A phase Ia/Ib, open label, dose-escalation study of the combination of BI 907828 with BI 754091 (ezabenlimab) and BI 754111 and the combination of BI 907828 with BI 754091 (ezabenlimab) followed by expansion cohorts, in patients with advanced solid tumors

Published: 04-07-2022
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-511352-41-00 check the CTIS register for the current data. To investigate the maximum tolerated dose (MTD) of BI 907828 in combination with ezabenlimab based on dose limiting toxicities (DLT)…

Ethical review	Approved WMO
Status	Pending
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON53927

Source
ToetsingOnline

Brief title
1403-0002: BI907828 with ezabenlimab and BI754111 in solid tumors

Condition

- Metastases

Synonym
Cancer (solid tumors)

Research involving
Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: De opdrachtgever Boehringer Ingelheim

Intervention

Keyword: BI 907828, Ezabenlimab, sarcoma, solid tumors

Outcome measures

Primary outcome

Phase Ib:

- Objective response (OR), as assessed by the investigator according to RECIST v. 1.1, measured separately for each cohort. OR is defined as best overall response of confirmed complete response (CR) and/or confirmed partial response (PR) from the start of treatment until the earliest of disease progression (PD), death or last evaluable tumor assessment, and before start of subsequent anti-cancer therapy.

- Progression-Free Survival defined as the time from the start of treatment until the earliest of PD or death. Determination of progression is based on objective evaluation per RECIST v. 1.1 by investigators.

Secondary outcome

Phase Ib:

- Objective Response (OR) according to iRECIST as assessed by the investigator.

- Disease control (DC) according to RECIST 1.1 and iRECIST as assessed by the investigator.

- Overall survival (OS): defined as the time from start of treatment until

death from any cause.

- Number of patients with DLTs observed during the entire treatment period for

each combination treatment.

Study description

Background summary

The tumor suppressor TP53 is one of the most frequently mutated genes in human cancer. The function of TP53 is frequently attenuated by other mechanisms including overexpression/amplification of its key negative regulator HDM2, the human homolog of the murine double minute 2 (MDM2). The MDM2 protein binds to the TP53 protein and inhibits TP53 function. MDM2-TP53 antagonists are a unique opportunity to activate TP53 in TP53 wild type tumors.The MDM2-p53 antagonist BI 907828 is a new small molecule that inhibits the interaction between the tumor suppressor TP53 and its negative regulator MDM2.

In TP53 wild type syngeneic mouse model, MDM2 inhibition is able to trigger adaptive immunity which is further enhanced by PD-1/PDL1 pathway blockade. A synergistic effect was observed for BI 907828 in combination with anti-PD-1 in TP53 wild type syngeneic mouse models while the added benefit of anti-LAG-3 was not demonstrated in a number of BI sponsored trials. Consequently, the design of this study has changed from a dose finding triple combination of BI 907828 plus ezabenlimab (BI 754091, anti-PD-1 mAb) with BI 754111 to a dose-finding of a doublet combination therapy of BI 907828 with ezabenlimab in a variety of TP53 wild type solid tumors.

Study objective

This study has been transitioned to CTIS with ID 2024-511352-41-00 check the CTIS register for the current data.

To investigate the maximum tolerated dose (MTD) of BI 907828 in combination with ezabenlimab based on dose limiting toxicities (DLT) during the first treatment cycle and the recommended dose for expansion (RDE), safety and tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of the combination of BI 907828 with ezabenlimab in patients with advanced or metastatic solid tumors.

See protocol section 2.1.1.

Study design

Open-label, dose escalation study, followed by expansion cohorts.

See protocol section 3.1.

Intervention

Phase Ib - Dose Expansion:
The recommended dose for expansion (RDE) of BI 907828 in combination with a fixed dose of ezabenlimab, on Day 1 every 3 weeks, as established in Phase Ia. The RDE will be selected upon completion of the Phase Ia dose escalation/expansion part.

- BI 907828: Oral administration, immediately before the administration of ezabenlimab.
- Ezabenlimab: Intravenous administration (i.v.).

See protocol section 4.1.

Study burden and risks

Burden/ possible risk:
- Worsening of the disease
- Patient may experience side effects or adverse events of the study drug
- Patient may experience discomfort due to the procedures and measurements during the study
- Additional procedures and measurements will be performed (outside SoC), as described in the protocol
- Participating in the study will take extra time
- Patient will be asked to undergo fresh tumor biopsy
- Patient needs to adhere to the study schedule

The procedures that will be performed in this study are described in section E4, E5 and E6 of this ABR.

Possible benefit:
- The study medication may improve the symptoms associated with the respective malignancy
- Participation in the study helps researchers gain a better understanding of the disease.

See section 1.4 of the protocol for the benefit-risk assessment.

Contacts

Public
Boehringer Ingelheim

Basisweg 10
Amsterdam 1043AP
NL
Scientific
Boehringer Ingelheim

Basisweg 10
Amsterdam 1043AP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Provision of signed and dated, written informed consent form ICF in accordance with ICH-GCP and local legislation prior to any trial-specific procedures, sampling, or analyses.
2. Male or female >=18 years old at the time of signature of the ICF.
3. ECOG performance status of 0 or 1.
4. Life expectancy of at least 12 weeks after the start of the treatment according to the Investigator*s judgement.
5. Patients with radiologically documented disease progression or relapse during or after all standard of care treatments. Patients who are not eligible to receive standard of care treatments, and for whom no proven treatments exist, are eligible.
6. Previous treatment with an anti-PD-1/PD-L1 mAb is allowed as long as the last administration of the anti-PD-1/PD-L1 mAb on the previous treatment occurred a minimum of 28 days prior to the first administration of study treatment.

7. Patient must be willing to participate in the blood sampling for the PK, PD, and tumor mutation analysis.
8. Adequate organ function defined as all of the following (all screening labs should be performed locally within 10 days of treatment initiation):
Absolute neutrophil count >=1.5 x 10^9/L (or >= 1.5×10^3/µL or >= 1500/mm^3)
Platelets >=100 x 10^9/L (or >= 100×10^3/µL or >= 100×10^3/mm^3)
Hemoglobin >=8.5 g/dL or >=5.3 mmol/L (red blood cell transfusion allowed to meet eligibility criteria) or >= 85 g/L
Total bilirubin <= 1.5 times the upper limit of normal (ULN), (patients with Gilbert*s syndrome, total bilirubin must be <=3 x ULN)
AST and ALT <=2.5 x ULN OR <=5 x ULN for patients with liver metastases
Creatinine <=1.5 x ULN
Patients may enter if creatinine is >1.5 x ULN and estimated glomerular filtration rate (eGFR) >50 mL/min (assessed by Chronic Kidney Disease Epidemiology [CKDEPI] Collaboration equation); confirmation of eGFR is only required when creatinine is >1.5 X ULN
International Normalised Ratio (INR) or Prothrombin Time (PT). Activated Partial Thromboplastin Time (aPTT) <=1.5 x institutional ULN. Patients taking low dose warfarin must have their INR
followed closely and according to institutional guidelines.
9. Women of childbearing potential (WOCBP), and men able to father a child must be ready and able to use two medically acceptable methods of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly beginning at screening, during trial participation and until certain time has passed after the last administration of trial medication:
- Women: 6 months and 12 days after end of BI 907828; 6 months after end of ezabenlimab.
- Men: 102 days after end of BI 907828; 6 months after end of ezabenlimab.
A list of contraception methods meeting these criteria is provided in the patient information.

Inclusion criteria 10-14 are only applicable to Phase I a.

The following inclusion criteria are only applicable to Phase I b:
15. At least one target lesion that can be accurately measured per RECIST 1.1. In patients who only have one target lesion, the baseline imaging must be performed at least two weeks after any biopsy of the target lesion.
16. Patients with TP53 wild-type status confirmed on tumor tissue.
17. Provision of fresh tissue biopsy at screening (may be omitted if patient has archival tissue within 12 months prior to enrolment) and willingness to provide fresh tissue biopsy on study, if safe and feasible on either occasion.
18. Patients with the following tumor types:
- Cohort 1: Patients with unresectable, advanced and/or metastatic TP53 wt selected subtypes of soft tissue sarcomas as listed below, who received at least one line of systemic medical treatment in the advanced and/or metastatic setting:

- Liposarcoma excluding dedifferentiated liposarcoma
- Undifferentiated pleomorphic sarcoma
- Myxofibrosarcoma
- Synovial sarcoma
- Leiomyosarcoma
- Cohort 2: Patients with unresectable, advanced and/or metastatic TP53 wt MDM2-amplified tumors as listed below, who received at least one line of systemic medical treatment in the advanced and/or metastatic setting:
- NSCLC (patients with NSCLC harboring genomic aberrations for which approved targeted therapy is approved and available, must have received such prior treatment)
- Gastric adenocarcinoma
- Urothelial carcinoma
- Biliary tract carcinoma (including cholangiocarcinoma, intra-and extrahepatic biliary tree, gall bladder and ampulla of vater)

See protocol section 3.3.2.

Exclusion criteria

Patients must not enter the trial if any of the following exclusion criteria are fulfilled:
1. Previous administration of BI 907828 or any other MDM2-p53 or MDMX (MDM4)-p53 antagonist.
2. In Phase Ib (expansion phase) and Phase Ia expansion cohort only: a documented aminoacid altering mutation in TP53 occurring in the patient*s tumor.
3. Symptomatic brain metastases.
Note: Patients with previously treated brain metastases may participate but treated lesions should not be used as target lesions.
4. Exclusion criterion 4 is not applicable for patients enrolled after protocol version 4 is approved.
5. Active bleeding, significant risk of haemorrhage (e.g. previous severe gastrointestinal bleeding, previous haemorrhagic stroke at any time), or current bleeding disorder (e.g. haemophilia, von Willebrand disease).
6. Major surgery (major according to the Investigator*s assessment) performed within 12 weeks prior to start of study treatment or planned within 12 months after screening (e.g. hip replacement).
7. Any other documented active or suspected malignancy or history of malignancy within 3 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix, or other local tumors considered cured by local treatment.
8. Patients who must or wish to continue the intake of restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial.
9. Currently enrolled in another investigational device or drug trial, or less

than 4 weeks since receiving other investigational treatments. Patients who are in follow-up/observation for another clinical trial are eligible.
10. Exclusion criterion 10 is not applicable for patients enrolled after protocol version 4 is approved.
11. Patients who have not recovered from all clinically significant adverse events from their most recent therapy or intervention prior to study enrolment.
12. Known history of human immunodeficiency virus (HIV) infection.
13. Any of the following known laboratory evidence of hepatitis virus infection:
o Positive results of hepatitis B surface (HBs) antigen
o Presence of HBc antibody together with HBV-DNA
o Presence of hepatitis C RNA
14. Known hypersensitivity to the trial drugs or their excipients.
15. Serious concomitant disease or medical condition affecting compliance with trial requirements or which are considered relevant for the evaluation of the efficacy or safety of the trial drug, such as neurologic, psychiatric, infectious disease or active ulcers (gastro-intestinal tract, skin) or laboratory abnormality that may increase the risk associated with trial participation or trial drug administration, and in the judgment of the Investigator, would make the patient inappropriate for entry into the trial.
16. Chronic alcohol or drug abuse or any condition that, in the Investigator*s opinion, makes them an unreliable trial patient or unlikely to complete the trial.
17. Women who are pregnant, nursing, or who plan to become pregnant while in the trial; female patients who do not agree to the interruption of breast feeding from the start of study treatment until 6 months and 12 days after last dose of study treatment.
18. History of (including current) interstitial lung disease or pneumonitis within the last 5 years.
19. History of severe hypersensitivity reactions to other monoclonal antibodies
20. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of study treatment.
21. Active autoimmune disease or a documented history of autoimmune disease, that requires systemic treatment, i.e. corticosteroids or immunosuppressive drugs, except vitiligo or resolved childhood asthma/atopy, alopecia, or any chronic skin condition that does not require systemic therapy; patients with autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone and/or controlled Type 1 diabetes mellitus on a stable insulin regimen are eligible.
22. Active infection requiring systemic treatment (antibacterial, antiviral, or antifungal therapy) at start of treatment in this trial.
23. Any of the following cardiac criteria:
- Mean resting corrected QT interval (QTc) >470 msec
- Any clinically important abnormalities (as assessed by the Investigator) in rhythm, conduction, or morphology of resting ECGs, e.g., complete left bundle branch block, third degree heart block
- Any factor that increases the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, family

history of long QT syndrome or unexplained sudden death under 40 years-of-age, or any concomitant medication known to prolong the QT interval
- Patients with an ejection fraction (EF) <50% or the lower limit of normal of the institutional standard will be excluded. Only in cases where the Investigator (or the treating physician or both) suspects cardiac disease with negative effect on the EF, will the EF be measured during screening using an appropriate method according to local standards to confirm eligibility (e.g., echocardiogram, multi-gated acquisition scan). A historic measurement of EF no older than 6 months prior to first administration of study drug can be accepted provided that there is clinical evidence that the EF value has not worsened since this measurement in the opinion of the Investigator or of the treating physician or both.

See protocol section 3.3.3.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	05-09-2022
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Brigimadlin
Product type:	Medicine
Brand name:	Ezabenlimab

Ethics review

Approved WMO Date:	04-07-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-10-2022
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-04-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	

Date:	28-08-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-12-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-02-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-05-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-511352-41-00
EudraCT	EUCTR2019-001173-84-NL
CCMO	NL81551.056.22