A KRAS G12C inhibitor is a type of targeted cancer therapy designed to inhibit a specific mutant form of the KRAS protein, where the glycine (G) at position 12 is replaced by cysteine (C) — hence “G12C”. This mutation is a common driver mutation in several cancers, including:

Non-small cell lung cancer (NSCLC)

Colorectal cancer

Pancreatic cancer

Key Points: What is KRAS? KRAS is a gene that encodes a small GTPase, a protein involved in signaling pathways that control cell growth and division.

Mutations in KRAS can lead to uncontrolled cell growth and cancer.

 What makes G12C unique? The G12C mutation creates a unique binding pocket that is not present in the wild-type KRAS, allowing for selective targeting by small molecules.

Approved KRAS G12C Inhibitors: Sotorasib (Lumakras / AMG 510)

Approved by FDA for NSCLC with KRAS G12C mutation (2021).

Manufacturer: Amgen.

Adagrasib (Krazati / MRTX849)

Also FDA-approved for NSCLC and being evaluated for other tumors.

Manufacturer: Mirati Therapeutics (now part of Bristol Myers Squibb).

Mechanism of Action: These drugs irreversibly bind to the cysteine residue at the G12C mutation site.

They lock KRAS in its inactive GDP-bound state, preventing downstream signaling that promotes cancer cell survival and proliferation.

Clinical Considerations: Resistance mechanisms are emerging (e.g., secondary mutations in KRAS, pathway reactivation).

Combination therapies (e.g., with EGFR inhibitors or immune checkpoint inhibitors) are being explored in clinical trials.