A Phase I, open-label, dose escalation trial of BI 1701963 as monotherapy and in combination with trametinib in patients with *KRAS* mutated advanced or metastatic solid tumors

Poster #381

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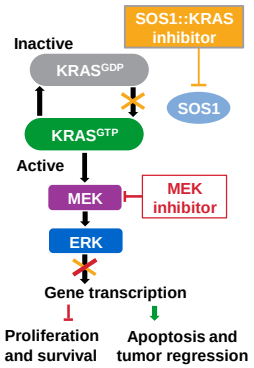
Introduction

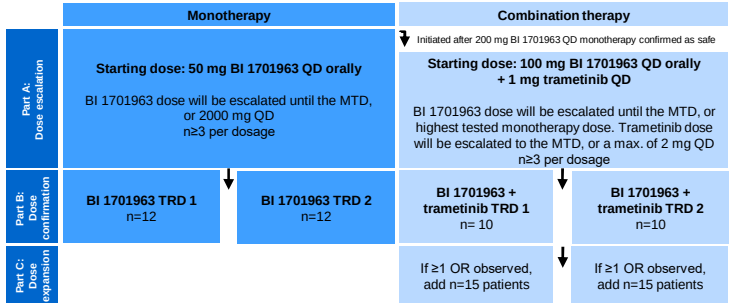
- Activating mutations of *KRAS* drive many types of cancer, including NSCLC[1]
- Activation of KRAS relies on guanine nucleotide exchange factors, such as SOS1, to mediate exchange of GDP for GTP[2,3]
- BI 1701963 is a small-molecule protein–protein interaction inhibitor that prevents the interaction between KRAS and SOS
  - Binding of BI 1701963 to the catalytic site of SOS1 inhibits binding of SOS1 to RAS–GDP, thereby hindering activation of KRAS proteins
  - 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



ERK, extracellular signal-regulated kinases; GDP, guanosine diphosphate; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma; MEK, MAPK kinase; SOS1, son of sevenless homolog 1

Objectives and study design

- NCT04111458 is a first-in-human dose escalation and expansion trial of BI 1701963 in patients aged ≥18 years with solid tumors harboring *KRAS* mutations[4]
  - Primary objectives are to determine the MTD and/or RP2D of BI 1701963 as a monotherapy and in combination with trametinib, based on DLTs
  - Secondary objectives are to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy



- Two TRDs will be established in each arm in Part A. In Part B, patients will be randomized (1:1) to groups receiving one of the TRDs
- The TRD 1 and TRD 2 combination groups will include patients with NSCLC only
- Treatment will continue until confirmed loss of clinical benefit, defined toxicities, or withdrawal of consent

DLT, dose-limiting toxicity, MTD, maximum tolerated dose; QD, once-daily; TRD, therapeutic relevant dose; RP2D, recommended Phase II dose

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

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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

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Patients

Key inclusion criteria

- Aged ≥18 years
- Tumors with activating *KRAS* mutations
- ≥1 evaluable lesion (RECIST v1.1)
- ECOG PS ≤1
- Adequate organ function

Key exclusion criteria

- Previous RAS, MAPK or SOS1 targeted therapies
- Retinal vein occlusion
- Retinal pigment epithelial detachment
- Decreased cardiac function

- Parts B and C will be conducted in patients with advanced NSCLC only

ECOG PS, Eastern Cooperative Oncology Group performance status; RECIST, response evaluation criteria in solid tumors

Endpoints and assessments

		Endpoints	
		Primary	Secondary
Part A	Mono	MTD; number of patients with DLTs during Cycle 1	Pharmacokinetics
	Combo		
Part B	Mono	Number of patients with DLTs	Pharmacokinetics; number of patients with Grade ≥3 TRAEs
	Combo	OR (CR + PR)	OR duration; tumor shrinkage; PFS rate at 6 months; number of patients with Grade ≥3 TRAEs; pharmacokinetics
Part C	Combo	OR (CR + PR)	OR duration; tumor shrinkage; PFS rate at 6 months; number of patients with Grade ≥3 TRAEs; pharmacokinetics

- MTD will be based on the number of patients with DLTs during Cycle 1 (4 weeks)
- Pharmacokinetic parameters include C_{max} and $AUC_{0\text{-}tz}$
- Tumor response will be evaluated according to RECIST v1.1 every 8 weeks until PD, death, or withdrawal
- PFS rate at 6 months, defined as time from first administration until PD or death, will be determined according to RECIST v1.1

$AUC_{0\text{-}tz}$, 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_{max}, maximum measured plasma concentration of the trial drugs; CR, complete response; OR, objective response; PR, partial response; PFS, progression-free survival; TRAE, treatment-related adverse event

Current status

- Target enrolment 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

Presented at the American Society of Clinical Oncology Congress (ASCO) Annual Meeting, Virtual Format, May 29-31, 2020

This study was funded by Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version.
Medical writing assistance, supported financially by Boehringer Ingelheim, was provided by Hannah Simmons, of GeoMed, an Ashfield company, part of UDG Healthcare plc, during the development of this poster