Background

KRAS-Driven NSCLC

- KRAS\(^{G12C}\) mutations act as oncogenic drivers and occur in approximately 14% of NSCLC (adenocarcinomas).\(^{11}\)
- Mutations in codon 12 of KRAS are associated with a poor prognosis, and although KRAS has historically been considered undruggable, recent research has now been published.\(^{12}\)
- KRAS\(^{G12C}\) inhibitors are under investigation for NSCLC.\(^{12,13}\)

Adagrasib in KRAS\(^{G12C}\) NSCLC

- Adagrasib is a covalent inhibitor of KRAS\(^{G12C}\) that irreversibly and selectively locks KRAS\(^{G12C}\) and locks it in the initiating G12C - a Phase 1/2 study, demonstrated antitumor activity and durable complete responses (CRs).\(^{12,13}\)
- KRAS\(^{G12C}\) mutations act as oncogenic drivers and occur in approximately 14% of NSCLC patients.\(^{12,13}\)
- KRAS\(^{G12C}\) mutations are found in a subset of NSCLC patients.\(^{12,13}\)

Synergy Between KRAS\(^{G12C}\) Inhibitors and Immune Checkpoint Inhibition

- Preclinical studies have demonstrated synergy between KRAS\(^{G12C}\) inhibitors and immune checkpoint inhibitors (ICI).\(^{12,13}\)
- KRAS\(^{G12C}\) inhibitors demonstrate synergistic activity in combination with PD-1/PD-L1 inhibitors.\(^{12,13}\)
- Adagrasib treatment alters tumor expression of factors implicated in antitumor immunity and could potentially enhance tumor immunogenicity.\(^{12,13}\)

Adagrasib in KRAS\(^{G12C}\) NSCLC

- KRAS\(^{G12C}\) antagonists have been shown to improve immune checkpoint inhibitor (ICI) efficacy in KRAS\(^{G12C}\) NSCLC.\(^{12,13}\)
- Patients with KRAS\(^{G12C}\) NSCLC have been shown to benefit from dual combination therapy with a KRAS\(^{G12C}\) inhibitor and ICI.\(^{12,13}\)
- These data support the rationale to further evaluate adagrasib in combination with ICI in patients with first-line advanced/metastatic NSCLC.\(^{12,13}\)

Clinical Benefit (DCR) was observed in 96.1% (49/51) of patients

- Nausea, diarrhea, vomiting, and fatigue were the most common AEs (TRAEs) related to AEs (TRAEs) related to adagrasib treatment.\(^{20}\)
- No cases of grade 5 TRAEs were reported.\(^{20}\)

Data as of 30 August 2020. Pooled data includes patients with NSCLC who received adagrasib 600 mg BID in Phase 1/1b and Phase 2 studies of NSCLC patients with KRAS\(^{G12C}\) mutations.\(^{2,3,5-7,9,10}\)