A Phase I, open-label, dose-escalation trial of BI 1701963 (SOS1::KRAS inhibitor) in patients with *KRAS* mutated solid tumours: a snapshot analysis

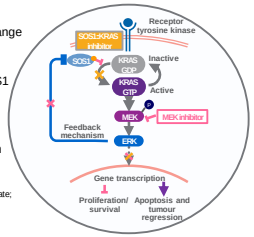
#524P

Melissa Johnson,[1]* Eelke Gort,[2] Shubham Pant,[3] Martijn Lolkema,[4] Martin Sebastian,[5] Matthias Scheffler,[6] Jimmy Hwang,[7] Ulrich Dünzinger,[8] Kathrin Riemann,[9] Holger Fritsch,[10] Pasi A. Jänne[11]

[1]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA; [2]Department of Medical Oncology, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Department of Investigational Cancer Therapeutics, MD Anderson Cancer Center, Houston, TX, USA; [4]Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [5]Department of Hematology and Oncology, University Hospital, Frankfurt, Germany; [6]Department of Internal Medicine, University Hospital of Cologne, Center for Integrated Oncology Cologne, Germany; [7]Department of Oncology, Levine Cancer Institute, Charlotte, NC, USA; [8]TA Oncology Medicine, Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany; [9]Global Clinical Operations, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riß, Germany; [10]Translational Medicine and Clinical Pharmacology, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach an der Riß, Germany; [11]Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA, USA

Introduction

- Activating mutations of *KRAS* drive many types of cancer[1]
- Activation of wild-type KRAS is mediated by guanine nucleotide exchange factors, such as SOS1, which regulate exchange of GDP for GTP[2,3]
- BI 1701963 is a small-molecule protein–protein interaction inhibitor, which prevents KRAS activation by binding to the catalytic site of SOS1
- Binding of BI 1701963 to the catalytic site of SOS1 inhibits binding of SOS1 to RAS–GDP, thereby hindering activation of KRAS proteins
- NCT04111458 is a first-in-human dose escalation and expansion trial of BI 1701963 as a monotherapy and in combination with trametinib in patients with *KRAS* mutation-positive solid tumours[4]; here, we report preliminary results from the monotherapy arm



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

- Primary objectives are to determine the MTD and/or RP2D of BI 1701963 as a monotherapy, based on DLTs
- Secondary objectives are to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy

DLT, dose limiting-toxicities; MTD, maximum tolerated dose; RP2D, recommended Phase II dose

Methods

Part A: dose escalation

Starting dose: 50 mg BI 1701963 once-daily orally
BI 1701963 dose escalated until the MTD, or 2000 mg once-daily. n≥3 per dosage

→

Part B: dose confirmation

BI 1701963 TRD 1: n=12

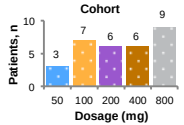
BI 1701963 TRD 2: n=12

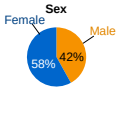
- Two TRDs will be established in each arm in Part A. In Part B, patients will receive one of the TRDs
- Primary endpoints are the MTD (Part A) and number of patients with DLTs during Cycle 1 (Parts A and B)

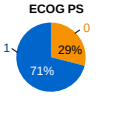
TRD, therapeutic relevant dose

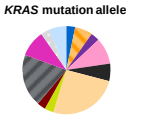
Patients

- As of July 2021, 31 patients have been treated and three patients remain on treatment (all 800 mg)







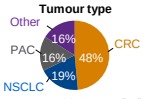


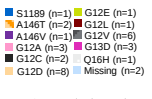
Median number of previous therapies

3

Median age, years

55





CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small cell lung cancer; PAC, pancreatic adenocarcinoma

Key findings and conclusions

- NCT04111458 is a first-in-human dose escalation and expansion trial of BI 1701963 in patients aged ≥18 years with solid tumours harbouring *KRAS* mutations
- To date, 31 patients have been treated with BI 1701963 as a monotherapy
- 50 mg, 100 mg, 200 mg, 400 mg, and 800 mg once-daily doses of BI 1701963 were generally well tolerated, and the majority of drug-related AEs were manageable
- The MTD was reached at the 800 mg dose level as two DLTs were reported (grade 4 decreased platelet count and grade 3 congestive cardiomyopathy)
- No clinical responses were observed, but seven patients experienced stable disease lasting up to 18 weeks
- At 200–800 mg, exposure was above the predicted therapeutic active exposure seen in xenograft models
- An additional 600 mg monotherapy cohort is recruiting

https://bit.ly/3BCDODj

Scan this QR code or visit the URL for an electronic copy of the poster and supplementary content†

https://bit.ly/2Tz2Z8o

Scan this QR code or visit the URL for a webpage featuring all BI-supported publications at ESMO 2021

*Corresponding author email address: mjohnson@tnonc.com

References

1. Cox AD, et al. Nat Rev Drug Discov 2014;13:828–51; 2. Liu F, et al. Acta Pharm Sin B 2018;8:552–62; 3. Evelyn CR, et al. Chem Biol 2014;21:1618–28; 4. ClinicalTrials.gov identifier: NCT04111458

Safety

N=31	All grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade ≥3 n (%)
Any AE*†	30 (97)	3 (10)	10 (32)	17 (57)
Fatigue	11 (36)	7 (23)	4 (13)	0
Abdominal pain	10 (32)	6 (19)	2 (7)	2 (7)
Nausea	8 (26)	3 (10)	4 (13)	1 (3)
Anaemia	8 (26)	5 (16)	2 (7)	1 (3)
Hypertension	6 (19)	1 (3)	3 (10)	2 (7)
Vomiting	6 (19)	4 (13)	0	2 (7)
Pyrexia	6 (19)	3 (10)	3 (10)	0
Diarrhoea	6 (19)	5 (16)	1 (3)	0
Blood alkaline phosphatase increased	6 (19)	6 (19)	0	0
Hypokalaemia	6 (19)	6 (19)	0	0

- Grade >3 AEs were reported in five (16%) patients, including: grade 4 platelet count decrease (800 mg); and grade 5 disease progression (two patients; 100 mg and 800 mg), death (200 mg), and malignant neoplasm progression (200 mg)
- Drug-related AEs occurred in 21 (68%) patients (50 mg, n=2; 100 mg, n=5; 200 mg, n=1; 400 mg, n=6; 800 mg, n=7); most commonly reported were diarrhoea, fatigue, and decreased platelet count (all n=4, 13%)
- Three drug-related grade ≥3 AEs were observed: grade 3 hypertension; grade 3 congestive cardiomyopathy; and grade 4 decreased platelet count
- Serious AEs were reported in 16 (52%) patients, most commonly abdominal pain (n=3, 10%), disease progression, and pyrexia (both n=2, 7%)
- Two DLTs were reported: grade 4 decreased platelet count and grade 3 congestive cardiomyopathy (both 800mg); the MTD was therefore considered reached

*Maximum Common Terminology Criteria for Adverse Events; †Includes ten most common AEs; all presented AEs occurred in >5 patients. AE, adverse event

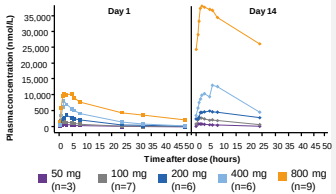
Preliminary efficacy

- Among the 31 treated patients, no clinical responses were observed, but seven patients experienced stable disease, lasting up to 18 weeks. Of the remaining 24 patients, 15 had progressive disease

Preliminary pharmacokinetics

- BI 1701963 was rapidly absorbed, with a t_{max} of 0.5–3 hours post first dose
- Exposure increased proportionally with increasing doses post first dose. After repeated doses of >400 mg, there was a greater than proportional increase in exposure; the reason for this effect is currently under evaluation
- Dose-normalised C_{max} and $AUC_{0–24h}$ values were 22.1 nmol/L/mg and 222.6 nmol*h/L/mg, respectively
- Apparent terminal half-life is 12–26 hours
- Beginning at 200 mg, exposure (C_{max} and $AUC_{0–24h}$) is above the predicted therapeutic active exposure seen in xenograft models

Geometric mean plasma concentration-time profiles of BI 1701963 following single dose (Day 1) and repeated daily doses (Day 14)



AUC_{0-24h}, area under the curve from 0 to 24 hours; C_{max}, maximum plasma concentration; T_{max}, time taken to reach C_{max}

Presented at the European Society for Medical Oncology (ESMO), Virtual Format, September 16–21, 2021

The authors would like to thank Thomas Kitzing, of Boehringer Ingelheim, for their contribution towards abstract development for this study. 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.
The authors did not receive payment related to the development of the poster. Medical writing support for the development of this poster, under the direction of the authors, was provided by Hannah Simmons MSc, of Ashfield MedComms, an Ashfield Health company, and funded by Boehringer Ingelheim. To access Dr Johnson's conflicts of interests please scan the QR code