Setting the Benchmark for *KRAS*^{G12C}-Mutated NSCLC

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Activating mutations in the *KRAS* proto-oncogene were identified and characterized more than 40 years ago across several distinct human cancers, including pancreatic and colorectal cancers as well as non–small-cell lung cancer (NSCLC). *KRAS* somatic alterations are found in approximately 25 to 30% of lung adenocarcinomas and represent the most prevalent genomic driver event in NSCLC.[1] Within *KRAS* variants in NSCLC, the *KRAS* p.G12C single-nucleotide mutation (glycine-to-cysteine substitution at codon 12) is found in approximately 13% of lung adenocarcinomas.

KRAS-mutated NSCLCs are generally associated with smoking (current or former use), increased programmed death ligand 1 (PD-L1) expression on tumor cells, an increased tumor mutational burden, and increased tumor-infiltrating lymphocyte counts. Taken together, these factors are certainly correlated with a substantial efficacy of immune checkpoint inhibitors in *KRAS*-mutated NSCLCs, particularly the *KRAS* p.G12C subtype, as compared with *KRAS* wild-type disease.[1,2]

From a therapeutic standpoint, beyond the established efficacy of immunotherapy-based approaches, *KRAS*-mutated NSCLC differs from the well-known, other highly therapeutically actionable "oncogene-addicted" NSCLC subsets, such as those bearing *ALK* rearrangements or *EGFR* mutations. *KRAS* gene alterations in NSCLC have evaded successful targeting until recently.

In past decades, the development of KRAS or downstream signaling pathway inhibitors, such as mitogen-activated protein kinase kinase (MEK) or farnesyltransferase inhibitors, failed to show meaningful activity or provide additional treatment opportunities.[3] KRAS proteins are membrane-localized members of the family of guanine nucleotide-binding proteins, functioning as a molecular switch between the active form, guanosine triphosphate (GTP), and the inactive form, guanosine diphosphate (GDP).[4] The mutant form of the protein disrupts the GTPase-activating protein–mediated GTPase activity, resulting in abnormally high persistence of the active GTP-bound state with downstream pathway constitutive activation and uncontrolled cell growth (see the Science behind the Study editorial in this issue of the *Journal*). Hence, the theoretical process would have been to design innovative strategies to correct an impaired enzymatic state, thereby representing a biologic and pharmacologic challenge as compared with the expanding paradigm of receptor tyrosine kinase inhibition. To complicate matters, the picomolar affinity of KRAS for GTP, which is abundant in cancer cells, made any attempt to develop competitive inhibitors a failure.[4]

Unlike other *KRAS* mutations, *KRAS* p.G12C retains intrinsic GTPase activity, allowing for sufficient GDP-bound (inactive) KRAS protein to be targeted by specific KRAS^{G12C} covalent inhibitors, to trap the protein in its dormant state.[4] In May 2021, sotorasib was the first selective KRAS inhibitor to be granted accelerated approval from the Food and Drug Administration on the basis of the results of the phase 2 CodeBreaK100 trial. In this trial involving 124 previously treated patients affected by *KRAS*^{G12C}-mutated NSCLC, oral sotorasib showed a magnitude of antitumor activity far above that of second-line docetaxel, with an objective response rate of 37.1%, a median progression-free survival of 6.8 months, and a median overall survival of 12.5 months.[5]

In this issue of the *Journal*, Jänne et al.[6] report the results of the registrational phase 2 cohort KRYSTAL-1 trial, in which oral adagrasib was given to 116 patients with *KRAS*^{G12C}-mutated NSCLC that was refractory to at least one standard treatment, including platinum-based chemotherapy and an immune checkpoint inhibitor (median of two previous systemic therapies; 12% of the patients had received at least four). The trial showed an objective response rate of 42.9%, a median duration of response of 8.5 months, a median progression-free survival of 6.5 months, and a median overall survival of 12.6 months. Efficacy was consistent across all distinct clinical subgroups, including sex, age, smoking history, previous therapies, Eastern Cooperative Oncology Group performance-status score, and site of distant metastases. The results appear to be consistent with the previously published data on sotora-

sib and confirm the activity of this new class of compounds that are defined by a similar mechanism of action.

As we remain conscious of the limitations of the exercise of intertrial comparisons, the results from the two trials of sotorasib and adagrasib look alike, with similar response rates (37.1% and 42.9%, respectively), progression-free survival (6.8 months and 6.5 months), and overall survival (12.5 months and 12.6 months) and a similar incidence of drug discontinuation due to adverse events (7.1% and 6.9%). For both compounds, responses were observed across all PD-L1 expression levels and molecularly defined subgroups, in which the role of co-occurring mutations (in *STK11*, *KEAP1*, and *TP53*) was evaluated.

Although sharing the exact mechanism of action, these two selective $KRAS^{G12C}$ inhibitors might have noticeable differences, potentially defining distinct treatment opportunities. On the basis of the rapid turnover and resynthesis of $KRAS^{G12C}$, adagrasib was sufficiently adapted for a sustained target inhibition through its distinctive pharmacokinetic properties, including KRAS–GTP loading inhibition with a 50% maximal inhibitory concentration of 89.9 nM (vs. 47.9 nM for sotorasib) and a long half-life (approximately 24 hours vs. 5.5 hours for sotorasib), as well as its twice-daily administration schedule (vs. once daily for sotorasib).[5] Adagrasib is characterized by a clinically meaningful penetration of cerebrospinal fluid,[7] with an unbound brain-to-plasma concentration of 0.47, similar to or exceeding values for known central nervous system (CNS)–penetrant tyrosine kinase inhibitors in preclinical mouse models.

In the trial by Jänne et al., a retrospective exploratory analysis of patients enrolled with previously treated brain metastases at baseline showed an intracranial objective response rate of 33% and a median intracranial progression-free survival of 5.4 months, according to modified Response Assessment in Neuro-Oncology (RANO) criteria. Although these results may have been affected by the possible interference of previous CNS-directed therapy, a specific cohort of the phase 1b KRYSTAL-1 trial further supports the CNS activity of adagrasib.[8] Among 25 patients with NSCLC and untreated CNS metastases, adagrasib showed an intracranial objective response rate of 32%, according to RANO criteria. Although the authors suggest a concordance between intracranial and systemic disease control for adagrasib, the unusual use of RANO criteria (vs. Response Evaluation Criteria in Solid Tumors, version 1.1, for systemic disease in KRYSTAL-1 and as a standard in solid tumors) formally limits this assessment as well as comparisons with historical data regarding the use of alternative anticancer therapies in patients with NSCLC. Nevertheless, adagrasib is today the only $KRAS^{G12C}$ inhibitor with demonstrated clinical activity in patients with treated CNS metastases and those with untreated CNS metastases, a fact that remains relevant in a disease characterized by a high propensity for brain metastases (27 to 42% at diagnosis), which are associated with poor prognosis.[8] This compartment-specific efficacy was not formally shown for sotorasib, for which CNS activity remains under evaluation (in the CodeBreaK 101 trial [ClinicalTrials.gov number, NCT04185883] and the S1900E group of the Lung-MAP trial [NCT04625647]).

The compatibility of KRAS inhibitors with standard therapies for NSCLC, including immune checkpoint inhibitors, represents a crucial factor from a safety point of view. Preliminary results from a phase 1b study of adagrasib plus pembrolizumab involving seven patients showed a tumor regression ranging from 37 to 92%, with disease control observed in 100% of the patients and no treatment-related adverse events leading to treatment discontinuation and no grade 4 or 5 adverse events observed (Mirati Therapeutics press release, November 8, 2021). A recent report suggested that sotorasib in patients receiving immune checkpoint inhibitors might trigger immune-related hepatitis.[9] Although the cause of such a hepatocellular injury has not been identified to date and given that both sotorasib and adagrasib are selective to $KRAS^{G12C}$, whether such a safety issue should be considered to be a class effect or to be due to specific properties of the molecule or formulation remains unclear. The current clinical trials landscape (Table 1) supports the second hypothesis, and more data are eagerly awaited on this immunotherapy-sensitive disease.

Despite the initial clinical benefit, all patients with $KRAS^{G12C}$-mutated disease eventually have disease progression due to various distinct intrinsic or acquired resistance mechanisms, as

Table 1. KRAS^{G12C} Inhibitor Combination Strategies under Evaluation.*

Agent	Sotorasib†	Adagrasib	JDQ433	BI 1823911‡	GDC-6036§	LY3537982¶	MK-1084‖
PD-1 or PD-L1 inhibitor	AMG-404, pembrolizumab, atezolizumab**	Pembrolizumab**††	Spartalizumab,§§ tislelizumab		Atezolizumab	Pembrolizumab	Pembrolizumab
Chemotherapy	Carboplatin, pemetrexed+docetaxel**						
EGFR inhibitor	Afatinib**	Afatinib**††	Cetuximab¶¶		Cetuximab, erlotinib	Cetuximab, erlotinib	
SHP2 inhibitor	RMC-4630, TNO155	TNO155‖	TNO155		GDC-1971	TNO155	
SOS1 inhibitor		BI 1701963***		BI 1701963			
MEK or ERK inhibitor	Trametinib		Trametinib¶¶			Temuterkib	
VEGF inhibitor					Bevacizumab		
mTOR inhibitor	Everolimus						
CDK4/6 inhibitor	Palbociclib		Ribociclib¶¶			Abemaciclib	
PI3K inhibitor					Inavolisib		
Aurora kinase inhibitor						LY3295668	

* Data reported in the table are not exhaustive. CDK4/6 denotes cyclin-dependent kinases 4 and 6, EGFR epidermal growth factor receptor, ERK extracellular signal-regulated kinase, MEK mitogen-activated protein kinase kinase, mTOR mammalian target of rapamycin, PD-1 programmed death 1, PD-L1 programmed death ligand 1, PI3K phosphatidylinositol 3-kinase, SHP2 Src homology 2 domain–containing protein tyrosine phosphatase 2, SOS1 SOS Ras/Rac guanine nucleotide exchange factor 1, and VEGF vascular endothelial growth factor.

† ClinicalTrials.gov number, NCT04185883.

‡ ClinicalTrials.gov number, NCT04973163.

§ ClinicalTrials.gov number, NCT04449874.

¶ ClinicalTrials.gov number, NCT04956640.

‖ ClinicalTrials.gov number, NCT05067283.

** Shown are combinations investigated in patients with non–small-cell lung cancer only; combinations investigated in patients with colorectal cancer only are not listed.

†† ClinicalTrials.gov number, NCT03785249.

‡‡ ClinicalTrials.gov number, NCT04613596.

§§ ClinicalTrials.gov number, NCT04699188.

¶¶ ClinicalTrials.gov number, NCT05358249.

‖‖ ClinicalTrials.gov number, NCT04330664.

*** ClinicalTrials.gov number, NCT04975256.

characterized in a small proportion of evaluable tissue or plasma of treated patients.[10,11] The heterogeneous patterns of resistance include secondary on-target mutations in *KRAS*, alterations in RTK–RAS signaling transduction pathways that do not directly alter KRAS itself, oncogenic fusions, gene amplification, and histologic transformation to squamous-cell carcinoma.[8,10] These molecular features strongly suggest that a subgroup of patients may potentially benefit from cotargeting of additional central nodes in RAS signaling pathways (e.g., MAPK pathway or SOS1 inhibitors). Further exploration and a deep understanding of the tumor microenvironment and co-mutation assets will be critical to improving our treatment strategies.

Several new $KRAS^{G12C}$ inhibitors that are highly selective and potent (e.g., JDQ443, LY3537982, BI 1823991, and RMC-6261) are in development. Some of these (e.g., RMC-6261) have a different mechanism of action, in which the agent binds to the active GTP-bound conformation of $KRAS^{G12C}$ and increases the durability of pathway inhibition and antitumor activity.

In this evolving scenario, the therapeutic index of the new $KRAS^{G12C}$ inhibitors as monotherapy or in combination, their safety profile, and their intracranial activity represent some of the opportunities to highlight their unique specificities. The role of combination strategies — including KRAS inhibitors plus chemotherapy, immune checkpoint inhibitors, or new compounds (targeted or not) — in obviating and overcoming both de novo and acquired resistance is being evaluated in a series of ongoing clinical trials (Table 1).

In the context of a new class of drugs that is entering a niche in which improvements are dramatically needed, the results of KRYSTAL-1 deserve attention and dissemination. Results from the two independent, nonrandomized series using sotorasib or adagrasib confirm the considerable usefulness of this class of drugs and the actionability of $KRAS^{G12C}$, previously considered to be "undruggable." Given the complexity and redundancy of KRAS signaling and the broad spectrum of resistance mechanisms to $KRAS^{G12C}$ inhibitors, searching for biologically relevant, active, and safe therapeutic synergies will be the main challenge for the development of additional approaches targeting $KRAS^{G12C}$-mutated NSCLC.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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