First-in-human, open-label, multicenter, Phase I/IIa, dose escalation trial with expansion cohorts to evaluate safety and preliminary efficacy of BNT142 in patients with CLDN6-positive advanced solid tumors

Published: 26-01-2023
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This study has been transitioned to CTIS with ID 2024-512639-58-00 check the CTIS register for the current data. _____PRIMARY OBJECTIVESFor Parts 1 and 2: To assess the safety and tolerability of BNT142 at all dose ...

Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON53910

Source
ToetsingOnline

Brief title
BNT142-01 (4781/0029)

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, tumors

Research involving
Human

Sponsors and support

Primary sponsor: BioNTech SE
Source(s) of monetary or material Support: industry/ the Sponsor as in B.7

Intervention

Keyword: BNT142, CLDN6, Phase 1/2

Outcome measures

Primary outcome

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PRIMARY ENDPOINTS

• Occurrence of TEAEs including Grade >=3, serious, or fatal TEAEs by causal relationship to trial treatment.
• Occurrence of dose reductions and discontinuation of BNT142 due to TEAEs.

• Occurrence of DLTs during the DLT evaluation period during the dose escalation.

• For part 2: ORR is defined as the proportion of patients in whom a confirmed CR or PR, per RECIST 1.1, and per GCIG criteria incorporating RECIST 1.1 and CA 125 for the ovarian cancer population is the best overall response.

Secondary outcome

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SECONDARY ENDPOINTS

• PK parameters including but not limited to AUC, CL and Vd, Cmax, tmax, Ctrough, Cmin.

• ORR (Part 1 only; this is a primary endpoint for Part 2) is defined as the proportion of patients in whom a confirmed CR or PR, per RECIST 1.1, is the best overall response.
• DCR is defined as the proportion of patients in whom a CR or PR or SD (per RECIST 1.1 [and per GCIG criteria for ovarian cancer patients], SD assessed at least 6 weeks after first dose) as best overall response.
• DOR is defined as the time from first objective response (CR or PR per RECIST 1.1) to first occurrence of objective tumor progression (progressive disease per RECIST 1.1) or death from any cause, whichever occurs first.

Study description

Background summary

Outcomes of standard of care (SOC) remain poor for patients with relapsed or refractory advanced solid tumors. Treatment options include further palliative chemotherapy, which might be less tolerated after previous repeated exposure to cytotoxic compounds, best supportive care, and investigational treatments without proven benefit. Therapy in this population is not curative, with an expected overall survival (OS) of a few months. The medical need therefore remains high for various cancer types in the relapsed or refractory advanced disease setting and addressing it with a novel targeted therapy against oncofetal antigen CLDN6 may offer a new treatment opportunity to patients.

To address this need, the sponsor has developed BNT142, an experimental therapeutic targeting CLDN6, based on the RiboMab platform. Currently, there are no approved anticancer therapies targeting CLDN6. Preclinical experiments with BNT142 show that the BNT142 (CCI)

Of the various formats of (CCI) antibodies that have been explored (Garber 2014), the most successful example is blinatumomab (BLINCYTO®), an anti-CD19/anti-CD3 bi-(scFv)2, approved for the treatment of relapsed/refractory B-cell precursor acute lymphocytic leukemia (Goebeler and Bargou 2020). However, single-chain variable fragment (scFvs) antibodies have manufacturing challenges, including poor solubility and stability, tendency to aggregate and wide variation of size and impurity profiles.
Importantly, due to the absence of the constant fragment (Fc) portion, the serum half-life of those antibodies is short, thus requiring infusion pumps for continuous delivery (Garber 2014). Preclinical data indicate that BNT142 shows a favorable PK profile with sustained exposure of the encoded RiboMabXXX and potent anti-tumor activity in human tumor xenograft-bearing mice, thus having the potential to circumvent these limitations.

The main purpose of Part 1 (Dose escalation), the Phase I dose escalation, is to determine the MAD/MTD and the RP2D, as well as safety, PK, PD, and preliminary efficacy of BNT142. The RP2D of BNT142 will then be tested further in Part 2 (Expansion), the Phase IIa expansion part of the trial to investigate preliminary efficacy signals in three cohorts of patients with advanced solid tumors. Eligibility for this trial requires CLDN6 expression in the patient*s tumor, enriching the trial populations for patients with a higher probability of benefit from BNT142 and excluding patients not expressing the tumor target.

Study objective

This study has been transitioned to CTIS with ID 2024-512639-58-00 check the CTIS register for the current data.

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PRIMARY OBJECTIVES

For Parts 1 and 2: To assess the safety and tolerability of BNT142 at all dose levels tested.

For Part 1: To identify the MAD/MTD/RP2D of BNT142 based on the occurrence of DLTs using the following definitions:
• The MTD is defined as the highest tolerated dose where less than 1/3 patients experience a DLT. The MAD is defined as the highest dose administered, where all dose levels were tolerated during dose escalation.
• The RP2D will be defined based on integrated evaluation of safety, tolerability, clinical benefit, PK, and PD data from all dose levels tested.

For Part 2: To evaluate the anti-tumor activity of BNT142 according to RECIST 1.1 and for ovarian cancer patients according to definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the GCIG.

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SECONDARY OBJECTIVES

For Part 1: To characterize the PK profile of the BNT142-encoded protein RiboMabXXX

For Parts 1 and 2: To evaluate the anti-tumor activity of BNT142 according to RECIST 1.1, and for ovarian cancer patients according to definitions for response and progression in ovarian cancer clinical trials incorporating RECIST 1.1 and CA 125 agreed by the GCIG.

Study design

This trial is an open-label, multicenter, Phase I/IIa, dose escalation, safety, and PK trial of BNT142 followed by expansion cohorts in patients with CLDN6-positive advanced tumors.

Intervention

The trial treatment consists of BNT142, which is an LNP-formulated mixture (CCI) BNT142 will be administered at up to ten or more dose levels (CCI).

(CCI)

Study burden and risks

The 'Risk assessment' is provided in the protocol, Section 2.3.1. An extract is provided below:

There is no previous human experience with BNT142, hence no risks in humans have been identified at this time.

As the BNT142-01 trial includes the FIH dose of BNT142, all precautions indicated when testing a new systemically active compound in a FIH trial will be taken, including choosing a patient population with a high medical need. There will be a minimum of 14 days between the first, second and third patient, and 3 days for the other patients, in the first two dose cohorts. (CCI) The trial will be conducted at centers experienced in FIH trials, and trial-related procedures will only be performed by qualified physicians and trained nurses. The sponsor will also prepare and train the investigators to closely monitor, dose delay, dose-reduce (where applicable) or withdraw patients based on AEs that may occur with BNT142. Furthermore, there will be regular safety data review by the sponsor and by the SRC to identify and evaluate potential safety concerns. All patients enrolled in this trial will be monitored by qualified healthcare professionals who will provide care and evaluate the patient*s response to the trial drug in terms of its safety.

Beyond that, the sponsor has performed a risk assessment based on non-clinical data to identify and assess risks specific to BNT142, related to either the translated protein, i.e., RiboMabXXX, or to the LNP-formulated RNA. In particular, the following data sources were used:
(i) in vitro assessments of binding specificity and T-cell activation by RiboMabXXX
(ii) RNA-LNP platform-based toxicity/tolerability studies in vitro and in vivo, and
(iii) non-clinical and clinical literature data published on other similar compounds either still in development or approved. This group of compounds encompasses drugs in the same drug class (RNA-based therapies), drugs with similar formulation (e.g., LNP) and drugs which are similar to the expressed protein (CCI) or have the same target (e.g., antibodies as well as cellular therapies targeting CLDN6).
...
In conclusion, the non-clinical and literature data collected so far do not show any potential unacceptable toxicities that cannot be mitigated or managed in the clinical setting.

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The 'Benefit assessment' is provided in the protocol, Section 2.3.2:
As summarized in Section 2.2, the poor treatment outcomes in patients with advanced solid tumors present an unmet medical need for more effective therapies. Preclinical in vivo and in vitro data show strong BNT142 anti-tumor activity against CLDN6-expressing tumor cells. This trial will determine the safety, PD, PK, and preliminary efficacy of BNT142 in relapsed or refractory CLDN6-positive advanced solid tumors. This information will provide the basis for subsequent trials, and thus ultimately support the development of a novel targeted therapy against oncofetal antigen CLDN6 that may offer a new treatment opportunity to patients.

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The 'Overall benefit/risk conclusion' is provided in the protocol, Section 2.3.3:
Taking into account the measures taken to minimize risk to patients participating in this trial, the potential risks identified in association with BNT142 are justified by the anticipated benefits that may be afforded to patients with advanced or metastatic solid tumors.
Additional information is provided in the BNT142 Investigator*s Brochure.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

For both parts:
• Histological or cytological documentation of a solid tumor that is metastatic or unresectable via a pathology report.
• CLDN6-positive tumor sample as assessed by central laboratory testing using a validated IHC assay (CCI) in formalin-fixed paraffin-embedded (FFPE) neoplastic tissues or alternatively from fresh tissue if archival tissue is unavailable.
If archival tissue samples from several points of time are available, the most recent one is preferred.

(CCI)

• Measurable disease per RECIST 1.1 (measurable per RECIST 1.1 or evaluable per Gynecologic Cancer Intergroup [GCIG] criteria for ovarian tumors).

For Part 1 (Dose escalation):
• Patients with advanced/metastatic ovarian (including fallopian tube and peritoneal), non-squamous NSCLC, endometrial, or testicular cancer, for whom there is no available standard therapy likely to confer clinical benefit, or patients with NOS tumors (as confirmed by histological diagnosis), rare tumors (defined as those occurring in <15 out of 100,000 people each year as per NCI guidelines) and CUP, not included in the pre-defined eligible tumor types.
Patients must have received all available standard therapies, including targeted therapies based on mutation status (per guidelines form the US Food and Drug Administration [FDA], American Society of Clinical Oncology [ASCO], European Society for Medical Oncology [ESMO] or local guidelines used at the site), and failed at least first line SOC therapy prior to enrollment.

(CCI)

Exclusion criteria

Patients who meet any of the following exclusion criteria will not be eligible for trial entry:

• Chemotherapy, or molecularly-targeted agents within 3 weeks or 5 half-lives (whichever is longer) of the start of trial treatment; immunotherapy/monoclonal antibodies within 3 weeks of the start of trial treatment; nitrosoureas, antibody-drug conjugates, or radioactive isotopes within 6 weeks of the start of trial treatment.
• Radiotherapy in the last 6 weeks prior to the first dose of BNT142 (excluding brain radiotherapy for which 3 weeks prior to the first dose of BNT142 is allowed). Previously irradiated tumor lesions cannot be considered as target lesions or nontarget lesions in this study.
• Concurrent systemic (oral or intravenous [IV]) steroid therapy >10 mg prednisone daily or its equivalent for an underlying condition apart from physiologic corticosteroid replacement therapy.
• Major surgery within 4 weeks before the first dose of BNT142.
• Ongoing or active infection requiring IV treatment with anti-infective therapy that has been administered less than 2 weeks prior to the first dose of BNT142.
• Prior treatment with a CLDN6 targeting therapy.
• Side effects of any prior therapy or procedures for any medical condition not recovered to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.5 Grade <=1, except for anorexia, fatigue, hyperthyroidism, hypothyroidism, and peripheral neuropathy which must have recovered to Grade <=2. Alopecia of any grade is allowed.
• Current evidence of new or growing brain or leptomeningeal metastases during screening. Patients with known brain metastases may be eligible if they:
* Had radiotherapy, surgery or stereotactic surgery for the brain metastases;
* Have no neurological symptoms (excluding Grade <=2 neuropathy);
* Have stable brain metastasis on the computer tomography (CT) or magnetic resonance imaging (MRI) scan within 4 weeks before signing the informed consent form (ICF); and
* Are not undergoing acute corticosteroid therapy or steroid taper. Notes: Patients with central nervous system (CNS) symptoms should undergo a CT scan or MRI of the brain to exclude new or progressive brain metastases. Spinal bone metastases are allowed, unless imminent fracture with cord compression is anticipated.
• Pregnant or breastfeeding or planning to get pregnant within 6 months of the last dose of BNT142.

Study design

Design

Study phase:	2
Study type:	Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2023
Enrollment:	14
Type:	Anticipated

Ethics review

Approved WMO Date:	26-01-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-08-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	09-04-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-06-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	CTIS2024-512639-58-00
EudraCT	EUCTR2021-005481-18-NL
ClinicalTrials.gov	NCT05262530
CCMO	NL83219.000.23