One Step at a Time — Clinical Evidence That KRAS Is Indeed Druggable

Patricia M. LoRusso, D.O., and Judith S. Sebolt-Leopold, Ph.D.

Overall survival among patients with advanced-stage KRAS<sup>G12C</sup> non–small-cell lung cancer (NSCLC) or colorectal cancer is approximately 1 to 2 years; this startling statistic has fueled nearly four decades of research dedicated to the search for a KRAS-targeted drug. Because RAS has picomolar affinity for guanosine triphosphate (GTP) and intracellular GTP concentrations are exceedingly high, early strategies to find compounds that preferentially bind to the RAS–GTP pocket failed. Other strategies have attempted to interfere with RAS activation by preventing its membrane localization or by inhibiting downstream kinase signaling, but these also failed because of resistance stemming from compensatory signaling. Renewed interest in therapeutic strategies to directly target RAS was triggered by a seminal report by Shokat and colleagues, who designed covalent small-molecule inhibitors that irreversibly targeted the cysteine residue at codon 12 of KRAS, locking the protein into an inactive state. This major advance opened the door for a precision-medicine approach to targeting KRAS<sup>G12C</sup>-mutant tumors.

Sotorasib (AMG510) was reported to be the first KRAS<sup>G12C</sup> inhibitor to enter clinical testing after encouraging evidence was shown of preclinical efficacy and inhibition of KRAS signaling in KRAS<sup>G12C</sup>-mutant models. MRTX849, another small molecule targeting KRAS<sup>G12C</sup>, has also shown significant preclinical efficacy. These data provided preclinical proof of concept for covalent small-molecule inhibition of KRAS<sup>G12C</sup>. However, the critical question facing any oncology drug development program, independent of the target, is whether drug exposures associated with preclinical efficacy can be achieved safely in patients.

Hong and colleagues now present in the Journal the results of an early-phase clinical trial of sotorasib in expansion cohorts of patients with KRAS<sup>G12C</sup> NSCLC, colorectal cancer, and other tumor types. This monotherapy trial showed responses across all dose levels tested, with no dose-limiting toxic effects identified. Responses were seen in patients with KRAS<sup>G12C</sup> tumors of various histologic subtypes, including NSCLC (32.2%), colorectal cancer (7.1%), and appendiceal, endometrial, and pancreatic cancers and melanoma (1 patient each). Benefit was also seen with respect to progression-free survival, with a median progression-free survival of 6.3 months and 4.0 months in patients with NSCLC and colorectal cancer, respectively. The most common toxic effects included diarrhea, fatigue, and nausea of any grade occurring in up to 30% of patients. The main grade 3 toxic effects were reversible elevations of alanine aminotransferase levels, diarrhea, vomiting, and anemia (each in less than 5% of the patients). This favorable safety profile, compounded with responses across multiple doses, indicates a potential for minimal overlap of toxic effects with those of other agents and points to the possibility of combination therapy strategies.

Tumor responses were much better than those seen with the current standard of care for patients with similar disease profiles. Despite these encouraging results, no complete responses were observed, perhaps because tumors harboring KRAS mutations often have multiple oncogenic drivers. Neither serial biopsy data nor serial circu-
lating tumor DNA (ctDNA) data were presented, leaving key questions unanswered — namely, can particular differences in the mutational signatures of KRASG12C NSCLC and colorectal cancers explain the substantial differences in response of these two tumor types, and could other driver mutations have contributed to the lack of complete responses? Serum pharmacokinetics showed clinical drug exposure profiles that were consistent with exposure levels that led to 100% inhibition of phosphorylated extracellular signal-regulated kinase (ERK) in preclinical models. However, whether inhibition of phosphorylated ERK in tumors was achieved is unknown from this report, and therefore whether the appropriate dose or schedule of the drug was used is unclear.

Overall, the results of this trial are very encouraging, showing the first step in “drugging the undruggable.” Informed combination strategies may improve the likelihood of achieving complete responses to KRASG12C inhibition. A recent study showed that KRASG12C colorectal cancer cells have higher basal epidermal growth factor receptor (EGFR) activity than NSCLC cells, leading to a rapid rebound in mitogen-activated protein (MAP) kinase signaling and resistance to KRASG12C inhibition. This observation is consistent with the weaker observed clinical activity of sotorasib in patients with colorectal cancer, a problem that may be addressed by combining it with an EGFR inhibitor (e.g., cetuximab), as seen preclinically. However, the specific receptor tyrosine kinase driving the rebound in MAP kinase signaling can vary widely among tumors. Since the protein tyrosine phosphatase SHP2 activates RAS downstream of receptor tyrosine kinases, the scientific rationale exists for combining sotorasib with a SHP2 inhibitor to benefit a broader patient population. Preclinical data have triggered clinical trials evaluating a SHP2 inhibitor–based combination strategy in patients with KRASG12C-bearing tumors. Signaling context is a major determinant of outcome, and in some cases, such as KRASG12C-mutant NSCLC, resistance driven by adaptive signaling of the phosphatidylinositol 3-kinase–mechanistic target of rapamycin (PI3K–mTOR) pathway should not be overlooked.

The article by Hong et al. shows that, through meaningful scientific collaborations, clinical inhibition of this previously untouchable target is now possible. The early development of KRASG12C-targeted agents is just the beginning, lending hope that the ability to target not only other KRAS mutations but also other targets previously thought to be undruggable may be within reach.

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

From Yale Cancer Center, New Haven, CT (P.M.L.); and the University of Michigan Rogel Cancer Center, Ann Arbor (J.S.S.-L.).

This editorial was published on September 20, 2020, at NEJM.org.


DOI: 10.1056/NEJMe2026372

Copyright © 2020 Massachusetts Medical Society.