Editorial Commentary

MRTX1133's promise for treating KRAS^{G12D}-mutant pancreatic cancer

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Pancreatic cancer, namely pancreatic ductal adenocarcinoma (PDAC), is the seventh leading cause of cancer-related mortality worldwide, with a 5-year survival rate of only 10% (1). Its aggressive nature, along with late-stage diagnosis, typically precludes curative surgical procedures, leaving chemotherapy as the primary therapeutic option, with little survival benefits. Unlike other cancer types, whose fatality rates have dropped due to therapeutic improvements, PDAC mortality remains high due to diagnostic issues, necessitating the urgent development of more effective treatments (2). The genomic landscape of PDAC reveals that oncogenic Kirsten rat sarcoma viral oncogene homologue (KRAS) mutations are the most common driver, accounting for 95% of cases, followed by TP53, CDKN2A, and SMAD4 alterations (3). Notably, the majority of KRAS mutations occur at codon 12, with the G12D mutation dominating. Unfortunately, targeted therapies for these changes remain difficult, prompting research into downstream signaling effectors such as MEK, epidermal growth factor receptor (EGFR), and PI3K inhibitors, but with limited clinical effectiveness in PDAC (1,4).

The oncogenic KRAS mutation is a key driver of uncontrolled cell proliferation and cancer progression in PDAC (5). Historically, targeting mutant KRAS has been difficult due to a lack of suitable molecule inhibitor binding sites. Various screening methodologies, including virtual, high-throughput, and fragment-based approaches, have been used to identify small compounds capable of targeting KRAS (6-9). These strategies target key regions of the KRAS protein involved in its activation and signaling cascade, such as the switch regions (switch I and switch II) critical for guanine nucleotide exchange factors (GEFs) interaction and effector binding. The switch regions (I and II) are key domains in the KRAS protein structure that undergo conformational change when activated (10). When inactive KRAS binds guanosine diphosphate (GDP) to the nucleotide-binding pocket, a GEF catalyzes the exchange of GDP for guanosine triphosphate (GTP) upon activation by extracellular signals. This exchange leads to a change in conformation in the switch region. This conformational change exposes binding sites for downstream effector proteins, allowing KRAS-GTP to interact with and activate signaling pathways essential for cell proliferation, survival, and differentiation (10,11).

Furthermore, targeting the nucleotide-binding site and neighboring surface pockets has been investigated. Studies focusing on generating G12C inhibitors with improved efficacy and drug-like properties led to the discovery of ARS-1620 and AMG510 (sotorasib) as potential therapeutic agents (8,12,13). Both these compounds are covalent inhibitors that form irreversible bonds with the cysteine residue at position 12 of KRAS^{G12C}, locking the protein in its inactive GDP-bound state and preventing downstream signaling activation. ARS-1620 suppressed RAS-GTP and downstream protein phosphorylation in G12C-mutant lung cancer cells in a dose-dependent and selective manner (13). This compound has great potency and selectivity for mutant KRAS alleles, resulting in growth inhibition and apoptosis

in mutant cells. ARS-1620's selectivity for the G12C allele was supported by a variety of tests. In a phase 1/2 trial, patients with advanced KRAS G12C-mutant solid tumors were treated with AMG 510, which resulted in stable disease and tumor shrinkage in certain cases. Patients with highly pretreated advanced $KRAS^{G12C}$ colorectal cancer (CRC) showed an objective response rate of 7.1% and a disease control rate of 73.8%. Tumor shrinkage was reported in a large proportion of patients at all dose levels (12). The Food and Drug Administration (FDA) granted AMG 510 fast-track status for treating individuals with previously treated metastatic non-small cell lung cancer (NSCLC) carrying a $KRAS^{G12C}$ mutation.

Building on this achievement, MRTX1133, a noncovalent and selective small molecule inhibitor capable of binding the inactive state of the $KRAS^{G12D}$ protein was developed (14). MRTX1133 offers a different approach, specifically targeting the $KRAS^{G12D}$ mutation. It binds reversibly to the $KRAS^{G12D}$ protein, stabilizing it in the inactive GDP-bound conformation. This non-covalent interaction is significant because it avoids the permanent modification of the protein, potentially reducing the likelihood of resistance mechanisms that can arise with covalent inhibitors. Preclinical investigations indicate that this molecule has the potential to revolutionize PDAC treatment, especially considering that approximately 93% of PDACs harbor KRAS mutations, with G12D (~42% of cases) and G12V (~32% of cases) being the most common mutations. In this context, Wei *et al.* reviewed recent studies on the development and therapeutic implications of MRTX1133 in PDAC, focusing on its powerful inhibition of KRAS pathway signaling (15). Furthermore, they highlighted its high selectivity for $KRAS^{G12D}$ mutations and efficacy in PDAC treatment, as demonstrated in both *in vivo* and patient-derived xenograft models (16). The study assessed MRTX1133's efficiency in addressing alternative KRAS mutations. MRTX1133 binds to $KRAS^{G12D}$ with strong affinity and selectivity when compared to $KRAS^{WT}$. It substantially inhibited activated $KRAS^{G12D}$ and significantly reduced cell viability in $KRAS^{G12D}$-mutant cell lines. In PDAC models, MRTX1133 inhibited KRAS-mediated signal transduction and tumor regression in a dose-dependent manner. Co-targeting $KRAS^{G12D}$ with other pathways, including EGFR or PI3Kα, increased anti-tumor effectiveness. These findings indicate that $KRAS^{G12D}$-mutant cancers can be specifically targeted with high-affinity small molecules and rely on mutant KRAS for growth and survival (16).

PDAC is distinguished by a desmoplastic reaction that alters the tumor microenvironment (TME), resulting in decreased vascularization, increased immune cell infiltration, and poor medication delivery, all of which contribute to disease progression and resistance (17). Thus, targeting the TME appears to be a potential strategy for increasing the efficacy of combination medicines in PDAC treatment. In the current article, Wei *et al.* highlighted the relevance of immune monitoring in pancreatic cancer, as well as the challenges posed by an immunosuppressive TME, which is responsible for the poor efficacy of immune treatments in the treatment of PDAC. They also shed insight on studies that showed MRTX1133's immune-mediated anti-cancer activity, particularly when combined with immune checkpoint inhibitor therapy targeting CTLA-4 and PD-1 (18). MRTX1133's impact on early and advanced PDAC, as well as the TME, was investigated using 16 distinct models of $KRAS^{G12D}$-driven PDAC. MRTX1133 was found to reverse early PDAC growth, enhance intratumoral $CD8^+$ effector T cells, diminish myeloid infiltration, and modify cancer-associated fibroblasts (18). Furthermore, MRTX1133 caused regression of both established precursor lesions [pancreatic intraepithelial neoplasia (PanINs)] and advanced PDAC, with the latter requiring $CD8^+$ T cells for regression. Combining immune checkpoint blockade (ICB) with MRTX1133 eliminated PDAC and increased overall survival. In addition, inhibiting $KRAS^{G12D}$ mutations in advanced PDAC and human patient-derived organoids increased FAS expression in cancer cells and promoted $CD8^+$ T cell killing (18). Based on these findings, a synergistic combination of MRTX1133 and ICB in clinical studies has been proposed.

Despite MRTX1133's prominent efficacy in developing KRAS-targeted PDAC treatment, its application faces major challenges. Wei *et al.* addressed these issues, including the development of resistance to MRTX1133, because not all PDAC cells with $KRAS^{G12D}$ mutations respond to treatment, and cancer cells can develop resistance over time (15). Treatment with MRTX1133 has been shown to increase EGFR and HER2 expression and phosphorylation, implying that blocking ERBB signaling may boost MRTX1133's anticancer action (19). Afatinib, a pan-ERBB inhibitor, worked in combination with MRTX1133 *in vitro* and maintained potency against cancer cells resistant to MRTX1133. In orthotopic PDAC mice models, the combination of MRTX1133 and afatinib reduced tumor size and improved survival rates. These findings highlight the potential synergistic effect of addressing both the ERBB and KRAS signaling pathways to overcome acquired

resistance in patients with KRAS-mutant pancreatic cancer (19).

Furthermore, MRTX1133 treatment has been demonstrated to cause reversible growth arrest in KRAS^{G12D}-mutant CRC cells while partially reactivating RAS effector signaling (20). A synthetic lethality screen revealed that MRTX1133 inhibits the EGFR and is synthetically deadly. MRTX1133 inhibits ERRFI1 expression, a negative regulator of EGFR, resulting in EGFR feedback activation. Surprisingly, wild-type RAS isoforms (H-RAS and N-RAS), rather than oncogenic K-RAS, influence downstream signaling upon EGFR activation, resulting in RAS effector signaling rebound and reduced MRTX1133 effectiveness. However, inhibiting activated EGFR using therapeutically used antibodies or kinase inhibitors improves MRTX1133 monotherapy efficacy, causing regression of KRAS^{G12D}-mutant CRC organoids and cell line-derived xenografts. This study highlights EGFR feedback activation as a critical biological event limiting the effectiveness of KRASG12D inhibitors and proposes a viable combination therapy for individuals with KRAS^{G12D}-mutant CRC (20).

Other genetic changes, such as the inactivation of tumor suppressors and the activation of mutations in the p110α subunit of PI3K (PIK3CA), contribute to PDAC's aggressiveness and resistance. Mouse models with constitutively active PI3K in the pancreas showed an increased number of pre-neoplastic lesions and invasive pancreatic cancer (21). Dual PI3K/mTOR inhibition has demonstrated great efficacy, particularly in tumors with elevated PI3K pathway activation, as well as a reduction in enhanced ERK1/2 signaling, which is typical in human pancreatic malignancies. Thus, addressing the PI3K pathway with inhibitors shows promise for patients with PIK3CA mutant pancreatic tumors (21). In light of these findings, Wei *et al.* proposed establishing MRTX1133-resistant cancer cell lines, testing combination therapy, and developing more effective KRAS-mutant inhibitors (15). Importantly, some studies have started looking for alternatives to overcome the resistance to MRTX1133 treatment that could emerge in pancreatic cancer. It was demonstrated that MRTX1133-resistant PDAC cells were sensitive to KPT-8602 (inhibitor of the nuclear transport exportin I), and the combination enhanced the inhibition of KRAS downstream pathways. In a xenograft model, the combination significantly reduced tumor burden in mice (22). Another study tested the combination of MRTX1719 (an MTA-cooperative PRMT5 inhibitor) with either adagrasib or MRTX1133, showing enhanced anti-tumor activity in CDX models with both KRAS mutations and MTAP deletion. For instance, in the pancreatic KP4 model, combining MRTX1719 with MRTX1133 prevented adaptive resistance observed with monotherapy and led to sustained tumor regression. Mechanistically, the combination strongly inhibited both PRMT5 and RAS signaling pathways, enhancing the inhibition of RB-1 phosphorylation (23).

Finally, this publication provides a detailed assessment of MRTX1133's potential for developing KRAS-targeted PDAC therapy and the problems involved with its implementation. Additional research is needed to overcome constraints that may limit its efficacy and to evaluate the implications of combining MRTX1133 with other medications for better treatment outcomes. The development of more effective and broad-spectrum KRAS-mutant inhibitors is also crucial for enhancing the efficacy of KRAS-targeted treatments in PDAC.

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Footnote

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