HOW AN IMAGE CHANGED KRAS DRUGGABILITY: THE DEVELOPMENT OF LUMAKRAS

The RAS family of proteins are GTP/GDP on-off switches that regulate downstream cell signaling. They are some of the most widely studied targets for cancer drug development as about 25% of human cancers reportedly have a RAS mutation. The three RAS genes are KRAS, NRAS and HRAS where KRAS is reported to be the most frequently mutated gene[1]. Mutations in KRAS result in the switch being permanently turned on resulting in uncontrolled cell proliferation and tumor formation. Mutated KRAS is frequently seen in lung, colorectal and pancreatic caners and the most common mutations are around the glycine residue G12[2]. Despite the detailed knowledge of KRAS mutations, drug developers have not seen much success in developing anti-KRAS therapies targeting G12. Indeed, KRAS has been labeled as an "undruggable" target largely due to the protein structure. KRAS is a smooth ball shaped protein that has one GTP binding pocket, so it was thought that there are no other binding pockets for a small molecule inhibitor to bind.

However, this dogma was challenged in 2013 when a group at the University of California, San Francisco published a paper detailing the crystal structure of KRAS that showed the formation of a new binding pocket beneath the effector binding region called switch-II[3]. This led to a new strategy for small molecule inhibitors targeting KRAS G12C that bind to active GTP-bound KRAS to change binding preference from GTP to GDP, thus locking KRAS in an off position and shutting down downstream signaling and uncontrolled cell proliferation[4]. This breakthrough accelerated the hunt for novel small molecules that had the right pharmacological properties and structure. Amgen was the first company to identify a small molecule called AMG 510 or sotorasib in collaboration with Araxes Pharmaceuticals. The company took risks by expediting drug development in both preclinical assay testing and clinical trials as well as starting manufacturing earlier[5].

Sotorasib demonstrated good efficacy in a clinical trial of non-small cell lung cancer patients with KRAS G12C mutations along with acceptable side effects[5]. The drug is formulated as an oral once-daily medication that is ideal for patients. Currently, there are a few clinical trials ongoing combining sotorasib with various other therapies including the PD-1 inhibitor pembrolizumab and docetaxel. Based on the positive outcome data from the non-small cell lung cancer trial, the FDA has approved sotorasib (now known as Lumakras) as the first KRAS targeted therapy for non-small cell lung cancer patients with the G12C mutation[6]. This patient segment represents 13% of mutations in non-small cell lung cancer, which is a significant number of patients.

Amgen is not the only company working on the KRAS inhibitor. Mirati Therapeutics is also working on a KRAS inhibitor called adagrasib, which locks mutant KRAS in the off conformation and is reported to have higher tumor reduction potential than Lumakras[7]. Based on the early clinical trial data and growing pharma interest, KRAS inhibitors are shaping up to be breakthrough targeted drug therapies especially in combination with other available therapies to shut down compensatory signaling in tumors. It is important to remember that the development of targeted KRAS inhibitors is a fascinating story that started with a photographic image of an undruggable protein.

References:

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