New Target Associate Specific Drug Levels Within Race Against Cancer

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Deemed undruggable for almost 40 years since its discovery, mutated KRAS protein has now found its match with Amgen's sotorasib (LUMAKRAS)—the first drug that specifically inhibits KRAS activity in non-small cell lung cancer (NSCLC) recently approved by the US Food and Drug Administration (FDA).

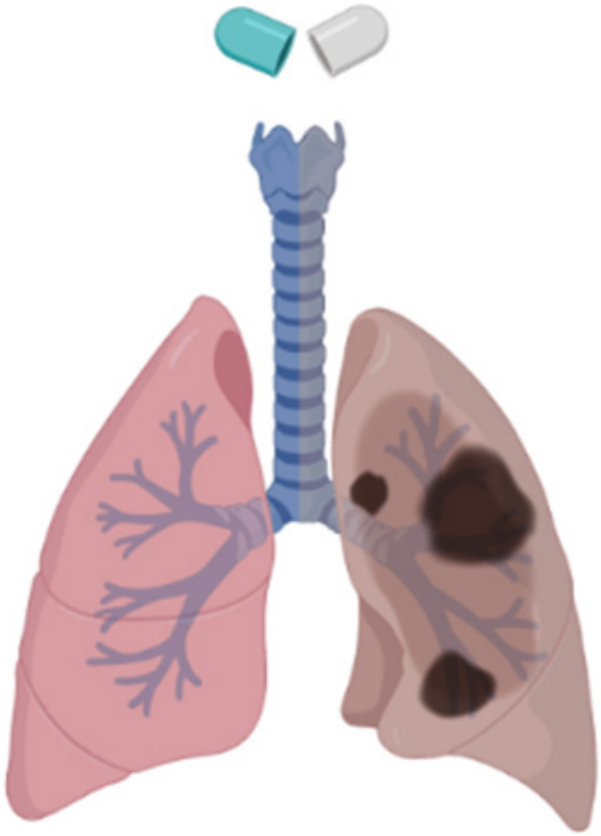
NON-SMALL CELL LUNG CANCER (NSCLC) AND KRAS MUTATION

Lung cancer refers to tumors originating in the cells lining the bronchi, bronchioles, or alveoli. It is classified by the morphology of the cell in which the cancer starts growing: small and non-small cell. Non-small cell lung cancer (NSCLC) appears larger than its counterpart under the microscope, with the main subtypes are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. These subtypes are grouped together regardless of the initial location affecting the lung because their treatment and prognoses are alike.

Similar to other cancers, NSCLC harbors a complex phenotype as the results of dynamic changes in the genome. Multiple genes are responsible for the progressive transformation of normal lung cells into malignant derivatives, such as tumor suppressor p53 and the growth factor EGFR. Among many somatic mutations in NSCLC, the alteration of one particular gene, the Kirsten rat sarcoma viral oncogene homolog (KRAS) is the most prevalent, accounting for 40% cases of newly diagnosed lung adenocarcinomas.

KRAS is a signalling pathway regulator responsible for activating other molecules, known as effectors, to exert effects on cell proliferation, differentiation, and survival. KRAS acts as a signal switch between its active and inactive state. As a member of the RAS human gene family, KRAS is activated when guanosine triphosphate (GTP) attaches to the KRAS surface. It is inactivated when one phosphate is removed to become guanosine diphosphate (GDP). The balance of this GDP/GTP cycling is governed by another molecule called GTPase that hydrolyzes the phosphate.

Mutation in the KRAS gene will produce oncogenic KRAS protein resistant to GTPase, resulting in KRAS signal amplification that gets passed to its downstream effectors. Different mutations have been mapped by scientists. They are named after the type of amino acid exchange and the position. Among many KRAS alterations, the most widely found is single point mutation that occurs in codon 12 where an amino acid glycine (G) is replaced by cysteine (C).



Therefore, the mutated form of this specific protein is named KRAS (G12C).

Usually, a single point mutation happens without any observable change in a phenotype, called silent mutation. This occurs when the former amino acid is replaced by another amino acid that has the same properties. However, this is not the case with glycine and cysteine. Glycine, consisting of only one hydrogen atom making up its side chain, is neutral in the cellular environment. Meanwhile cysteine, a sulfur-containing amino acid, is highly hydrophobic. Replacement of glycine by cysteine changes the tertiary structure of KRAS, lessening its binding affinity to GTPase.

HOW DOES SOTORASIB WORK?

Mutant cysteine resides in the middle of a pocket present in

the inactive GDP-bound KRAS, separating out one normal pocket into two unique grooves. Despite the exploitable area owned by KRAS (G12C), researchers hit a snag trying to develop its inhibitor. This owes to the smaller volume available for the drug candidate to fit in, which limits the researchers ability to get creative during the drug structure optimization process. Interestingly, at the far end of the abnormal pocket lies the amino acid histidine equipped with a strange alternative orientation. Turns out, this particular behaviour of histidine is KRAS-mutant achilles' heel as indicated in a paper published in Nature.

Using a software-aided simulation, the researchers found that designing an aromatic structure greatly enhances the covalent binding capacity of the inhibitor to KRAS (G12C), increasing the overall potency of AMG-510—the chosen name for this drug candidate. Their finding was confirmed through a series of preclinical studies that showed the binding halts the structural change of the protein when they receive a signal, subsequently blocking the growth signalling passed by KRAS to their effectors. The signal blockade was assessed by measuring the activation state of one of KRAS effectors, namely ERK, in two different types of cancer cell lines. Low level of activated ERK and reduced cell viability after AMG-510 treatment prove the effectiveness of this drug candidate.

Beyond the petri dish, a mice model injected with human tumour cells and small clinical trials with 4 volunteers were also studied. Different doses of AMG-510 were given to both immuno-competent and T-cells-lacking mice for one month. Higher dose administration resulted in tumour shrinkage after 29 days. However, different results were obtained with the mice that lacked T cells as this group showed tumor regression without total cures. Similar trend was observed in human volunteers where doubling the dose of AMG-510 reduced the tumour half its original size.

SOTORASIB ENCOURAGING CLINICAL FINDING AND THE ACCELERATED APPROVAL

With positive results from the preclinical studies, Amgen scientists continued moving to the clinical phase. In a phase I trial, 129 KRAS-mutation cancer patients were recruited to study the safety of once-daily 960 milligrams oral sotorasib. Without mortality and dose-limiting toxic effects observed, the benefit of sotorasib outweighs the risk of adverse reaction occurrence, including diarrhea, fatigue, and nausea. Satisfied with the tolerability profile of sotorasib, the researchers pivoted their curiosity to investigate the activity of this drug in a population level.

124 participants with KRAS G12C mutation-positive in phase II trial were given the same amount of sotorasib as the first trial. The efficacy was measured in terms of objective response, duration of response, disease control, progression-free survival, and overall survival. According to the Amgen press release, 36% patients showed more than 30% tumor decrease with 81% demonstrated disease control. The duration of response lasted for 10 months. The tolerability was also reinvestigated in which expanded adverse events from the first trial were recorded. Musculoskeletal pain, hepatotoxicity, and cough were added to the list of adverse events. Only 9% patients permanently discontinued the use of sotorasib.

The line of research performed is enough to convince the FDA to grant an approval for sotorasib 2 months earlier than planned. The principal investigator, Bob T. Li, MD, PhD, MPH said in a statement that "sotorasib represents a major advancement in oncology and changes the treatment paradigm for patients with KRAS G12C-mutated non-small cell lung cancer. Patients with non-small cell lung cancer who have progressed beyond first-line treatment face a poor prognosis and have limited treatment options available to them. Sotorasib delivers a new option for these patients, and it is the first KRAS-targeted therapy to be approved after nearly four decades of research."

Sotorasib was approved as the second line treatment for adult patients with KRAS (G12C)-mutated locally advanced or metastatic NSCLC whose prior systemic therapy rendered ineffective. Despite the early nod from the FDA, sotorasib trial still needs to be continued to test whether lowering the dose will achieve similar maximum therapeutic response. Larger scale and longer trials to evaluate sotorasib use and safety compared with chemotherapy beyond just one year study are also expected as Amgen is now entering the phase III trial.

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