ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Targeting the *KRAS* G12C Mutation in Patients With Advanced Solid Tumors

David S. Hong, MD
Professor
Deputy Chair of the Department of Investigational Cancer Therapeutics
Division of Cancer Medicine
Associate Vice President of Clinical Research
University of Texas MD Anderson Cancer Center
Houston, Texas

H&O What is the *KRAS* G12C mutation?

DH *RAS* mutations are one of the most common mutations in cancer (after the *P53* mutation). Estimates suggest that up to 40% of all cancers exhibit a *RAS* mutation, most frequently, *KRAS*. (Other *RAS* mutations include *NRAS* and *HRAS*.) *KRAS* mutations are prevalent in common malignancies, such as lung and colorectal cancer. The most common variants of the *KRAS* 12 codon mutation include V, D, and C. Research has shown that these gene mutations occur in nearly 40% of patients with lung cancer. Among patients with colorectal cancer, as many as 5% have a *KRAS* p.G12C mutation.

KRAS has been difficult to target. RAS is a protein that binds to guanosine-5'-triphosphate (GTP); it uses GTP as fuel. It has been difficult to target the GTP pocket of *RAS*. In 2013, Ostrem and colleagues reported on the first series of molecules in the switch-II region of the *KRAS*-mutated protein leading to *KRAS* in the inactive guanine diphosphate (GDP) state.

H&O Do patients with a *KRAS* G12C mutation share any other similarities?

DH It is not known whether there is a defining phenotype for patients with the *KRAS* G12C mutation. No large epidemiologic studies have examined this question. My institution maintains a database of patients with this mutation. The most common tumor types are lung and colorectal cancer. *KRAS* G12C mutations have also been found, albeit far less frequently, in malignancies such as endometrial, pancreatic, and ovarian cancer. It is not known why the *KRAS* G12C mutation is more common in lung and colorectal cancer.

> Estimates suggest that up to 40% of all cancers exhibit a *RAS* mutation, most frequently, *KRAS*.

H&O What has been learned by previous attempts to target the *KRAS* mutation?

DH Previous studies examined indirect attempts to target the *KRAS* mutation. Investigators tried to hit targets downstream of *KRAS*, such as *BRAF* and *MEK*. This strategy has been successful in patients with *BRAF* V600E mutations and in several different tumor types, such as melanoma. However, no studies have shown any benefits in *KRAS*-mutated patients to hitting downstream targets such as *BRAF* or *MEK*. For example, I was involved in early studies evaluating tipifarnib, a farnesyltransferase inhibitor, in combination with a BRAF inhibitor or sorafenib (Nexavar, Bayer). Farnesylation is a process by

which the RAS protein is modified so that it can bind to the cellular membrane and combine with receptors and other components to exert signals downstream. Tipifarnib was not effective in RAS-mutated patients, we think to a large extent because there is an alternative kind of prenylation called geranylgeranylation. More recent studies of tipifarnib suggest that inhibition of farnesylation may be effective in the rare subset of patients with *HRAS* mutations, which are seen in head and neck squamous cell cancers. These new studies of KRAS G12C inhibitors were the first to show that it is possible to target the GTP pocket. Future drugs may be able to target not just G12C, but other variants, such as V and D.

H&O What are the challenges in targeting *KRAS*?

DH One challenge is that these mutations are located in the guanosine triphosphate phosphohydrolase (GTPase) pocket. The experience with the *BRAF* mutation has lessons for *KRAS* research. Flaherty and colleagues published phase 1 data showing that inhibition of BRAF was effective in patients with metastatic melanoma. The response in melanoma was not anticipated; it had been thought that patients with colorectal cancer were most likely to respond. Likewise, patients with colorectal cancer had minimal responses to KRAS G12C inhibition. Better responses were seen in patients with lung cancer. It is too early to say whether KRAS inhibition will be effective beyond these malignancies because studies enrolled few patients with other phenotypes.

I predict that patients who respond to KRAS inhibition will eventually develop resistance to treatment, as typically occurs in patients with point mutations, such as *EGFR*, *ALK-ROS*, and *BRAF*. To maintain progress in this area, future research must recognize that patients will develop resistant mutations.

H&O What were the findings from your study of the KRAS G12C inhibitor AMG 510?

DH At the 2019 American Society of Clinical Oncology meeting, my colleagues and I presented initial results from a phase 1 trial evaluating AMG 510, a novel small-molecule KRAS G12C inhibitor, among patients with advanced solid tumors. The preclinical data for AMG 510 were equivalent, if not superior, to data published by Ostrem and colleagues in 2013 on the development of small molecules that target *KRAS* G12C. The pharmacokinetic analyses showed that even low dose levels of AMG 510 exceeded the 90% inhibitory concentration level that would lead to downstream inhibition of markers of RAS inhibition. There were clinical responses to AMG 510, even at lower dose levels. At the highest dose level of 960 mg, a response was seen in every patient with lung cancer.

The study showed clear activity, and it was possible to reach the highest dose level. AMG 510, like other next-generation targeted agents, is very specific for *KRAS* G12C. The toxicities were minimal, and mostly grade 1 or 2. The unique tolerability will allow future studies to evaluate AMG 510 in combination with other treatments, such as chemotherapy and immunotherapy.

> AMG510 is the first agent to successfully target *KRAS* 12C.

H&O What are the potential advantages to the use of AMG 510?

DH AMG 510 is the first agent to successfully target *KRAS* G12C. *RAS* had been considered untargetable. This discovery will likely prompt many organic chemists and companies to investigate the possibilities of targeting other *KRAS* variants. *KRAS* is a resistance marker for many different therapies, such as cetuximab (Erbitux, Lilly) in colorectal cancer. It also appears that patients with *KRAS* mutations do not respond to phosphoinositide 3 (PI3) kinase inhibitors. It may be possible to combine AMG 510 with therapies such as PI3 kinase inhibitors and epidermal growth factor receptor agents to overcome resistance to these drugs, thereby achieving responses in a larger population of patients. This initial research will likely lead to many other breakthroughs in targeting the *KRAS* mutation in the next decade.

H&O Is there any other promising research in this area?

DH Research of RAS inhibitors in combination with treatments such as chemotherapy, immunotherapy, and other targeted agents is rapidly moving forward. Investigators are still trying to understand the landscape. It may be possible to use cell-free DNA to monitor these patients. It is an exciting time in the field of *RAS* mutations.

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Suggested Readings

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