KRAS G12C mutations was from the CodeBreaK 100/101 studies, in which patients with *KRAS* G12C-mutated NSCLC received sotorasib at varying dose levels in combination with either atezolizumab 1200 mg q3w or pembrolizumab 200 mg q3w (see Table 1). Of patients enrolled, 67% had received prior immunotherapy, with a median of 1 prior line of therapy (range 0–7). Patients received sotorasib either concurrent with IO or sequentially with a sotorasib safety lead-in before starting IO. The combination was deemed unsafe to proceed with additional development, given that 57% (33/58) of patients had a grade 3 or 4 treatment-related adverse events, primarily hepatotoxicity. Despite the limiting toxicity, the combination showed that KRAS inhibitors plus immunotherapy could be efficacious, and lead to durable responses. The ORR was 29% (17/58), 83% disease control rate (48/58), and the duration of response was 17.9 months (95% CI: 5.6–not estimable (NE)). Median OS was 15.7 months (95% CI: 9.6–17.8).[95]

Olomorasib is a second-generation KRAS G12C inhibitor with significant single-agent activity and tolerability.[96] It has been studied in combination with pembrolizumab in 43 previously treated patients with NSCLC, of which 81% (35/43) had received prior immunotherapy. The ORR was 40% (17/43). The most common grade 3 toxicities observed were diarrhea (13%), ALT (6%), and AST (8%).[97] Data have not matured sufficiently to know the mPFS or mOS of this group.

Divarasib is a KRAS G12C inhibitor with high potency and selectivity that binds irreversibly in the inactive state.[98] Single-agent activity in a heavily pretreated patient population demonstrated an ORR was 53.4% (95% CI: 39.9–66.7), with an mPFS of 13.1 months (95% CI, 8.8 to could not be estimated).[98] Divarasib at a 200 and 400 mg dose has been combined with atezolizumab 1200 mg IV q3w in 39 patients who were previously treated, of which 90% (35/39) had received prior PD-1/PD-L1 inhibitor, 95% (37/39) received prior platinum chemotherapy, and 28% (11/39) had received a prior KRAS G12C inhibitor. The combination was safe, with no dose-limiting toxicities observed, and only 5% of grade 3 AST and ALT elevations were reversible. Confirmed ORR was 42.1% ($n=38$), with an ORR of 55.6% ($n=27$) for those without a prior KRAS G12C inhibitor.[98,99] These trials taken together demonstrate that the combination of IO and KRAS G12C inhibition can be efficacious, though tolerability varies between KRAS G12C inhibitors.

Immunotherapy combinations in the first line

Given the clinical efficacy of KRAS G12C inhibitors and single-agent immunotherapy in the second line and beyond, there is significant interest in moving the combination up to the frontline. Adagrasib is a KRAS G12C inhibitor that binds irreversibly and selectively to KRAS in the inactive state.[3] As a single agent in the second line, it has an ORR of 32% with a PFS of 5.5 months, and a DOR of 8.3 months.[62] KRYSTAL-7 studied the efficacy and safety of adagrasib plus pembrolizumab in patients with treatment-naïve, advanced NSCLC with *KRAS* G12C mutations. Safety data were presented for 148 patients; while ALT and AST elevations were still frequently observed (38% and 32%, respectively), grade 3 elevations were uncommon (9% and 13%, respectively). Treatment discontinuations were limited, with discontinuation rates of adagrasib at 6% (9/148), pembrolizumab at 11% (16/148), and 4% discontinuing both (6/148). Of the 51 patients with PD-L1 $\geqslant$50%, ORR was 63% (32/51, 95% CI: 48%–76%) with a disease control rate (DCR) of 84% (43/51; 95% CI: 71–93). Both median PFS and DOR were not reached with a median follow-up of 10.1 months.[100] Efficacy data for PD-L1 <50% have not been presented. Regarding future trials, for patients with TPS <50%, adagrasib will be studied in combination with pembrolizumab plus chemotherapy (ClinicalTrials.gov identifier: NCT05609578).

MK-1084 is a KRAS G12C inhibitor that binds covalently.[101] The combination of MK-1084 plus pembrolizumab 200 mg IV q3w was administered in patients with untreated, metastatic NSCLC with PD-L1 $\geqslant$1%. Of the 27 patients who were response evaluable, the ORR was 70% (95% CI: 50%–86%) at MK-1084 doses ranging from 25 to 400 mg daily. Responses were seen both in patients who were PD-L1 1%–49% and PD-L1 $\geqslant$50%. The combination was well tolerated, with grade 1/2 ALT elevation in 26% (8/31) and grade 3–5 in 13% (4/31); grade 1/2 AST elevation in 23% (7/31) and grade 3–5 in 10% (3/31).[102] The combination of MK-1084 plus pembrolizumab versus pembrolizumab plus placebo is being studied in a prospective, phase III trial of patients with *KRAS* G12C mutations and a PD-L1 $\geqslant$50%.[103]

Two cohorts of the LOXO-RAS-20001 study enrolled previously untreated patients with *KRAS* G12C to be treated with the combination of olomorasib plus pembrolizumab in the frontline setting, as well as olomorasib plus pembrolizumab plus chemotherapy. For patients treated with pembrolizumab plus olomorasib, there was an ORR of 77% (13/17). The data are not mature enough to be able to estimate PFS and OS.[97] The combination of olomorasib, pembrolizumab, and chemotherapy similarly showed a tolerable toxicity profile in 21 treatment-naïve patients. The ORR was 50%, with 48% (10/21) of patients having a PD-L1 <1%.[104] Both of these combinations will be pursued in the SUNRAY-01 trial. For patients who are PD-L1 $\geqslant$50%, patients will be randomized to pembrolizumab plus olomorasib versus placebo.[97] Patients with any PD-L1 expression will be treated with platinum, pemetrexed, and pembrolizumab plus olomorasib versus placebo.[97]

These data demonstrate that combinations of KRAS G12C inhibitors plus single-agent

immunotherapy can be tolerable with significant clinical efficacy. We look forward to prospective, randomized data in the next few years. While outside the scope of this review on the role of immunotherapy in *KRAS* G12C NSCLC, the combinations of chemotherapy plus sotorasib will be studied in the randomized, phase III clinical trial CodeBreaK 202 in patients who are PD-L1 $\leqslant$1%.[105] In addition, KRAS on-target inhibitors, pan-KARS inhibitors, or novel combination strategies may play a role in the treatment of *KRAS* G12C-mutated NSCLC.[106] It remains to be seen whether a single strategy will maximize efficacy, minimize toxicity, and increase CNS treatment activity, or whether an individualized approach based on patient characteristics, PD-L1, and co-mutations will be the best path forward.

Novel combinations with KRAS G12C inhibitors

As detailed above, there are multiple resistance mechanisms that have been identified after treatment with KRAS G12C inhibitors, including on-target resistance mechanisms, bypass mechanisms, and histologic transformation.[60] Currently, the genomic and histologic resistance profile following treatment with the combination of immunotherapy plus KRAS G12C inhibitors is unknown. Novel combinatorial strategies will be needed both to treat patients after the development of resistance to KRAS G12C inhibitors, as well as to prevent the initial development of resistance using novel combinations upfront. Many combination strategies with KRAS G12C inhibitors are under development, including the HER2 antibody–drug conjugate trastuzumab deruxtecan, a SOS1 inhibitor BI 1701963, the CDK4/6 inhibitor palbociclib, the PARP inhibitor olaparib, the EGFR inhibitor cetuximab, and the SHP2 inhibitor TNO155.[107,108] Each of these combinations will have variable efficacy and toxicity, and may not be the correct treatment for an unselected, *KRAS* G12C-mutated population, but rather small subsets of patients. One aspirational goal is the treatment of every patient's individual resistance mechanism with a combinatorial strategy that also minimizes toxicity, though much work needs to be done for this to be realized.

Conclusion

KRAS G12C inhibitors have demonstrated single-agent efficacy in later lines of therapy, although response rate and durability have been limited in randomized clinical trials. This has led to the investigation of immunotherapy-based strategies combined with KRAS G12C inhibition in the frontline, which have demonstrated promising response rates in multiple single-arm, phase I trials. The toxicity of KRAS G12C inhibitors appears drug-specific rather than a class effect, which has led to tolerability differences with unique combinations. It will be important to incorporate what we know about genomic and phenotypic changes with co-alterations to establish treatment paradigms in different subgroups such as *STK11* or *KEAP1* co-alterations. As the efficacy and tolerability of these combination strategies improve, moving them into earlier stages will be a viable strategy to improve survival for patients with *KRAS* G12C mutations.

Declarations

Ethics approval and consent to participate

Ethical approval such as IRB approval was not required given this is a review article. Consent to participate: not applicable.

Consent for publication

Not applicable.

Author contributions

Nadia Ghazali: Conceptualization; Writing – original draft; Writing – review & editing.

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Natasha B. Leighl: Conceptualization; Writing – original draft; Writing – review & editing.

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