TARGETED THERAPIES

KRAS-G12C in the crosshairs

KRAS is commonly mutated in a broad spectrum of cancers; the KRAS-G12C mutation commonly occurs in non-small-cell lung cancer (NSCLC), and is also found in several other cancer types (albeit at lower frequency), such as pancreatic ductal adenocarcinoma (PDAC) and colorectal adenocarcinoma. The first selective KRAS-G12C inhibitor was reported in 2013 by Ostrem et al., but identifying similar inhibitors with properties suitable for clinical development has proved challenging. Two papers have now reported the discovery and preclinical analyses of two different covalent inhibitors of KRAS-G12C (AMG 510 and MRTX849) as well as the first data on the efficacy of these inhibitors in cancer patients.

KRAS is a GTPase, and inhibitors selective for KRAS-G12C were initially designed to bind to the mutant Cys12 residue in the KRAS switch II pocket. These inhibitors lock KRAS-G12C in an inactive GDP-bound state. AMG 510 and MRTX849 act in a similar manner: both bind in the switch II pocket, but AMG 510 also includes aromatic rings that bind to a hidden surface groove formed by an alternative position of His95, which improves its potency relative to a previously reported compound (ARS-1620).

Canon et al. and Hallin et al. showed that AMG 510 and MRTX849, respectively, inhibited phosphorylation of ERK and of the ribosomal protein S6 downstream of KRAS in two KRAS-G12C-mutant cancer cell lines (NCI-H358 NSCLC cells and MIA PaCa-2 PDAC cells). Both inhibitors also reduced cell viability, at least in part by inducing apoptosis.

Across larger KRAS-G12C-mutant and non-mutant cell line panels, AMG 510 and MRTX849 effectively inhibited cell growth in both two-dimensional and three-dimensional spheroid cultures in the majority of KRAS-G12C-mutant cells only. However, both inhibitors had a range of IC_{50} values suggesting that factors other than KRAS-G12C expression contribute to inhibitor sensitivity.

Both AMG 510 and MRTX849 induced dose-dependent reduction of tumour growth in mice bearing NCI-H358 or MIA PaCa-2 xenografts, and in mice with KRAS-G12C-mutant patient-derived xenografts from several cancer types.

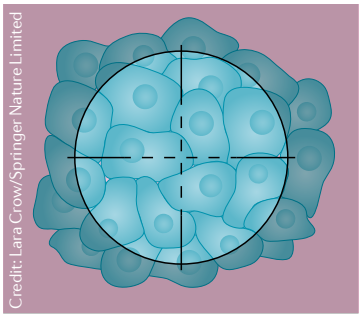
Hallin et al. found that MRTX849 inhibited tumour growth in 26 different KRAS-G12C-mutant cell-line and patient-derived xenograft models; however, anti-tumour efficacy varied from delayed growth to regression. Furthermore, no clear biomarker of therapeutic response emerged.

As Hallin et al. did not find any specific genetic alterations that predicted sensitivity to MRTX849, they conducted a CRISPR–Cas9 screen in NCI-H358 and NCI-H2122 NSCLC cells in vitro and in NCI-H2122 xenografts and found that loss of several cell cycle and mTOR pathway genes as well as *SHP2* and *MYC* further reduced tumour growth in the presence of MRTX849. A small-molecule screen then found that the EGFR and HER2 inhibitor afatinib, the SHP2 inhibitor RMC-4550, the mTOR inhibitors vistusertib and everolimus, and the CDK4 and CDK6 inhibitor palbociclib all improved the response of KRAS-G12C-mutant xenografts to MRTX849.

Canon et al. similarly examined the combination of AMG 510 with other therapies and found that adding a MEK inhibitor or carboplatin chemotherapy enhanced the anti-tumour response.

Canon et al. also examined the efficacy of AMG 510 in syngeneic KRAS-G12C-expressing CT-26 colorectal tumours in immunocompetent mice. Durable cures were obtained in most mice; this depended on the presence of T cells, as tumours in mice lacking T cells regressed after AMG 510 treatment, but the mice eventually relapsed. This suggested a role for the immune system in driving cure. The combination of PD1 immune checkpoint inhibition and a lower dose of AMG 510 in this model led to complete responses in nine of ten mice, whereas either treatment alone induced complete responses in only one of ten tumours. AMG 510 increased tumour infiltration of a number of immune cell types and induced an inflammatory microenvironment. AMG 510 also increased the expression of MHC class I antigens on tumour cells; as such, tumours did not grow in cured mice that were re-challenged with CT-26 KRAS-G12C cells. Interestingly, although non-KRAS-mutant cells formed tumours in these mice, CT-26 cells expressing KRAS-G12D did not grow, suggesting the development of adaptive immunity to shared antigens.

> “Both inhibitors have entered into phase I/II clinical trials”



Credit: Lara Crow/Springer Nature Limited

Both inhibitors have entered into phase I/II clinical trials, and initial data on these were reported. Objective partial responses to AMG 510 were observed in two of four patients with NSCLC; partial responses to MRTX849 occurred in one patient with NSCLC and one patient with colon adenocarcinoma.

Although moving KRAS-G12C inhibitors into the clinic is undoubtedly a big step forwards, much work remains to determine the molecular contexts that define response and resistance in order to best define which cancer types will be most sensitive to these inhibitors and how they should be combined with other therapies. Furthermore, G12C is only one of many mutations in KRAS, and strategies to target the other mutations are still lacking.

Sarah Seton-Rogers

ORIGINAL ARTICLES Canon, J. et al. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature* **575**, 217–223 (2019) | Hallin, J. et al. The KRASG12C inhibitor, MRTX849, provides insight toward therapeutic susceptibility of KRAS mutant cancers in mouse models and patients. *Cancer Discov.* https://doi.org/10.1158/2159-8290.CD-19-1167 (2019)

RELATED ARTICLES Ostrem, J. M. et al. K-Ras(G12C) inhibitors allosterically control GTP affinity and effector interactions. *Nature* **503**, 548–551 (2013) | Li, S. et al. A model for RAS mutation patterns in cancers: finding the sweet spot. *Nat. Rev. Cancer* **18**, 767–777 (2018)