New light shining on the 'undruggable' KRAS in Non-Small Cell Lung Cancer

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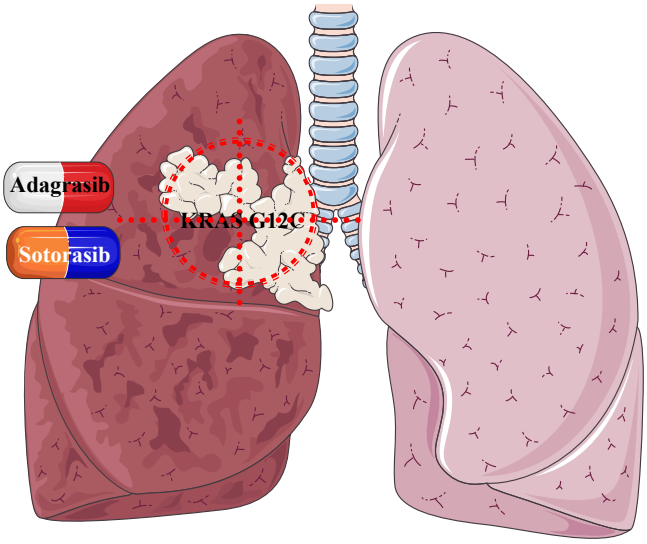

Lung cancer is the number one cause of cancer-related deaths worldwide, accounting for 140,730 deaths in 2020. Non-small cell lung cancer (NSCLC) is the most frequent lung cancer subtype, and patients who are diagnosed with metastatic disease have a reported 5-year overall survival rates of only 6%. KRAS is one of the most frequently mutated oncogenes in human cancers, and roughly 30% of patients with NSCLC harbour KRAS mutations. In 1982, orthologs of the viral ras oncogenes with point mutations were identified in transforming DNA fragments from human cancer cells both for HRAS and KRAS. The identification of such oncogenes marked the beginning of molecular oncology in human cancer research.

Cancers with a KRAS mutation rely on the continued activation and signalling of KRAS; making it an attractive therapeutic target. However, KRAS has historically been considered 'undruggable' due to structural and biochemical obstacles. Unlike other oncogene drivers, such as EGFR and ALK, KRAS has a high affinity for guanosine triphosphate (GTP) and the catalytic sites are small and hard to target. Due to the failure in specifically targeting KRAS, much effort focused around inhibition of its membrane association/subcellular localization, identification of synthetic lethality partners, and inhibition of downstream effectors. Unfortunately, these strategies have been largely unsuccessful. Traditionally, to treat NSCLC patients with KRAS mutations, oncologists utilize chemotherapy, immunotherapy and a combination of both. However, the overall survival rate for these patients is less than 22 months. Consequently, the search for therapies that successfully target KRAS remains the holy grail in cancer research.

Advanced technologies in drug development and novel mechanistic insights into KRAS biology, has opened windows of opportunities in revisiting efforts to directly target KRAS. These advances, has led to the availability of novel therapeutics, and this 'undruggable' target now has therapeutic inhibitors undergoing clinical trials; transforming the landscape of KRAS treatments. Collectively, the trials demonstrate that targeting KRAS potentially improves different efficacy outcomes for patients with KRAS mutant NSCLC.

In February 2021, sotorasib (formerly AMG 510), the first-in-class KRAS G12C inhibitor from Amgen, was granted Priority Review by the U.S. Food and Drug Administration (FDA) for the treatment of patients with KRAS G12C-mutated locally advanced or metastatic NSCLC, following at least one prior systemic therapy. Based on the Priority Review designation, the Prescription Drug Free User Action (PDUFA) date for sotorasib is August 2021, four months earlier than standard review cycle. Amgen submitted the New Drug Application (NDA) due to results from the CodeBreak 100 clinical trial, which examined patients with locally advanced or metastatic NSCLC whom had progressed despite treatment with chemotherapy and/or immunotherapy. The open-label phase 1/2 study enrolled 126 NSCLC patients with a confirmed KRAS G12C mutation, 124 of whom had centrally evaluable lesions by RECIST at baseline. Patients were followed for a median of 12.2 months and of the 124 patients, 46 patients had a confirmed response (3 complete responses), resulting in an objective response rate of 37.1%; 80.6% achieved disease control. The median time to response was 1.4 months, and the median duration of response was 10 months. Treatment without disease progression was observed in 43% of responders, and median progression-free survival was 6.8 months. Most treatment-related adverse events (TRAEs) associated with the drug were mild to moderate (grade 1 or 2), and no treatment related deaths occurred. Grade 3 TRAEs were reported in 19.8% patients, including alanine aminotransferase increase (6.3%), aspartate aminotransferase increase (5.6%), and diarrhea (4%). TRAEs led to treatment discontinuation in 7.1% of patients. Amgen have also launched a global Phase 3 randomized active-controlled study (CodeBreak 200), comparing sotorasib to docetaxel in patients with KRAS G12C-mutated NSCLC and they have over 10 Phase 1b combination studied (CodeBreak 101) across various solid tumors.

Hot on the heels of Amgens drug, Mirati Therapeutics have reported promising clinical activity in NSCLC patients with another KRAS G12C inhibitor, adagrasib (MRTX-849). These reports are from the phase 1/2 KRYSTAL-1 study, which evaluated adagrasib in 79 patients with advanced or metastatic NSCLC and a confirmed mutant in KRAS G12C, most of whom (92%) received prior chemotherapy and a PD-1/L1 inhibitor. Of these, 18 patients were enrolled in the phase 1/1b dose-escalation and dose-expansion phase of the study, and 61 patients participated in the phase 2 portion. From the 51 patients available for clinical activity, partial response was detected in 45% of patients and stable disease in 51%, translating to a 96% disease control rate. The median duration of response for 14 patients in the phase 1/1b group was 8.2 months, with 4 of 6 responders in this group continuing with adagrasib therapy after more than 11 months of treatment. TRAEs of any grade occurred in 85% of patients, and 30% of patients had grade 3-4 events. The most frequently reported adverse grade 3-4 TRAEs were fatigue (6%), increased alanine aminotransferase and aspartate aminotransferase (5% each), QT prolongation (3%), anaemia (2%), nausea (2%), and vomiting (2%). Two grade 5 adverse events were observed; one case of pneumonitis in a patient with recurrent pneumonitis and one case of cardiac failure. TRAEs led to discontinuation in 4.5% of patients. Interestingly, Mirati Therapeutics have also reported that patients whom have a co-mutation in STK11 had an improved response to adagrasib. Patients with co-mutations in STK11 (n=14) had an overall response rate of 64% compared with 33% in those with wild type tumors (n=30). Moreover, 4 patients with STK11 mutations achieved stable disease and only 1 had progressive disease. By contrast, KEAP1 or TP53 mutations did not appear to be linked to response rates. This findings highlight the need for continued research and additional data to offer more insight into why patients with STK11 mutations appear to achieve additional benefits from adagrasib.

The quest to discover a drug that can target KRAS has been 40 years in the making; and it is now finally tempting to suggest, that the oncology field may be dropping the adjective 'undruggable' when describing KRAS.