Phase I/IIa, first-in-human, open-label, dose escalation trial with expansion cohorts to evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of BNT141 as a monotherapy and in combination with other anti-cancer agents in patients with CLDN18.2-positive solid tumors

Published: 25-01-2023
Last updated: 07-04-2024

To assess the safety and tolerability ofBNT141 at different dose levels.To identify the maximum tolerated dose (MTD) or maximally administered dose (MAD) /recommended Phase IIdose (RP2D) of BNT141 based on theoccurrence of dose-limiting toxicities(...

Ethical review	Approved WMO
Status	Pending
Health condition type	Soft tissue neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON53640

Source
ToetsingOnline

Brief title
BNT141-01

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
CLDN18.2-positive solid tumors / malignant tumor

Research involving
Human

Sponsors and support

Primary sponsor: BioNTech SE
Source(s) of monetary or material Support: Industry namely BioNTech

Intervention

Keyword: BNT141-01, CLDN18.2, open-label, Phase I/11a

Outcome measures

Primary outcome

Occurrence of treatment-emergent adverse events

(TEAEs) within a patient including Grade >= 3, serious, fatal

TEAE by relationship.

Occurrence of dose reductions and discontinuation of

BNT141 due to TEAEs.

Occurrence of DLTs within a patient during the DLT

evaluation period

Secondary outcome

PK parameters including but not limited to area-under-theconcentration-

time curve (AUC), clearance (CL), volume of

distribution (Vd), maximum concentration (Cmax), time to

Cmax (tmax), measured concentration at the end of a dosing

interval [taken directly before next administration] (Ctrough), and half-life (t*).

Objective response rate (ORR) is defined as the proportion of patients in whom a complete response (CR) or partial response ([PR], per RECIST 1.1) is confirmed as best overall response.

Disease control rate (DCR) is defined as the proportion of patients in whom a CR or PR or SD (per RECIST 1.1, SD assessed at least 6 weeks after first dose) is observed as best overall response.

• Duration of 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.

Progression-free survival (PFS) is defined as the time from first dose of BNT141 to first objective tumor progression (progressive disease per RECIST 1.1), or death from any cause, whichever occurs first.

• Overall survival (OS) is defined as the time from first dose of BNT141 to death from any cause.

Correlation of CLDN18.2 expression level with clinical outcomes.

Evaluation of PD biomarkers compared to baseline.

Anti-drug antibodies [ADAs] response.

Evaluate pre-treatment lipid status and potential

influence on BNT141 response.

Study description

Background summary

The study drug is a possible treatment for patients with solid tumors that are called CLDN18.2. This type of tumor is expressed in various cancers and is involved in the growth of cancer cells. The outcome of the assessment of the CLDN18.2 status is used to select patients who might benefit from the treatment with BNT141.

Study objective

To assess the safety and tolerability of
BNT141 at different dose levels.

To identify the maximum tolerated dose (MTD) or maximally administered dose (MAD) /recommended Phase II
dose (RP2D) of BNT141 based on the
occurrence of dose-limiting toxicities
(DLTs) using the following definitions:
The MTD will be defined as the
highest tolerated dose, where less
than one-third of the patients
experience a DLT.
• The maximally administered dose
(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,
pharmacokinetic (PK), and PD
data, for all dose levels tested.
To characterize the PK profile of the
BNT141-encoded protein RiboMab01.
To evaluate the anti-tumor activity of

BNT141 according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Exploratory objectives
To evaluate the efficacy of BNT141.
To assess Claudin 18.2 (CLDN18.2) expression level as a potential biomarker to predict clinical response to BNT141.
To assess potential PD biomarkers of BNT141.
To evaluate the immunogenicity of BNT141.
To assess other exploratory markers that may be collected in the trial to better understand BNT141 treatment.

Study design

This trial is an open-label, multi-site, Phase I/Iia dose escalation, safety, and PK trial of BNT141 followed by expansion cohorts in patients with CLDN18.2-positive tumors. CLDN18.2 positivity will be determined by a central laboratory during the pre-screening phase using a validated immunohistochemistry assay, and is defined as moderate-tostrong CLDN18.2 expression.
The trial design consists of three parts.
Please refert to section 4 of the protocol

Intervention

The trial design consists of three parts:
• Part 1A is a dose escalation of BNT141 as monotherapy in patients with unresectable or metastatic CLDN18.2-positive solid tumors for which there is no available standard therapy likely to confer clinical benefit, or the patient is not a candidate for such available therapy. Patients must have received all available standard therapies and failed at least first-line standard of care (SOC) therapy prior to enrolment. The dose of BNT141 will be escalated until the MTD and/or RP2D of BNT141 as monotherapy are defined. Eligible tumor types are gastric cancer, gastroesophageal junction (GEJ) and esophageal adenocarcinoma, pancreatic, biliary tract (cholangiocarcinoma and gallbladder cancer), and mucinous ovarian cancers. Additionally, patients with specific tumors (including colorectal

cancer,
non-small-cell lung cancer, gastric subtype of endocervical adenocarcinoma) where
there is scientific evidence that the CLDN18.2 could be elevated can be tested for
CLDN18.2 expression.
• Part 1B is a dose escalation of BNT141 in combination with nab-paclitaxel and gemcitabine in patients with advanced unresectable or metastatic CLDN18.2-positive pancreatic adenocarcinoma or cholangiocarcinoma who are eligible for treatment with nab-paclitaxel and gemcitabine. Part 1B intends to define the MTD and/or RP2D of the combination.
• Part 2 (Expansion) consists of the following pre-defined expansion cohorts:
* CLDN18.2-positive unresectable locally advanced or metastatic pancreatic adenocarcinoma eligible for treatment with nab-paclitaxel and gemcitabine.
* CLDN18.2-positive unresectable locally advanced or metastatic cholangiocarcinoma eligible for treatment with nab-paclitaxel and gemcitabine.
Part 2 will be further defined via an amendment after careful evaluation of all available
safety, PK and PD, and efficacy data generated in Parts 1A and 1B by the Safety Review
Committee (SRC).

Study burden and risks

The trial is considered completed when all patients have had at least 12 months survival
follow up or are lost to follow up or have withdrawn consent or have died or the sponsor
discontinues the trial. However, the maximum trial duration is 3 years after the last
subject*s first treatment in the trial.

Please refer to the schedule of events in the protocol for more information

Contacts

Public
BioNTech SE

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

For all parts:
• Metastatic or unresectable solid tumor.
• Histological or cytological documentation of a solid tumor via a pathology report.
CLDN18.2-positive tumor sample defined as moderate-to-strong CLDN18.2 protein expression defined as intermediate (2+) to strong (3+) staining intensity in >= 50% of
tumor cells as assessed by central testing using a CLIA-validated immunohistochemistry assay in formalin-fixed, paraffin-embedded (FFPE) neoplastic tissues. New biopsies and archival bio-samples are allowed. Bone biopsies are not allowed. Cytology specimens (including fine needle aspirates) will
not be accepted for CLDN18.2 examination. If archival tissue samples from several
points of time are available, the most recent one is preferred. Patients with a lower
expression level or with CLDN18.2-negative cancers are not eligible.
Trial part-specific inclusion criteria:
• For Part 1A: Patients with solid tumors, for which there is no available standard
therapy likely to confer clinical benefit, or the patient is not a candidate for such
available therapy. Patients must have received all available standard therapies and

failed at least first-line SOC therapy prior to enrolment. Measurable or evaluable
disease per RECIST 1.1. Eligible tumor types are gastric cancer, gastroesophageal
junction (GEJ) and esophageal adenocarcinoma, pancreatic, biliary tract (cholangiocarcinoma and gallbladder cancer), and mucinous ovarian cancers. Additionally, patients with specific tumors (including colorectal cancer, non-smallcell
lung cancer, gastric subtype of endocervical adenocarcinoma) where there is scientific evidence that the CLDN18.2 could be elevated can be tested for CLDN18.2 expression.
• For Part 1B: Patients with advanced pancreatic adenocarcinoma or cholangiocarcinoma who are eligible for treatment with nab-paclitaxel and gemcitabine. Measurable or evaluable disease per RECIST 1.1.
• For Part 2 (Expansion):
* Cohort 1 - Pancreatic adenocarcinoma: pancreatic adenocarcinoma eligible for treatment with nab-paclitaxel and gemcitabine. Measurable disease per RECIST 1.1.
* Cohort 2 - Cholangiocarcinoma: cholangiocarcinoma eligible for treatment with nab-paclitaxel and gemcitabine. Measurable disease per RECIST 1.1.
(Page 5 of the protocol)

Exclusion criteria

Patients who meet at least one of the following exclusion criteria will not be eligible for trial
entry:
• Receiving: radiotherapy, 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
(excluding BNT141); nitrosoureas, antibody-drug conjugates, or radioactive isotopes within 6 weeks of the start of trial treatment. Palliative radiotherapy will be
allowed.
• Receives concurrent systemic (oral or intravenous [IV]) steroid therapy > 10 mg prednisone daily or its equivalent for an underlying condition. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form
of systemic treatment and is permitted.
• Major surgery within 4 weeks before the first dose of BNT141.
• Prior treatment with a CLDN18.2 targeting mAb other than BNT141.
• 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 BNT141.
• Side effects of any prior therapy or procedures for any medical condition not recovered to National Cancer Institute Common Terminology Criteria for AEs (NCICTCAE)
v.5 Grade <= 1, with the exception of 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 or leptomeningeal metastases may be eligible
if they have:
* Radiotherapy, surgery or stereotactic surgery for the brain or leptomeningeal metastases.
* No neurological symptoms (excluding Grade <= 2 neuropathy).
* Stable brain or leptomeningeal disease on the computer tomography (CT) or magnet resonance imaging (MRI) scan within 4 weeks before signing the informed consent form (ICF).
* Not undergoing acute corticosteroid therapy or steroid taper.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	30-09-2023
Enrollment:	58
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	BNT141

Generic name:	Ribonucleic Acid

Ethics review

Approved WMO Date:	25-01-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-04-2023
Application type:	First submission
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
EudraCT	EUCTR2022-001843-25-NL
ClinicalTrials.gov	NCT04683939
CCMO	NL83022.000.23