Ezabenlimab (BI 754091), an anti-PD-1 antibody, in combination with BI 836880, a VEGF/Ang2-blocking nanobody, in patients with previously treated advanced solid tumours

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Introduction

- The combination of anti-PD-1 antibodies with other immunomodulatory or targeted therapies has the potential for synergistic effects[1]
- VEGF and Ang2 play key roles in tumour angiogenesis and have an immunosuppressive effect in the tumour microenvironment. Combining anti-VEGF/Ang2 with an anti-PD-1 therapy promotes an immunopermissive state supportive of T-cell-mediated tumour cell death.[1,2] An ongoing Phase Ib trial investigating this therapeutic approach has observed manageable safety and preliminary antitumour activity[3,4]
- In this open-label, multicentre, Phase II platform trial (NCT03697304), ezabenlimab, an anti-PD-1 antibody, is being assessed in combination with other agents.[5] Here, we report preliminary data from the module assessing ezabenlimab in combination with BI 836880, a humanised bispecific nanobody® that targets VEGF and Ang2

Ang2, angiopoietin-2; PD-1, programmed cell death protein 1; VEGF, vascular endothelial growth factor

Objectives

- To investigate the safety and efficacy of ezabenlimab in combination with BI 836880, in patients with previously treated advanced solid tumours

Methods

- 150 patients are being enrolled into five cohorts (approximately 30 per cohort), and will receive intravenous infusions of ezabenlimab (240 mg) and BI 836880 (720 mg) every 3 weeks

Cohort 1:	Locally advanced/metastatic GEC with ≥1 prior treatment (anti-PD-[L]1 naïve)
Cohort 2:	Any advanced/metastatic solid tumour (excluding non-squamous NSCLC or melanoma) with prior anti-PD-(L)1 treatment* for ≥2 months, which progressed after achieving at least SD for ≥4 months (secondary resistance)
Cohort 3:	Advanced/metastatic solid tumours† with no benefit from prior anti-PD-(L)1 treatment* (SD <4 months or PD in <4 months; primary resistance)
Cohort 4:	Locally advanced/metastatic microsatellite stable colorectal cancer with ≥1 prior treatment (anti-PD-[L]1 naïve) **[RECRUITMENT COMPLETE]**
Cohort 5:	Advanced metastatic microsatellite stable and mismatch repair-proficient endometrial carcinoma, which progressed after one line of chemotherapy (anti-PD-[L]1 naïve)

- All patients are aged ≥18 years, with an Eastern Cooperative Oncology Group performance status of 0–1, and ≥1 measurable lesion according to RECIST version 1.1

Primary endpoint
Objective response per RECIST version 1.1, as assessed by the Investigator
Secondary endpoints
Duration of response
Disease control
Progression-free survival

Further endpoints
Antitumour activity by iRECIST
Safety and tolerability of ezabenlimab and BI 836880
Safety and biomarker measurements
Pharmacokinetics and pharmacodynamics
Overall survival

*A maximum of one line of prior anti-PD-(L)1-based therapy permitted; †Eligible tumour types: previously treated colorectal cancer; Merkel cell carcinoma; squamous cell skin carcinoma; other squamous cancers (head and neck, cervical, anal, penile, oesophageal, and vulvar); other gastrointestinal cancers (biliary tract, gastric, oesophageal, gastrointestinal stromal tumour); other thoracic cancers (small cell lung cancer, mesothelioma); urothelial cancers; renal cell carcinoma; neuroendocrine tumours; soft-tissue sarcomas; thyroid cancer; gynaecological tumours (ovary, endometrial, cervical); other tumour types for which no therapy of proven efficacy exists, or which are not amenable to standard therapies and where anti-PD-(L)1 therapy may be considered in exceptional cases. GEC, gastroesophageal cancer; iRECIST, immune Response Evaluation Criteria In Solid Tumors; PD, progressive disease; PD-(L)1, programmed death ligand-1; SD, stable disease

Key findings and conclusions

- NCT03697304 is a Phase II platform trial evaluating ezabenlimab (anti-PD-1 antibody) in combination with other agents
- Here, we report data from the module evaluating ezabenlimab plus BI 836880 (a humanised bispecific antibody that targets VEGF and Ang2)
- Ezabenlimab in combination with BI 836880 had a manageable safety profile; most frequently reported AEs were nausea (29%) and fatigue (25%)
- The combination showed preliminary activity; confirmed PRs were observed in the GEC (n=1), secondary resistance (n=1), and endometrial cancer (n=2) cohorts
- The colorectal cancer cohort has completed recruitment; others are continuing to recruit

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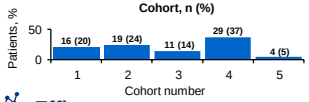
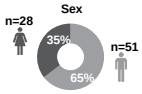
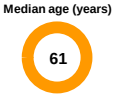
Patients

- As of July 2021, 79 patients have been treated. Median duration of treatment is 99 days (range 16–232 days)

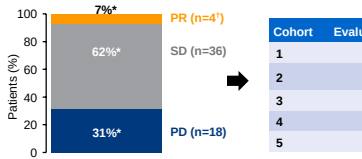






Efficacy

- As of July 2021, 59 patients are evaluable for response:



Cohort	Evaluable, n	PR, n	SD, n	PD, n
1	10	1	4	5
2	10	1	8	1
3	7	0	4	3
4	27	0	19	8
5	4	2	1	1

- The median duration of SD was 90 days (Cohort: 1, 43 days; 2, 107 days; 3, 63 days; 4, 126 days; 5, 83 days)

*Percentages based on confirmed responses (n=58); †Confirmed PR, n=4; unconfirmed PR, n=1 (Cohort 2). PR, partial response

Safety

Patients with:	All grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Any AE*	70 (89)	11 (14)	25 (32)	31 (39)	1 (1)	2 (3)
Nausea	23 (29)	13 (17)	8 (10)	2 (3)	0	0
Fatigue	20 (25)	11 (14)	7 (9)	2 (3)	0	0
Hypertension	15 (19)	0	6 (8)	8 (10)	1 (1)	0
Diarrhoea	14 (18)	9 (11)	1 (1)	4 (5)	0	0
Peripheral oedema	14 (18)	7 (9)	7 (9)	0	0	0
Treatment-related AEs	46 (58)	10 (13)	17 (22)	18 (23)	1 (1)	0
Immune-related AEs	8 (10)	2 (3)	5 (6)	1 (1)	0	0
Serious AEs	22 (28)	0	3 (4)	16 (20)	1 (1)	2 (3)

*Maximum Common Terminology Criteria for Adverse Events grade. AE, adverse event

- The two grade 5 AEs were aspiration pneumonia (Cohort 3) and cardiac arrest (Cohort 2); both were considered non-related
- Seven patients had infusion-related reactions (grade 1, n=1; grade 2, n=6)
- Two patients had adverse events that led to treatment discontinuation (grade 3 bile duct stone and grade 2 pain)

References

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