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Sticking it to KRAS: Covalent Inhibitors Enter the Clinic

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Abstract

Drugs that target KRAS 12C covalently, AMG 510 and MRTX849, are now in the clinic. Recent papers describe development of these compounds, their selectivity and properties, early clinical data, and potential combination therapies. These papers herald a new era in Ras research, with improved drugs and strategies certain to follow.

In 2013, Dr. Kevan Shokat's group published a landmark paper showing that KRAS G12C could be targeted by a covalent compound that locks the protein in its inactive, GDP-bound state (Ostrem et al., 2013). This brilliant insight, and the excellent work of his graduate student Jonathan Ostrem, was supported with some good luck: of all the common oncogenic RAS mutants, KRAS G12C retains the highest residual intrinsic GTPase activity. This allows the KRAS G12C protein to cycle from its predominant, GTP-bound state, to the GDP-bound state, with a t ½ of about 12 min. Therefore, in about 1 h, 95% the KRAS G12C protein cycles through the GDP-bound state in which it is vulnerable to attack. This would take about 15 h or more for G12V or Q61 mutants. For G12D, the most common KRAS mutant in cancer, 95% would cycle through the GDP-state in about 3 h: longer than G12C, but not out of reach. The approach of locking an oncogenic mutant in the inactive state is therefore highly appropriate for G12C. Even so, there were concerns that covalent attack on G12C could not work *in vivo*, because a covalent drug such as this needs to be potent enough to hit its target and mild enough to avoid irreversible damage to other important proteins. Another stroke of luck helped this approach advance: a lysine residue (Lys-16) in the binding site catalyzes the electrophilic warhead, making it more active in this specific context (Hansen et al., 2018). Employing a relatively weak warhead is obviously safer, but its activation on binding to KRAS G12C gives it the potency needed to be effective.

A race to translate these discoveries into the clinic was on. Compounds with better binding properties and pharmacologic properties needed to be developed and tested. ARS-853 was a major step forward (Patricelli et al., 2016). ARS-1620 followed (Janes et al., 2018), which showed the value of this approach *in vivo*. These compounds were made available as tool compounds for the academic community to explore. ARS-1620 elicits variable responses among a panel of G12C cancer lines, which can be increased significantly by inhibition of

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DECLARATION OF INTERESTS

F.M. is founder and shareholder in BridgeBio, Quanta, and Wellspring and is a consultant for Pfizer, Quartz, Amgen, Daiichi Sankyo, Kura, Wellspring, and BridgeBio.

PI3K (Misale et al., 2019). Two types of genes affect efficacy of ARS-1620: one set includes genes that affect the GDP state (*SHP2*, *EGFR*, and *FGFR1*) of KRAS and another set, referred to as collateral dependencies, support cancerous growth after KRAS G12C ablation. These include *CDK4*, *CCND1*, and *AXL* (Lou et al., 2019). IGF1R and mTOR inhibitors also increased the efficacy of ARS-1620 in lung cancer cell and mouse models (Molina-Arcas et al., 2019).

The first G12C inhibitors in the clinic came from Amgen, AMG 510, then from Mirati Therapeutics, MRTX849. Papers describing development of these compounds, early clinical data, and the potential of combining these drugs with other agents have just been published (Canon et al., 2019; Hallin et al., 2019). These represent first steps in what will surely be an ongoing story involving additional G12C compounds and eventually, drugs targeting KRAS by different approaches. Indeed, Janssen R&D and Eli Lilly have already launched phase 1 trials with additional G12C inhibitors, and Boehringer Ingelheim have opened a trial of BI 1701963, a pan-KRAS inhibitor.

One advantage of covalency is the relative ease with which their targets can be captured and analyzed (Patricelli et al., 2016). Using this approach, AMG 510 was shown to be remarkably specific: among 6,451 cysteine-containing peptides detected in a proteomic analysis, AMG 510 bound to only one, from KRAS G12C. Consistent with this clean profile, both AMG 510 and MRTX849 appear to be safe and well tolerated at the doses and time courses reported so far.

Consistent with data derived from ARS-1620, AMG 510 showed synergy, to varying degrees, with inhibitors of EGFR, SHP2, PI3K, AKT, and MEK and standard chemotherapy in preclinical models. The Mirati group also analyzed potential combinations of interest using conventional CRISPR/Cas9 as well as a panel of potential inhibitors. These screens identified MYC, SHP2, MTOR, RPS6, CDK1, CDK2, CDK4, CDK6, and RB1 as affecting fitness in the context of MRTX849, and KEAP1 and CBL as tumor suppressors.

Of all the possible combination therapies described in these two papers, and by their academic predecessors, the Amgen team chose to highlight combinations with immunotherapy. A cynic might suggest that this is simply a standard combination to test with any cancer drug or modality. However, there are compelling reasons to expect that blocking KRAS would render tumors more prone to immune attack. KRAS mutant cancers produce immune-suppressive cytokines and, indeed, upregulate expression of PD-L1 through stabilizing its mRNA (Coelho et al., 2017). Pancreatic cancers, which are almost always driven by mutant KRAS, are the “coldest” of tumors, because their extensive microenvironment is hostile to immune effector cells. AMG 510 treatment in mouse models and cell lines led to a pro-inflammatory environment through increased expression of Cxcl10 and Cxcl11, among other chemokines, and based on impressive preclinical efficacy data, a combination study has already started with AMG 510 and anti-PD-1.

Patients enrolled in the AMG 510 phase 1 trial had to have KRAS G12C, obviously, as well as local or metastatic disease, prior standard therapies, and no brain metastases. As of September 28, 2019, 76 patients had enrolled (34 non-small cell lung cancer [NSCLC], 36

colorectal cancer [CRC], and 6 others), and 52 remained on treatment. No dose-limiting toxicities or adverse events leading to discontinuation were reported, and the highest dose, 960 mg orally, was identified for the recommended phase 2 dose. In NSCLC, the disease control rate at this dose was 100% (no progressive disease was reported) with an objective response rate of 54% based on RECIST criteria. In CRC, disease control rate was 92%, but overall response rate was only 8%. Data from the Mirati trial of MRTX849 were presented at the 2019 AACR-NCI-EORTC meeting (October 28, 2019). At the highest dose, 600 mg BID, 3 of 5 evaluable patients with NSCLC and 1 of 2 evaluable patients with CRC achieved a partial response. A maximum tolerated dose was not established, but one dose-limiting toxicity effect was seen at the 600 mg dose.

These data together clearly establish that targeting KRAS G12C is safe and has potential clinical benefit. While the data may not be considered dramatic, they are the best responses ever seen in this patient population, and more importantly, there are clear paths ahead to improve efficacy. We know that blocking the RAS pathway relieves the tonic feedback of upstream signaling, leading to a burst of activity that helps keep cells alive. For KRAS G12C inhibitors, this is double trouble. As well as providing a survival advantage, upstream signaling shifts KRAS G12C toward the GTP-bound state in which G12C drugs cannot bind. Therefore, we expect that drugs targeting growth factor receptors or upstream signaling proteins like Shp2 or Sos will significantly enhance potency. Most likely, the drugs and pathways identified from preclinical analysis from Amgen and Mirati, as described in these papers, as well as from academic labs using ARS-1620, will be tested in the clinic in the coming years, along with other ways of targeting KRAS. Furthermore, these early studies will help lay a foundation for future developments and innovations that will undoubtably translate into improved patient benefit.

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