Background and rationale

Activating mutations of KRAS drive many types of cancer, including NSCLC.\(^6\) Activation of KRAS relies on guanine nucleotide exchange factors, such as SOS1, to mediate exchange of GDP for GTP, hindering activation of KRAS proteins.\(^1\) Preclinical studies demonstrated cytostatic effects for BI 1701963 in cancer cells with an activated KRAS pathway, and combination with a MEK inhibitor resulted in a more pronounced effect.\(^2\) BI 1701963 is a small-molecule protein–protein interaction inhibitor that prevents the interaction between KRAS and SOS1, inhibiting binding of SOS1 to RAS–GDP, thereby hindering activation of KRAS proteins.\(^3\) BI 1701963 in cancer cells with an activated KRAS pathway, and combination with a MEK inhibitor resulted in a more pronounced effect.\(^4\) BI 1701963 dose will be escalated until the MTD, or a max. of 2 mg QD or until an MTD dose causing confirmed as safe.\(^5\) The first patient was recruited in November 2019.\(^6\)

Endpoints and assessments

**Endpoints**

**Primary:** MTD, DLTs

**Secondary:** PK, OR, PFS rate at 6 months, Grade ≥3 TRAEs

**Current status**

As of February 11th, 2020, three patients have been treated

**Key points**

Objectives

- To determine the MTD and/or RP2D of BI 1701963 as a monotherapy and in combination with trametinib
- To evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy

Study design

- Multicenter, open-label, first-in-human dose escalation and expansion trial

**Endpoints**

**Primary:** MTD, DLTs

**Secondary:** PK, OR, PFS rate at 6 months, Grade ≥3 TRAEs

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**As of February 11th, 2020, three patients have been treated**

**Patients**

**Key inclusion criteria**

- Aged ≥18 years
- Tumors with activating KRAS mutations
- ≥1 evaluable lesion (RECIST v1.1)
- Pharmacokinetic parameters include C\(_{\text{max}}\), area under the concentration-time curve in plasma over the time interval from 0 to the last quantifiable time point for the for the trial drugs; C\(_{\text{AUC}}\), maximum measured plasma concentration of the trial drugs; CR, complete response; OR, objective response; PR, partial response; PFS, progression-free survival; TRAEs, treatment-related adverse events

**Key exclusion criteria**

- Previous RAS, MAPK, or KRAS targeted therapies
- Retinal vein occlusion
- Retinal pigment epithelial detachment
- Decreased cardiac function

**Endpoints and assessments**

**Endpoints**

**Primary**

- MTD: number of patients with DLTs during Cycle 1

**Secondary**

- Pharmacokinetics, number of patients with Grade ≥3 TRAEs

**Part A**

- Mono: MTD; number of patients with DLTs during Cycle 1

**Part B**

- Combo: OR (CR + PR)

**Part C**

- Combo: OR (CR + PR)

**Current status**

- Target enrollment is approximately 140 patients across all cohorts
- The first patient was recruited in November 2019
- As of February 11th, 2020, three patients have been treated