# First-in-human, Phase Ia/b, dose-finding study of KRAS G12C inhibitor BI 1823911, as monotherapy and combined with anticancer therapies, in patients with advanced or metastatic solid tumours harbouring a KRAS G12C mutation

#665P

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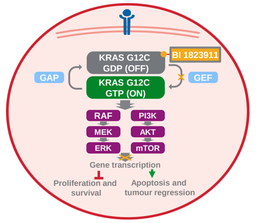
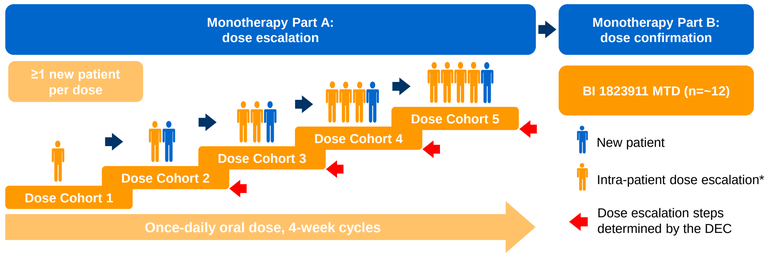
## Introduction

- BI 1823911 is a mutant-selective KRAS G12C inhibitor that covalently binds to G12C-mutant KRAS, irreversibly locking it in its inactive GDP form, thereby interfering with cell signalling, causing tumour cell apoptosis and blocking cell proliferation[1]
- In preclinical studies, BI 1823911 showed antitumour responses against KRAS G12C-mutant tumours; responses were enhanced when BI 1823911 was combined with BI 1701963, a pan-KRAS SOS1 inhibitor[2,3]
- NCT04973163, an ongoing first-in-human Phase Ia/b study, is assessing the safety, pharmacokinetics and preliminary efficacy of BI 1823911 as monotherapy and is designed to evaluate combinations with other anticancer therapies in patients with advanced or metastatic solid tumours expressing the KRAS G12C mutation[4]




AKT, protein kinase B; ERK, extracellular signal-regulated kinase; GAP, GTPase activating protein; GDP, guanosine diphosphate; GEF, guanine-nucleotide exchange factor; GTP, guanosine triphosphate; KRAS, Kirsten rat sarcoma virus; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; SOS1, son of sevenless homolog 1

## Methods




**Primary endpoints**

**Part A**: number of patients with DLTs during the MTD evaluation period (i.e. first 21 days of the first cycle)

**Part B**: OR (confirmed complete or partial response)

**Key inclusion criteria**

Patients with advanced or metastatic relapsed or refractory solid tumours harbouring a KRAS G12C mutation

**Key exclusion criteria**

Previous treatment with RAS, MAPK or SOS1 targeting agents (monotherapy arm only)

*Allowed but not mandatory.

- It was also planned to evaluate BI 1823911 in combination with other anticancer agents in a combination arm and as monotherapy in dose expansion cohorts (Monotherapy Part C); however, these parts have been cancelled

DEC, dose-escalation committee; DLT, dose-limiting toxicity; MAPK, mitogen-activated protein kinases; MTD, maximum tolerated dose; OR, objective response; RAS, rat sarcoma virus

## Baseline characteristics and treatment exposure

- As of 24 June 2023, 27 patients have received BI 1823911 monotherapy
  - 17 patients in Part A (50 mg, n=1; 100 mg, n=1; 200 mg, n=1; 400 mg, n=3; 600 mg, n=3; 900 mg, n=3; 1200 mg, n=5)
  - 10 patients in Part B (all 900 mg)
- 17 patients have discontinued treatment in the monotherapy arm
  - 14 patients in Part A (objective disease progression [n=10], adverse event [n=2], burden of study procedures [n=1] and withdrawal by patient [n=1])
  - 3 patients in Part B (all objective disease progression)
- 10 patients remain on treatment: 3 patients in Part A and 7 patients in Part B

| | Monotherapy Part A (n=17) | Monotherapy Part B (n=10) |
|---|---|---|
| **Median age at baseline, years (range)** | 58 (36–82) | 65 (30–79) |
| **Sex, n (%)** | | |
| Male | 9 (53) | 6 (60) |
| Female | 8 (47) | 4 (40) |
| **ECOG PS, n (%)** | | |
| 0 | 11 (65) | 4 (40) |
| 1 | 6 (35) | 6 (60) |

ECOG PS, Eastern Cooperative Oncology Group Performance Status

## Key findings and conclusions

- To date, 27 patients have been treated with BI 1823911 monotherapy (Part A, n=17; Part B, n=10); 10 patients remain on treatment (Part A, n=3; Part B, n=7)
- 3 patients had DLTs in the MTD evaluation period of monotherapy Part A; the MTD was selected as BI 1823911 900 mg
- Almost all (96%) patients experienced TEAEs; all TRAEs were manageable
- Preliminary efficacy results indicate that BI 1823911 demonstrates clinical activity in patients with advanced/metastatic solid tumours expressing the KRAS G12C mutation; 4 patients had OR, including 1 patient with a complete response (Part A) and 3 patients with partial responses (Part A, n=2; Part B, n=1)
- Recruitment is complete for both parts of this study

## Dose escalation and DLTs

| Monotherapy Part A (n=17) | DLTs during the MTD evaluation period |
|---|---|
| 50 mg (n=1) | - |
| 100 mg (n=1) | - |
| 200 mg (n=1) | - |
| 400 mg (n=3) | - |
| 600 mg (n=3) | - |
| 900 mg (n=3) | Grade 3 gastrointestinal stoma complication (n=1) |
| 1200 mg (n=5) | Grade 3 diarrhoea (n=2); Grade 3 fatigue (n=1) |

In Part A of the monotherapy arm:

**3** patients had DLTs in the MTD evaluation period (all recovered)

**2** patients had DLTs outside the MTD evaluation period (both Grade 3 diarrhoea; 600 mg; 400 and 900 mg)

**The MTD was selected as BI 1823911 900 mg for monotherapy Part B**

## Safety

| TEAEs*, n (%) | Monotherapy Part A (n=17) All | Part A (n=17) Grade ≥3 | Part B (n=10) All | Part B (n=10) Grade ≥3 | Total (N=27) All | Total (N=27) Grade ≥3 |
|---|---|---|---|---|---|---|
| **Any** | **17 (100)** | **8 (47)** | **9 (90)** | **0** | **26 (96)** | **8 (30)** |
| Nausea | 15 (88) | 0 | 8 (80) | 0 | 23 (85) | 0 |
| Diarrhoea | 15 (88) | 3 (18) | 6 (60) | 0 | 21 (78) | 3 (11) |
| Vomiting | 10 (59) | 0 | 8 (80) | 0 | 18 (67) | 0 |
| Fatigue | 11 (65) | 1 (6) | 2 (20) | 0 | 13 (48) | 1 (4) |
| Decreased appetite | 5 (29) | 0 | 3 (30) | 0 | 8 (30) | 0 |
| Pyrexia | 5 (29) | 0 | 0 | 0 | 5 (19) | 0 |

*Occurring in ≥5 patients in monotherapy Part A or B, respectively; preferred terms and worst Common Terminology Criteria for Adverse Events Grade.

- All patients in Part A of the monotherapy arm experienced any-cause TEAEs (Grade 3, n=8); 9 patients experienced any-cause TEAEs in Part B (Grade 3, n=0)
- Most of the TEAEs were gastrointestinal disorders
- 2 patients had TEAEs leading to treatment discontinuation (both Part A; 600 mg, Grade 3 diarrhoea; 400 mg, Grade 2 diarrhoea; both TRAEs)
- 11 patients had TEAEs leading to dose reduction
  - 7 patients in monotherapy Part A (1200 mg, Grade 1 nausea and vomiting, Grade 3 diarrhoea; 900 mg, Grade 2 diarrhoea [n=2], Grade 2 vomiting, Grade 3 gastrointestinal stoma complication; 600 mg, Grade 2 vomiting, Grade 1 ejection fraction decreased; 200 mg, Grade 2 decreased appetite and diarrhoea; all TRAEs)
  - 4 patients in monotherapy Part B (all 900 mg; Grade 1 decreased appetite, vomiting and diarrhoea; Grade 1 vomiting; Grade 2 diarrhoea and nausea, Grade 2 vomiting and nausea; all TRAEs)
- Overall, 26 patients experienced TRAEs (Grade 3, n=3); the majority were manageable either with dose reduction or interruption

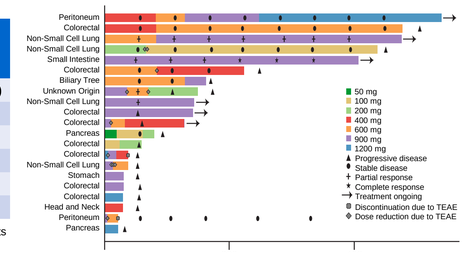
TEAEs, treatment-emergent adverse events; TRAEs, treatment-related adverse events

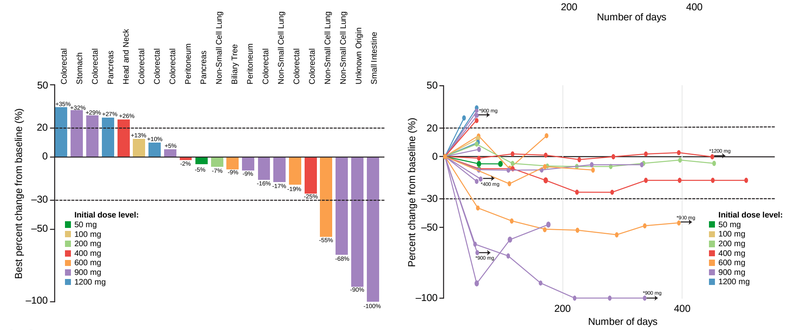
## Preliminary efficacy

- In the monotherapy arm, 4 patients had OR, including 1 complete response (Part A, 900 mg, small intestine) and 3 partial responses (Part A, n=2, 600 and 900 mg, lung cancer and unknown origin; Part B, n=1, 900 mg, non-small cell lung cancer)

| Best response, n (%*) | Monotherapy Part A (n=17) | Monotherapy Part B (n=10) | Monotherapy Total (N=27) |
|---|---|---|---|
| **Evaluable patients†** | **15 (100)** | **6 (100)** | **21 (100)** |
| **OR rate** | **3 (20)** | **1 (17)** | **4 (19)** |
| Complete response | 1 (7) | 0 | 1 (5) |
| Partial response | 2 (13) | 1 (17) | 3 (14) |
| Stable disease | 7 (47) | 0 | 7 (33) |
| Progressive disease | 5 (33) | 5 (83) | 10 (48) |

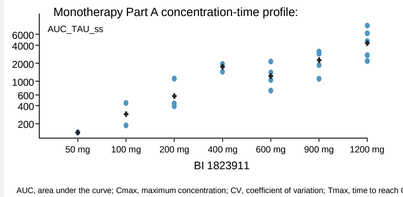
*% of evaluable patients; †patients with post-baseline measurements




*ongoing dosage at time of data cut-off

## Pharmacokinetics




AUC, area under the curve; Cmax, maximum concentration; CV, coefficient of variation; Tmax, time to reach Cmax

Monotherapy Part B:

- Mean $AUC_{0-t}$ of midazolam is slightly higher after concomitant treatment with BI 1823911 compared with midazolam alone during run-in (reference)
- The mean ratio test/reference for $AUC_{0-t}$ characterising the inhibition potential is 129% (23% CV) on Day 3 (n=9)
- On Day 8 at steady state (N=7) the ratio as measure of sum from inhibition and induction potential is 114% (24% CV)
- Midazolam ratio test/references of $C_{max}$ (97%) and median $T_{max}$ remain unchanged
- Observed interindividual variability of midazolam is moderate

## References

1. Boehringer Ingelheim, data on file; 2. Savarese F, et al. Poster presented at AACR 2021, Virtual Meeting, #1271; 3. Hofmann MH, et al. AACR 2021, Poster presented at AACR 2021, Virtual Meeting, #CT210; 4. ClinicalTrials.gov. NCT04973163. Available at https://clinicaltrials.gov/ct2/show/NCT04973163 (Accessed: September 2023).

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