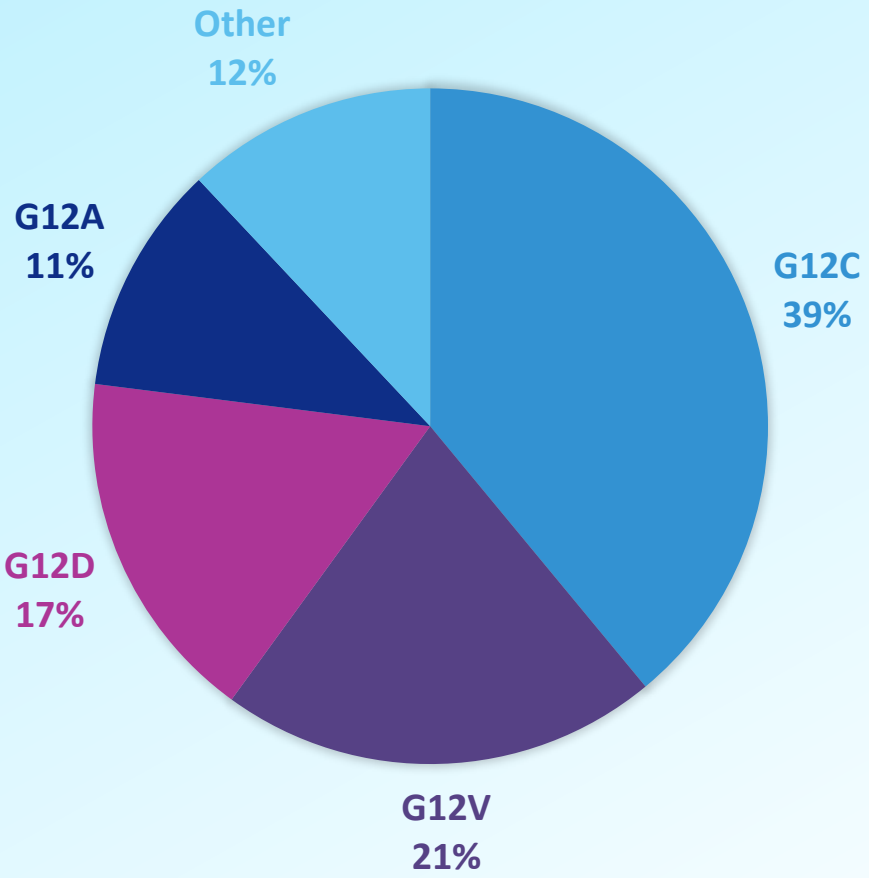
KRAS Mutations in NSCLC

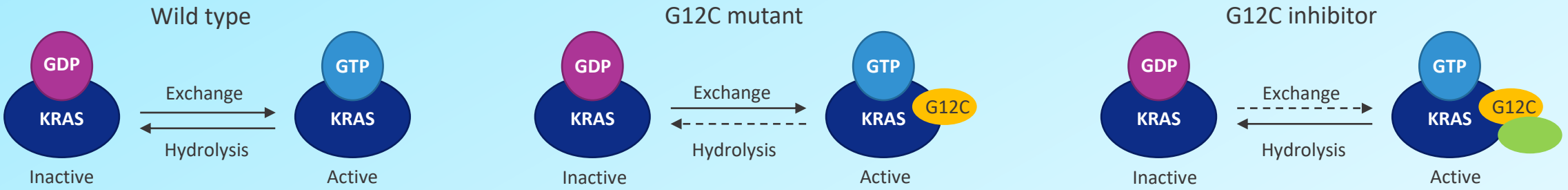
- *KRAS* mutations are the most prevalent driver mutations in NSCLC
- *KRAS* G12C is the most prevalent *KRAS* mutation in NSCLC
  - Occurs in about 13% of patients
  - Similar in prevalence to *EGFR* mutations
- *KRAS* mutations enriched in smokers
  - 34% of smokers
  - 6% of non-smokers



EGFR, epidermal growth factor receptor.

Dogan S et al. *Clin Cancer Res*. 2012;18:6169-77; Konig D et al. *Cancers*. 2021;13.

KRAS G12C Inhibitors: Mechanism of Action



- Wild type KRAS alternates between active and inactive states by hydrolyzing GTP to GDP
- KRAS signaling activates downstream pathways, including RAF-MEK-ERK and PI3K-AKT-mTOR, that are involved in control of cell division, proliferation, and death

- G12C mutation impairs the hydrolytic function, locking KRAS in an active state
- Increased signaling through downstream pathways leads to uncontrolled cell division and proliferation, promoting tumorigenesis

- The KRAS G12C inhibitors adagrasib and sotorasib covalently react with the cysteine at position 12, preventing a new guanine nucleotide from binding
- KRAS is locked in an inactive state
- Adagrasib and sotorasib can only react with cysteine so other KRAS mutations, including G12D, G12V, and G12A, are unaffected

GDP, guanosine diphosphate; GTP, guanosine triphophate.

Liu J et al. *Cancer Gene Ther*. 2022;29:875-878.