KRYSTAL-7: A Phase 2 Trial of Adagrasib (MRTX849) With Pembrolizumab in Patients With Advanced Non–Small-Cell Lung Cancer (NSCLC) With KRAS^{G12C} Mutation

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Background

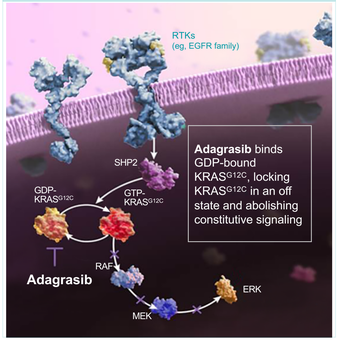
KRAS-Driven NSCLC

- KRAS^{G12C} mutations act as oncogenic drivers and occur in approximately 14% of NSCLC (adenocarcinomas)[1-3]
- Mutations in codon 12 of KRAS are associated with a poor prognosis, and although KRAS has historically been undruggable, KRAS^{G12C} can now be inhibited covalently[4,5]
- Emerging data demonstrate clinical activity of KRAS^{G12C} inhibitors in pretreated patients with NSCLC harboring KRAS^{G12C} mutations[6]

Adagrasib in KRAS^{G12C} Cancers

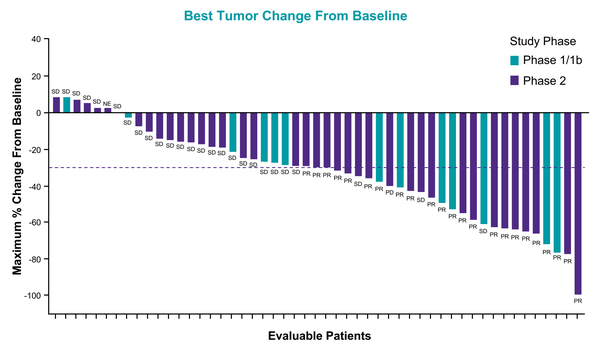
- Adagrasib is a covalent inhibitor of KRAS^{G12C} that irreversibly and selectively binds KRAS^{G12C} and locks it in its inactive, GDP-bound state[6] **(Figure 1)**
- Adagrasib inhibits KRAS^{G12C} mediated MAP/ERK signaling and tumor growth
- Adagrasib was optimized for desired properties of a KRAS^{G12C} inhibitor:
  - Potent covalent inhibition of KRAS^{G12C} (cellular IC_{50}: ~5 nM)
  - High selectivity (>1000X) for the mutant KRAS^{G12C} protein vs wild-type (WT) KRAS
  - Favorable PK properties, including oral bioavailability, long half-life (~24 h), and extensive tissue distribution[6]

Figure 1: Mechanism of Action (MOA) of Adagrasib



- Initial results from KRYSTAL-1, a Phase 1/2 study, demonstrated antitumor activity and tolerability of adagrasib monotherapy across multiple tumor types harboring KRAS^{G12C} mutation, including patients with NSCLC previously treated with both platinum-based chemotherapy and immune checkpoint inhibitors[5] **(Figure 2)**
- In a safety analysis of patients (n=110) from KRYSTAL-1, adagrasib was well tolerated, with few grade 3-4 treatment-related AEs (TRAEs)[6]
  - The most common TRAEs included nausea, diarrhea, vomiting, and fatigue

Figure 2. Adagrasib 600 mg BID in Patients With Pretreated NSCLC (KRYSTAL-1)[6]



- 45% (23/51) of patients with NSCLC had a confirmed ORR
- 51% (26/51) of patients with NSCLC achieved SD
- Clinical benefit (DCR) was observed in 96.1% (49/51) of patients

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

Combination With Immune Checkpoint Inhibition

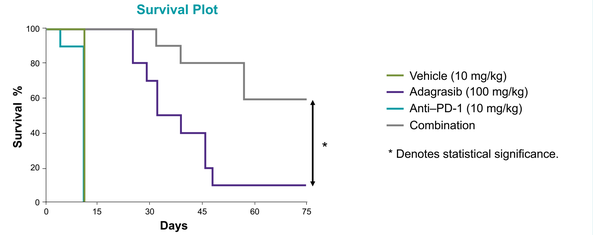
Synergy Between KRAS^{G12C} Inhibition and Immune Checkpoint Inhibition

- KRAS^{G12C} mutations are smoking-related transversion mutations associated with a relatively high tumor mutational burden (TMB) and PD-L1 positivity[7,8]
- Data suggest synergy between KRAS^{G12C} inhibition and immune checkpoint inhibition (CPI)[9]
- Adagrasib treatment alters tumor expression of factors implicated in the presentation of tumor antigens and/or mediates an immunosuppressive tumor microenvironment in multiple KRAS^{G12C} xenografts[9]
- These data support the rationale to further evaluate adagrasib in combination with CPIs in patients with first-line advanced/metastatic NSCLC
- The adagrasib + pembrolizumab combination (NSCLC) arm in KRYSTAL-1 has cleared the DLT observation period[10]

KRAS^{G12C} Syngeneic Mouse Model

- Adagrasib plus anti–PD-1 therapy led to durable complete responses (DCRs; cures) in the majority of mice and a survival advantage relative to either agent as monotherapy[7] **(Figure 3)**
- In mouse models showing complete response, reintroduction of tumor cell inoculum failed to result in re-formation of tumor, demonstrating durable antitumor immunity for the combination[7-9]

Figure 3. Preclinical Data Demonstrating Survival in a KRAS^{G12C} Syngeneic Mouse Model



* Denotes statistical significance.

Methods

Key Inclusion Criteria

- Aged 18 years or older and Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1
- Histologically confirmed diagnosis of NSCLC with KRAS^{G12C} mutation and known PD-L1 tumor proportion score (TPS)
- Unresectable or metastatic disease (ie, not a candidate for definitive therapy such as chemoradiation for locally advanced disease)
- Presence of measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1
- Expected availability of representative tumor specimen (fresh or archived) for central laboratory testing of correlative gene alterations

Key Exclusion Criteria

- Prior systemic treatment for locally advanced or metastatic NSCLC, including chemotherapy, CPI therapy, or a therapy targeting KRAS^{G12C} mutation
- Active brain metastases; patients are eligible if brain metastases are adequately treated and patients are neurologically stable for at least 2 weeks prior to the first dose of study treatment without the use of corticosteroids or are on a stable or decreasing dose of ≤10 mg daily prednisone (or equivalent)

Testing Procedures

Testing for PD-L1 Expression

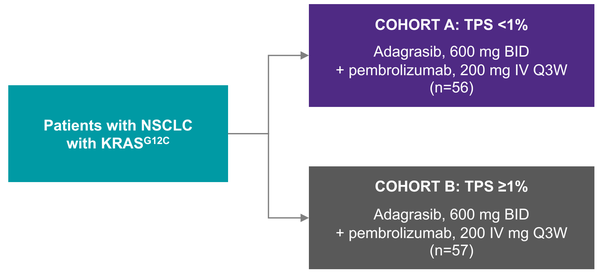
- Molecular testing for PD-L1 TPS should be performed centrally or locally using a sponsor-approved test and laboratory prior to or during the prescreening period
- Tumor tissue samples should be collected from the most recent biopsy or excision, preferably no more than 6 months earlier and without prior systemic treatment or radiation to the site of tissue collection

Detection of KRAS^{G12C} Mutation for Trial Eligibility

- The presence of KRAS^{G12C} mutation established using sponsor-approved methods and laboratories:
  - In tumor tissue, including polymerase chain reaction (PCR) and next-generation sequencing (NGS) platforms
  - In blood samples, for circulating tumor deoxyribonucleic acid (ctDNA) analysis, including NGS platforms

Methods

Figure 4. KRYSTAL-7 Study Design



BID, twice daily; IV, intravenously; NSCLC, non-small-cell lung cancer; Q3W, every 3 weeks; TPS, tumor proportion score.

Study Design

- KRYSTAL-7 (849-007) is a global, open-label, Phase 2 study evaluating the clinical activity of adagrasib administered in combination with pembrolizumab as treatment for patients with advanced NSCLC harboring a KRAS^{G12C} mutation
- An estimated 120 patients will be enrolled into 2 cohorts based on PD-L1 TPS: Cohort A (TPS <1) and Cohort B (TPS ≥1%) **(Figure 4)**
- Patients will receive study treatment until disease progression, unacceptable tolerability, or investigator decision to terminate treatment
- This study was initiated November 2020

Study Treatments

- Adagrasib is to be dosed at 600 mg (BID) in 3-week cycles administered orally on a continuous basis until disease progression
- Pembrolizumab is to be dosed at 200 mg every 3 weeks (Q3W); if permitted by local labeling, after 9 months or more on study treatment, individual patients may switch to 400 mg administered every 6 weeks (Q6W), at the investigator's discretion
  - Pembrolizumab treatment may continue for up to 24 months or in accordance with approved local labeling

Primary Endpoint

- Objective response rate (ORR), as defined by RECIST 1.1

Secondary Endpoints

- Safety, including adverse events and laboratory abnormalities
- PK, including blood plasma levels of adagrasib and potential metabolite concentrations
- Secondary efficacy endpoints:
  - Duration of response (DOR)
  - Progression-free survival (PFS)
  - 1-Year survival rate
  - Overall survival (OS)

Exploratory Endpoints

- Proportion of selected cell populations (including subpopulations of T-cells and myeloid cells) in the blood before and after study treatment
- T-cell receptor repertoire in the blood before and after study treatment
- Gene alterations in tumor tissue and ctDNA before treatment and at disease progression

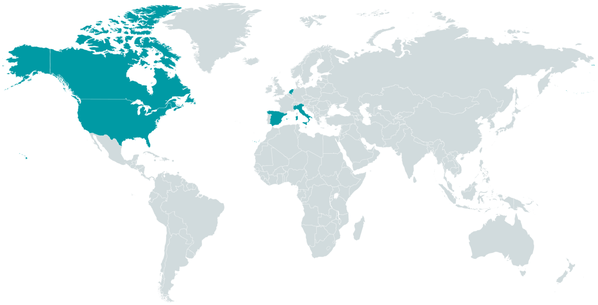
Statistical Methods

Simon's Optimal 2-Stage Design[11]

- Simon's optimal two-stage design will be used to calculate the sample size for each Phase 2 cohort
- The number of responses in the first stage of each Phase 2 cohort will be assessed for potential early study termination

Trial Progress

- Approximately 40 global sites are planned for this study
- Enrollment is currently ongoing at sites from the United States, Canada, Italy, the Netherlands, and Spain



Summary

- Adagrasib is a KRAS^{G12C}-selective covalent inhibitor with a long half-life and extensive predicted target coverage throughout the dosing interval[5]
- The adagrasib + pembrolizumab combination (NSCLC) arm in KRYSTAL-1 has cleared the DLT observation period
- KRYSTAL-7 is a global, open-label Phase 2 study designed to further evaluate the clinical activity of adagrasib in combination with pembrolizumab administered as first-line treatment for patients with advanced NSCLC harboring a KRAS^{G12C} mutation
- ClinicalTrials.gov identifier: NCT04613596

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