In a safety analysis (n=110) from KRYSTAL, 17% (3/18) of patients with CRC had a confirmed ORR and 78% (14/18) achieved SD. The most common (>20%) TRAEs included nausea, diarrhea, vomiting, and fatigue. A KRAS\textsuperscript{G12C} mutant NSCLC has been found to be dependent on SHP2 activity in vivo.

**Study Design**

KRYSTAL-2 is a multinational, Phase 1/2 study evaluating the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of adagrasib and TNO155 in combination of patients with solid tumors with transformation-selective covalent inhibition of KRAS\textsuperscript{G12C} mutation. Oral presentation at: EORTC International Conference on Molecular Targets and Cancer Therapeutics, 30 October, 2020 – virtual.

**Key Inclusion Criteria**

- Active or prior history of renal or hepatic impairment (creatinine clearance <60 mL/min or Child-Pugh class B/C, respectively).
- Presence of measurable or evaluable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.
- Karnofsky performance status (PS) of 70 or greater.

**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] metastases).
- History of active untreated or inadequately treated infection.
- Active second primary malignancy or treated malignancy within 5 years.

**Dosing**

- Adagrasib 600 mg BID.
- TNO155 at 250 mg/m\textsuperscript{2} or 250 mg/m\textsuperscript{2} for patients with lung tumors and at 125 mg/m\textsuperscript{2} for patients with solid tumors.

**Endpoints**

- Safety: characterized by type, incidence, severity, timing, surveillances, and relationship to study treatment of adverse events and laboratory abnormalities.
- Response: evaluation of KRAS\textsuperscript{G12C} mutation status and any metastatic sites.
- Clinical activity: tumor activity of the KRAS\textsuperscript{G12C} inhibitor MRTX849 is augmented by cetuximab in CRC tumor models.