KRYSTAL-2 (849-002): Phase 1/2, Open-Label, Multiple-Expansion-Cohort Trial of Adagrasib (MRTX849) + TNO155 (SHP2 Inhibitor) in KRAS^{G12C} Solid Tumors

TPS146

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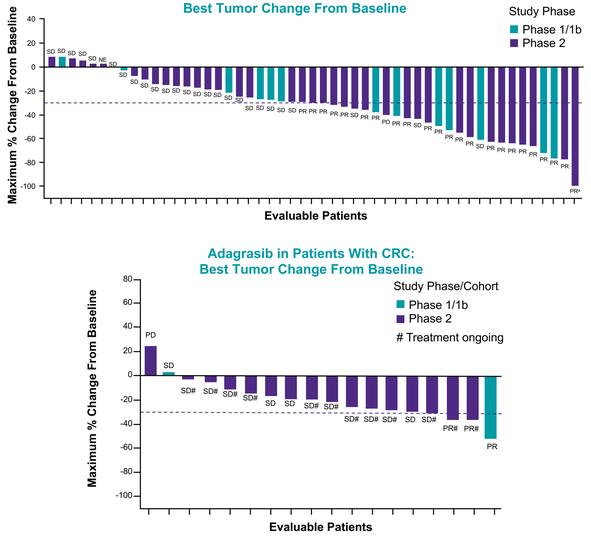
Background

- KRAS^{G12C} mutations act as oncogenic drivers and occur in approximately 14% of non–small-cell lung cancer (NSCLC, adenocarcinoma), 3%-4% of colorectal cancer (CRC), and 1%-2% of several other cancers[1-3]
- Src homology phosphatase 2 (SHP2), encoded by *PTPN11*, is a nonreceptor protein tyrosine phosphatase that transduces signaling from various receptor tyrosine kinases (RTKs) to promote the activation of RAS and subsequently the downstream MAPK pathway[4-6]
- Emerging data implicate SHP2 and receptor tyrosine kinase (RTK) dependency of KRAS-mutant cancers, particularly KRAS^{G12C}, and KRAS-mutant NSCLC has been found to be dependent on SHP2 activity in vivo[4,7]
- 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 IC50: ~5 nM)
  - High selectivity (>1000X) for the mutant KRAS^{G12C} protein vs wild-type (WT) KRAS
  - Favorable pharmacokinetic (PK) properties, including oral bioavailability, long half-life (~24 h), and extensive tissue distribution[8]
- TNO155 is a selective, orally bioavailable allosteric inhibitor of WT SHP2[5,6]

Adagrasib Monotherapy Clinical Data

- Initial results from KRYSTAL-1, a Phase 1/2 study, demonstrated antitumor activity and tolerability of adagrasib monotherapy across multiple tumor types harboring a KRAS^{G12C} mutation, including patients with NSCLC previously treated with both platinum-based chemotherapy and immune checkpoint inhibitors[8] (**Figure 1**)
- In a safety analysis (n=110) from KRYSTAL-1, adagrasib was well tolerated, with few grade 3-4 treatment-related adverse events (TRAEs)[8]
  - The most common (>20%) TRAEs included nausea, diarrhea, vomiting, and fatigue[8]

Figure 1. Clinical Efficacy of Adagrasib in Solid Tumors (KRYSTAL-1)[8,9]



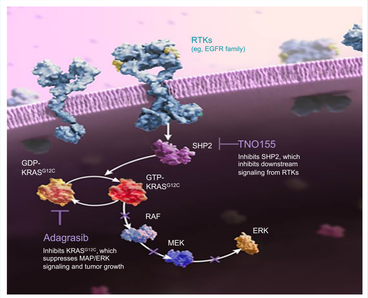
BID, twice daily; CRC, colorectal cancer; NE, not evaluable; NSCLC, non–small-cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease.
Data as of 30 August 2020.

- 45% (23/51) of patients with NSCLC had a confirmed objective response rate (ORR) and 51% (26/51) of patients achieved stable disease (SD)
- Clinical benefit (disease control rate; DCR) was observed in 96.1% (49/51) of patients with NSCLC
- 17% (3/18) of patients with CRC had a confirmed ORR and 78% (14/18) achieved SD[9]

Study Rationale

- Adagrasib is a covalent inhibitor of KRAS^{G12C} that irreversibly and selectively binds KRAS^{G12C} and locks it in its inactive, GDP-bound state[8]
- By inhibiting cycling to GTP-bound KRAS for both mutant and WT KRAS species, the addition of TNO155 to adagrasib may enhance irreversible target binding by adagrasib and may also augment antitumor activity through inhibition of feedback activation and consequently prevent resistance[5-7,10] (**Figure 2**)

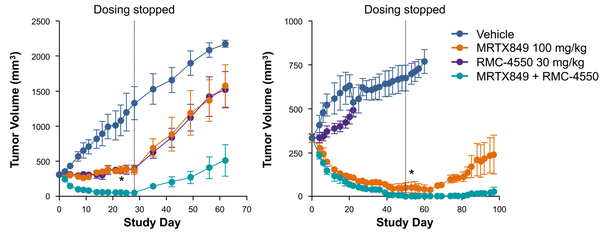
Figure 2. Roles of Adagrasib and TNO155 in the MAPK Pathway



Preclinical Combination Data

- Preclinical studies of adagrasib combined with SHP2 inhibition in several xenograft models of KRAS^{G12C} -mutant tumors have demonstrated greater activity for the combination compared to each agent alone[5,6,10] (**Figure 3**)

Figure 3. Preclinical Data Demonstrating Antitumor Activity For the Combination[7]



*P_{adj} <.05
RMC-4550, SHP2 inhibitor; KYSE-410 and H358, cell line xenografts.

- Adagrasib at 100 mg/kg, RMC-4550 at 30 mg/kg, or the combination was administered daily via oral gavage to mice bearing the KYSE-410 or H358 cell line xenografts (n=5/group). Combination treatment led to a statistically significant reduction in tumor growth compared with either single agent on the last day of dosing (P_{adj} <.05)

Methods

KRYSTAL-2 is a multicenter, Phase 1/2 study evaluating the safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of the combination of adagrasib and TNO155 in patients with advanced solid tumors with KRAS^{G12C} mutation (**Figure 4**)

Phase 1/1b Cohort Objectives

- To establish the maximum tolerated dose (MTD) of the combination of adagrasib and TNO155 using 1 or more dosing regimens
- To identify recommended Phase 2 combinatorial doses (RP2Ds) and regimens of adagrasib and TNO155

Phase 2 Cohort Objectives

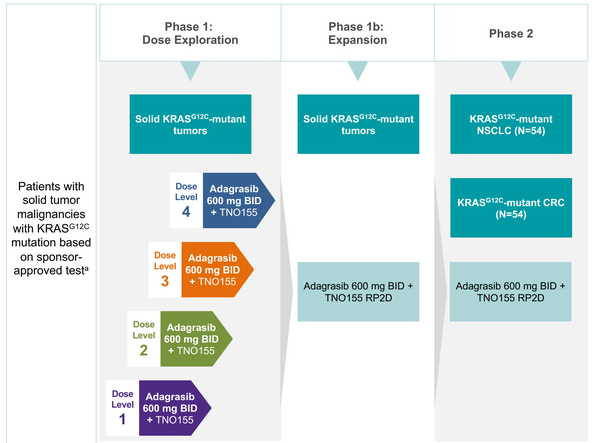
- To evaluate the clinical activity of adagrasib in combination with TNO155 in cohorts of patients with selected solid tumor malignancies with KRAS^{G12C} mutation

Endpoints

- Safety, characterized by type, incidence, severity, timing, seriousness, and relationship to study treatment of adverse events and laboratory abnormalities
- Blood plasma concentrations of adagrasib and potential metabolites
- Blood plasma concentration of TNO155
- Clinical activity/efficacy

Study Design

Figure 4. KRYSTAL-2 Study Design



BID, twice daily; CRC, colorectal cancer; NSCLC, non–small-cell lung cancer; RP2D, recommended phase 2 dose.
[a]Tissue test and/or circulating tumor deoxyribonucleic acid (ctDNA) allowed for Phase 1/1b eligibility.
Adagrasib is dosed continuously and TNO155 is dosed on a 2-week-on/1-week-off basis.

Key Inclusion Criteria

- Histologically confirmed diagnosis of an unresectable or metastatic solid tumor malignancy with KRAS^{G12C} mutation
  - Patients in the Phase 1/1b portions of the study are eligible based on detection of a KRAS^{G12C} mutation in tumor tissue or plasma circulating tumor DNA (ctDNA)
  - Patients enrolled into Phase 2 cohorts must have a diagnosis of **NSCLC** or **CRC** with KRAS^{G12C} mutation detected in tumor tissue
- Receipt of at least 1 prior regimen for metastatic disease and no available treatment with curative intent
  - Phase 2 NSCLC cohort: previously received treatment with a platinum-containing chemotherapy regimen and an immune checkpoint inhibitor
  - Phase 2 CRC cohort: previously received treatment with oxaliplatin, irinotecan, and a fluoropyrimidine
- Presence of measurable or evaluable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 in Phase 1/1b; measurable disease per RECIST 1.1 in Phase 2
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

Key Exclusion Criteria

- Active brain metastases; patient is eligible if brain metastases are adequately treated and patient is neurologically stable (except for residual signs or symptoms related to central nervous system [CNS] treatment) for at least 2 weeks prior to enrollment, without the use of corticosteroids or on a stable or decreasing dose of ≤10 mg daily of prednisone (or equivalent)
- Impaired heart function
- Lifetime anthracycline exposure >250 mg/m^2 of doxorubicin or equivalent
- Phase 2 cohorts only: prior treatment with a therapy targeting KRAS^{G12C} mutation

Statistical Methods

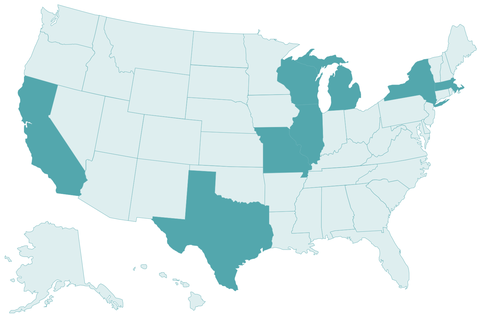
Phase 1 Study Design and Sample Size

- Modified toxicity probability interval (mTPI): Dose escalation steps for TNO155 administered with a fixed dose of adagrasib (600 mg BID) will proceed until the MTD for TNO155 is established
- Dose level cohorts in the mTPI model will include at least 3 patients

Phase 2 Study Design and Sample Size

- Simon's 2-stage optimal designs[11]:
  - NSCLC cohort: 54 patients
  - CRC cohort: 54 patients

Currently Active Study Sites



- UCLA Jonsson Comprehensive Cancer Center
- UC Irvine Health
- Washington University School of Medicine Siteman Cancer Center
- NYU Perlmutter Cancer Center
- New Experimental Therapeutics (NEXT) Oncology
- Froedtert Hospital & Medical College of Wisconsin
- Northwestern University Feinberg School of Medicine
- Memorial Sloan Kettering Cancer Center
- Dana-Farber Cancer Institute
- Massachusetts General Hospital
- Henry Ford Cancer Center

Summary

- Adagrasib is a KRAS^{G12C}-selective covalent inhibitor with a long half-life and extensive predicted target coverage throughout the dosing interval[9]
- KRYSTAL-1 demonstrated activity of adagrasib as a monotherapy in multiple solid tumors, including CRC, and in pretreated patient populations[8]
- TNO155 may augment the antitumor activity of adagrasib by inhibiting cycling of KRAS^{G12C} to its active, GTP-bound state; enhancing irreversible target binding by adagrasib; and may prevent feedback activation of KRAS^{G12C}, potentially preventing resistance[5,6,10]
- The Phase 1/2 KRYSTAL-2 study evaluating adagrasib plus TNO155 in solid tumors is open for enrollment and recruitment is ongoing
- Clinical trial registry number: NCT04330664

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