Pipeline Intelligence

American Association for Cancer Research Annual Meeting 2019

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Author Bio:

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The American Association of Cancer Research (AACR) hosted its 110th Annual Meeting in the Georgia World Congress Center, Atlanta, USA from 29 March – 3 April 2019. This meeting brought together over 21,000 delegates including laboratory researchers, clinicians and other oncology professionals to present and discuss the latest breakthrough research findings and ideas in the field of oncology and foster collaboration. The meeting provided a robust forum for cutting-edge, basic, translational and clinical discoveries, along with an opportunity to establish the research agenda for the international cancer community. Among the various therapies discussed at the meeting, the development of anti-KRAS therapies for cancer emerged as a key highlight. This report outlines the most recent progress in the exploration of KRAS-targeted anticancer strategies.

The Pipeline Intelligence team attends the AACR Annual Meeting each year to stay informed of significant findings related to novel therapies in oncology. There were over 5600 poster sessions and 950 presentations focusing on the development of small molecules and biologics for the treatment of cancer, including abstracts on tumor biology, immunology, molecular and cellular biology, clinical trials and experimental and molecular therapeutics.

Spotlight on KRAS-Targeted Therapies from AACR

Among various data findings related to the latest advancements in novel therapeutic strategies, the spotlight of the meeting shone on novel KRAS G12C mutant-selective small-molecule inhibitors. About 14% of nonsmall cell lung adenocarcinoma, 3-5% of colorectal cancer and 2% of other solid tumors possess KRAS, the single most frequently mutated oncogene which acts as the first of more than 700 genes to be causally implicated in human cancer. KRAS G12C is a well validated driver mutation. The drugs targeting this mutant are covalent inhibitors that bind to the cysteine at position 12, downregulating KRAS downstream signaling.

Amgen's AMG 510 is the first covalent inhibitor of a mutant form of KRAS to reach the clinical stage. Data presented at AACR showed that, in a syngeneic model of KRAS G12C mutant cancer, AMG 510 treatment resulted in significant tumor growth inhibition that caused tumor regression. In addition, AMG 510 in combination with standard-of-care and targeted agents exhibited improved tumor growth inhibition compared with either single agent. AMG 510 is currently under phase I evaluation in patients with advanced solid tumors harboring a KRAS G12C mutation.

Another novel promising therapeutic, which takes advantage of a hidden groove in the KRAS G12C-mutated protein, is Mirati's MRTX 1257. This product emerged as a research tool compound as it exhibited its ability to irreversibly modify KRAS G12C, trap it in its inactive GDP-bound state, and inhibit ERK1/2 with an IC50 value of 1 nM. In a small subset of KRAS G12C-positive models, MRTX 1257 treatment resulted in rapid initial tumor regression followed by tumor stasis. In the H358 tumor model, MRTX 1257 exhibited 77% target engagement at the 100 mg/kg dose. In addition, in the MIA PaCa-2 tumor xenograft model, MRTX 1257 showed sustained growth regression in the 3,10, 30, and 100 mg/kg dose groups. MRTX 1257 treatment at 100 mg/kg daily resulted in complete responses that were maintained more than 70 days after ending treatment.

Researchers at the Mitchell Cancer Institute (USA) also presented early preclinical findings from MCI 062, a KRAS inhibitor, in multiple pancreatic cancer models. In 3D spheroid models involving MIA PaCAa-2 tumor cells, MCI 062 treatment repressed tumor growth of non-adherent cells. Additionally, in the KRAS mutant CT26 mouse tumor xenograft model, MCI 062 exhibited antitumor activity with no discernable toxicity.

The Pipeline of KRAS-Targeted Therapies

According to IQVIA™ Pipeline Intelligence and as depicted in Figure 1, there are 5 KRAS-targeted therapies being investigated for cancer: one in discovery, two in preclinical, one in phase I and one in phase I/II. AstraZeneca/Ionis's AZD 4785 was discontinued after phase I, due to safety and efficacy concerns.
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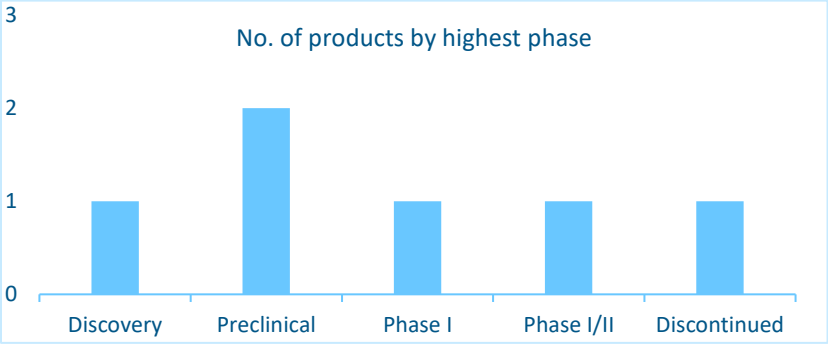

Figure 1: KRAS-targeted therapies in development per highest phase

AstraZeneca discovered that its own first attempt to hit the apparently "undruggable" target was unsuccessful over Amgen and Mirati projects, as these ventures hit mutated KRAS, while AstraZeneca/Ionis's AZD 4785 targeted the protein regardless of its mutation status. AZD 4785 had recently completed its first phase I trial, but development has been discontinued

Summary

Exciting early results presented at the AACR 2019 annual meeting show that KRAS-targeted anticancer drug discovery has emerged as a promising avenue of research in the field of cancer. AACR 2019 showed itself to be an important curtain raiser for the 2019 oncology research season.

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