STATISTICAL ANALYSIS PLAN (SAP)

BNT141-01

Version:	Final v1.0	**Date:**	07 Sep 2023
Sponsor:	BioNTech SE		

Protocol number:	BNT141-01
Protocol title:	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
Short Title / Acronym	Safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy trial of BNT141 in patients with unresectable or metastatic CLDN18.2-positive gastric, pancreatic, ovarian and biliary tract tumors
Trial Phase	I/IIa
Protocol version:	4.0
Protocol date:	13 June 2022
Compounds:	BNT141
SAP version:	Final v1.0
SAP date:	07 September 2023
CRO name:	Syneos Health
SAP author:	PPD

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1. SAP APPROVAL

This SAP has been prepared, reviewed, and approved in accordance with the sponsor's standard operating procedures (SOP). Documentation of this process is filed in the trial master file (TMF).

I confirm that I have reviewed this document and agree with the content.

Approvals		
Syneos Health Approval		
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2. VERSION HISTORY

Table 1: SAP version history summary

SAP version	Approval date	Rationale
Final version 1.0	07 September 2023	Initial version

3. INTRODUCTION

This is a 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.

The clinical trial protocol (CTP) v5.0, released on 15 March 2023, had not been implemented yet when the sponsor decided to terminate the study. Therefore, the Statistical Analysis Plan (SAP) is based on the CTP v4.0.

The trial was planned to consist of three parts:

- Part 1A was a dose escalation of BNT141 as monotherapy in patients with unresectable or metastatic CLDN18.2-positive solid tumors for which there was no available standard therapy likely to confer clinical benefit, or the patient was not a candidate for such available therapy; patients had to have received all available standard therapies and failed at least first-line standard of care (SOC) therapy prior to enrolment; the dose of BNT141 were escalated until the maximum tolerated dose (MTD) and/or RP2D of BNT141 as monotherapy were defined.
- Part 1B was planned to be 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 were eligible for treatment with nab-paclitaxel and gemcitabine; it intended to define the MTD and/or RP2D of the combination.
- Part 2 (Expansion) was planned to consist of two pre-defined expansion cohorts:
  - CCI

Part 2 was planned to be 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).

The sponsor stopped the study early, while only patients under Part 1A had been recruited. Therefore, this SAP outlines the planned analyses for Part 1A in the CTP v4.0, dated 13 June 2023, including three amendments:

- Amendment 1 (03 March 2021): This update was issued before first patient was enrolled into the trial. Minor editorial changes, such as correction of typing errors requested by the Food and Drug Administration (FDA). Changes has no impact on the planned objectives or trial conduct.
- Amendment 2 (06 August 2021): This update was issued before first patient was enrolled into the trial. Specification of unique identifiers to the inclusion criteria, to

correct an error in the implementation of the change to DLT definitions in Section 6.6.1 of protocol and minor administrative changes which has no impact on the planned objectives or trial conduct.

- Amendment 3 (13 June 2022): Major changes that included clarifications of PK endpoints, update of eligible indications to include patients with specific tumors, update of end of trial and patient completion definitions, definition of SAE regarding inpatient hospitalization or prolongation of existing hospitalization, etc.

The last amendment 4, released on 11 April 2023, is described in the CTP v5.0.

In addition, the SAP defines and describes the statistical methodologies to ensure complete and appropriate analyses and allow valid conclusions regarding the study objectives of Part 1A in the clinical study report (CSR). It must be finalized prior to the database lock of the final analysis.

The analyses to support the SRC data are not a part of this SAP.

Up to the early trial termination decision, four dose decision meetings (DDM) were held on 21 June 2022, 25 October 2022, 10 January 2023 and 11 April 2023. In addition, one investigational brochure was released on 30 March 2023 and one ad hoc analysis was released on 21 July 2023.

Syneos Health will perform the statistical analyses (using SAS® software version 9.4 or higher, and/or other statistical software as required) and is responsible for the production and quality control of all tables, figures, and listings (TFLs) for the final delivery.

PK analyses will be performed using Phoenix WinNonlin® version 8.3.4, which is validated by Syneos Health. Details of the PK analysis and corresponding PK tables, figures and listings shells are provided in a separate analysis plan.

Templates for each unique table, figure and patient listing are provided in a separate document “Data Presentation Plan” (“DPP”).

3.1 Objectives and endpoints

Trial objectives and endpoints are listed in Table 2.

Table 2: Objectives and endpoints

Objectives	Endpoints
Primary objectives	**Endpoints**
To assess the safety and tolerability of BNT141 at different dose levels.	• Occurrence of treatment-emergent adverse events (TEAEs) within a patient including Grade ≥ 3, serious, fatal TEAE by relationship.

Objectives	Endpoints
	• Occurrence of dose reductions and discontinuation of BNT141 due to TEAEs.
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 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 pharmacodynamic data, for all dose levels tested.	• Occurrence of DLTs within a patient during the DLT evaluation period

Secondary objectives	Endpoints
To characterize the PK profile of the BNT141-encoded protein RiboMab[CCI].	• PK parameters including but not limited to area-under-the-concentration-time curve (AUC), clearance (CL), volume of distribution (V_d), maximum concentration (C_{max}), time to C_{max} (t_{max}), measured concentration at the end of a dosing interval [taken directly before next administration] (C_{trough}), and half-life ($t_{½}$).
To evaluate the anti-tumor activity of BNT141 according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.	• 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 (BOR). • Disease control rate (DCR) is defined as the proportion of patients in whom a CR or PR or Stable Disease (SD) per RECIST 1.1 (SD assessed at least 6 weeks after first dose) is observed as BOR. • 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 (PD) per RECIST 1.1 or death from any cause, whichever occurs first.

Objectives	**Endpoints**
Exploratory objectives	**Endpoints**
To evaluate the efficacy of BNT141.	• Progression-free survival (PFS) defined as the time from first dose of BNT141 to first objective PD (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
To assess Claudin 18.2 (CLDN18.2) expression level as a potential biomarker to predict clinical response to BNT141.	• Correlation of CLDN18.2 expression level with clinical outcomes
To assess potential Pharmacodynamic biomarkers of BNT141.	• Evaluation of Pharmacodynamic biomarkers compared to baseline.
To evaluate the immunogenicity of BNT141.	• Anti-drug antibodies (ADAs) response.
To assess other exploratory markers that may be collected in the study to better understand BNT141 treatment.	• Evaluate pre-treatment lipid status and potential influence on BNT141 response.

ADAs = Anti-drug antibodies; AUC = Area-under-the-concentration-time curve; BOR = Best overall response; CL = Clearance; C_{max} = Maximum observed serum concentration; CR = Complete response; C_{trough} = Measured concentration at the end of a dosing interval; DCR = disease control rate; DLTs = Dose limiting toxicities; DOR = Duration of response; MAD = Maximal administered dose; MTD = Maximal tolerated dose; ORR = Objective response rate; OS = Overall survival; PD = Progressive disease; PFS = Progression-free survival; PK = Pharmacokinetic; PR = Partial response; RECIST = Response Evaluation Criteria in Solid Tumors; RP2D = Recommended Phase II dose; SD = Stable disease; $t_{1/2}$ = Half-life; t_{max} = Time to C_{max}; TEAE = Treatment emergent adverse event.

3.2 Trial design

Trial 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-to-strong CLDN18.2 expression. The trial design was planned to consist of three parts: • **Part 1A was a dose escalation of BNT141 as monotherapy** in patients with advanced 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 had to

	have received all available standard therapies and failed at least first-line SOC therapy prior to enrolment. The dose of BNT141 was escalated until the MTD and/or RP2D of BNT141 as monotherapy were defined. Once the MTD was reached, up to 10 additional patients with CLDN18.2 expressing pancreatic and biliary tract cancers were planned to be enrolled at the MTD level to obtain additional data on safety, PK and PD. 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 was scientific evidence that the CLDN18.2 could be elevated could be tested for CLDN18.2 expression. • **Part 1B was planned to consist of a dose escalation of BNT141 in combination with nab-paclitaxel and gemcitabine** in patients with locally advanced unresectable or metastatic CLDN18.2-positive pancreatic adenocarcinoma or cholangiocarcinoma who were eligible for treatment with nab-paclitaxel and gemcitabine. Part 1B intended to define the MTD and/or RP2D of the combination. Once the MTD was reached, up to 10 additional patients with CLDN18.2-expressing pancreatic adenocarcinoma or cholangiocarcinoma were planned to be enrolled at the MTD level to obtain additional data on safety, PK and PD. The MTD of BNT141 in combination with nab-paclitaxel and gemcitabine in Part 1B had not to exceed the monotherapy BNT141 MTD determined in Part 1A. • **Part 2 (Expansion)** was planned to consist of the following pre-defined expansion cohorts: CCI [redacted] [redacted] The trial design in the expansion cohorts was planned to be either a Simon two-stage design or a Khan one-stage design.

	The sample size and statistical design was planned to be further defined via a protocol amendment, based on careful evaluation of all available safety, PK and PD, and efficacy data obtained in Parts 1A and 1B.
Trial duration	The trial was considered completed depending on the design for Part 2 or when all patients had had at least 12 months survival follow-up or were lost to follow-up or had withdrawn consent or had died or the sponsor discontinued the trial. However, the maximum trial duration was 3 years after the last patient's first treatment in the trial.
Trial population	A maximum of approximately 48 DLT-evaluable patients were planned to be enrolled to trial treatment in each of the trial Parts 1A and 1B, depending on the DLTs which may occur. Non-DLT evaluable patients were replaced. Once the MTD was reached, up to 10 additional patients with CLDN18.2 expressing pancreatic and biliary tract cancers were planned to be enrolled at the MTD level in Part 1A and up to 10 additional patients with CLDN18.2 expressing pancreatic adenocarcinoma and cholangiocarcinoma in Part 1B, to obtain additional data on safety, PK and PD.
Trial centers	Approximately 20 sites in Europe and North America. Additional sites could be included during the trial.
Investigational medicinal product (IMP):	
IMP	BNT141
Composition	BNT141 is CCI [redacted] for IV administration. Each vial is intended for single use. Detailed information is found in the Pharmacy Manual for BNT141-01.
Administration	IV administration
Dosage regimen	Part 1A (monotherapy dose escalation) followed a classical 3+3 design with a starting dose of 0.15 mg/kg, followed by 0.30 mg/kg, 0.60 mg/kg, CCI [redacted] once every 3 weeks (Q3W). Intermediate dose levels (CCI 0.45, CCI [redacted] mg/kg) could be used. Part 1B was planned to involve dose escalation of BNT141 in combination with nab-paclitaxel and gemcitabine and also followed the classical 3+3 design like in Part 1A. CCI [redacted]

	CCI [redacted] Nab-paclitaxel was planned to be administered IV CCI [redacted] of each 28-day cycle at a dose of CCI [redacted] and gemcitabine administered IV on CCI [redacted] of each 28-day cycle at a dose of CCI [redacted]. Part 2 (expansion) was planned to be further defined via an amendment.
Duration of treatment	Each treatment cycle at Part 1A had a duration of 3 weeks (21 d), given until treatment discontinuation. Each treatment cycle in Part 1B had a duration of 4 weeks (28 d) given until BNT141 discontinuation.
Planned number of patients	In trial Part 1A and 1B, the sample size was driven by the classical 3+3 trial design and was ranged from 2 to 6 DLT-evaluable patients per cohort depending on the occurrence of DLTs. In each of the Parts 1A and 1B, the sample size will be up to 48 DLT-evaluable patients. Non-DLT-evaluable patients will be replaced. Once the MTD was reached, up to 10 additional patients with CLDN18.2 expressing pancreatic and biliary tract cancers were planned to be enrolled at the MTD level in Parts 1A and up to 10 additional patients with CLDN18.2 expressing pancreatic adenocarcinoma and cholangiocarcinoma in Part 1B, respectively, to obtain additional data on safety, PK and PD. Sample size for Part 2 was planned to be provided in a protocol amendment.
Randomization and blinding	This was an open-label non-randomized trial.
Tumor assessment schedule	Tumor assessment (TA) occurred in Part 1A at screening, at Week 6 (± 7 d), then every 6 weeks (± 7 d) for 24 weeks, and every 12 weeks (± 7 d) thereafter until PD, and in part 1B, was planned to occur at screening, at Week 8 (± 7 d), then every 8 weeks (± 7 d) for 24 weeks, and every 12 weeks (± 7 d) thereafter until PD. TA was not performed at the beginning of the trial if last TA was within 4 weeks before C1D1 and these images can be used. Patients who discontinued treatment for reasons other than PD continued scheduled TAs at the same frequency as would have been followed if the patient had remained on trial treatment.

	The same imaging method (CT/MRI) had to be used for a patient throughout the trial. Imaging was assessed by an experienced radiologist at site using RECIST 1.1 criteria.

Schema (graphical representation of the trial):

3.3 Schedule of activities

See protocol Section 1.3 for the schedule of activities (SoA) and Appendix 5 of this SAP.

4. STATISTICAL HYPOTHESES

There is no formal statistical hypothesis being tested in this first-in-human trial.

The primary objectives of trial Part 1A are to assess the safety and tolerability and to identify the MTD and/or RP2D of BNT141.

The primary objective of trial Part 1B was planned to assess the safety and tolerability, and to identify the MTD and/or RP2D of BNT141 in combination with nab-paclitaxel and gemcitabine.

For Part 2, statistical hypotheses were planned to be defined in a protocol amendment.

5. INTERIM ANALYSES AND ANALYSIS SEQUENCE

A formal interim statistical analysis was not planned for Part 1 of the study.

However, data were reviewed for each dose escalation cohort in Part 1A by the SRC.

Up to the early trial termination decision, four DDMs were held on 21 June 2022, 25 October 2022, 10 January 2023 and 11 April 2023. In addition, one investigational brochure was released on 30 March 2023 and one ad hoc analysis was released on 21 July 2023.

6. SAMPLE SIZE DETERMINATION

The sample size for trial Part 1A and 1B was driven by the classical 3+3 trial design and ranged from 2 to 6 DLT-evaluable patients per cohort depending on the occurrence of DLTs. In both trial Parts 1A and 1B, the sample size was up to 48 DLT-evaluable patients in each part depending on the DLTs, which may occur. Non-DLT-evaluable patients were replaced.

Once the MTD was reached, up to 10 additional patients with CLDN18.2 expressing pancreatic or biliary tract cancers were planned to be enrolled at the MTD level in Parts 1A and up to 10 additional patients with CLDN18.2 expressing pancreatic adenocarcinoma and cholangiocarcinoma in Part 1B respectively, to obtain additional data on safety, PK, and PD. Based on this sample size the probability to observe a particular AE with incidence of 15% would be 80.3%.

The final Part 2 sample size calculations was planned to be provided through an amendment when Part 2 design is available in the BNT141 CTP.

7. ANALYSIS SETS AND SUBGROUPS

7.1 Analysis sets

The following analysis sets are defined:

Table 3: Definitions of analysis sets

Analysis set	Description
Screened Set	All patients who signed informed consent form.
Treated Set	All patients who received IMP (i.e., at least one dose of BNT141).
Safety Set	All patients who received IMP (i.e., at least one dose of BNT141).
DLT Evaluation Set	All patients from the Safety Set who either have completed the DLT evaluation period and meet the minimum exposure criterion or have experienced a DLT during the DLT evaluation period (21 d for Part 1A,). Patients who do not experience any DLT during the DLT observation period are considered to be evaluable if they have been observed for minimum 21 d for Part 1A following the first target dose and are considered to have sufficient safety data to conclude that a DLT did not occur. A patient is considered to have met the minimum exposure criterion in Part 1A if the relative dose intensity of BNT141 in Cycle 1 is at least 80%. Patients who are excluded from the DLT Evaluation Set will be replaced. This analysis set may only be used in Part 1 of the trial.
Pharmacodynamic Set	All patients with baseline and at least one valid on-treatment/post-treatment pharmacodynamic assessment.
Pharmacokinetic Set	All patients with baseline and at least one valid on-treatment/post-treatment PK assessment.

DLT = Dose limiting toxicity; IMP = Investigational medicinal product.

The DLT Evaluation Set will be used for the evaluation of DLTs in order to assess the MTD and RP2D. The Safety Set will be used for all other safety analyses. The Treated Set includes all patients who received at least one complete/partial dose of BNT141. The Treated Set will be used for demographics, disease characteristics, medical history, prior and concomitant medication, other medical procedures, and efficacy analyses. The Screened Set and Treated Set will be used for disposition as applicable.

7.2 Protocol deviations

Protocol deviation management for this study is detailed in the trial specific Protocol Deviation and Non-compliance Management Plan. According to this plan, protocol deviations or site non-compliance are documented concisely in the Medidata Clinical Trial Management System (CTMS) and periodically reviewed as part of the project oversight by a wider trial team.

Protocol deviations are failures to adhere to the inclusion/exclusion criteria and protocol requirements and will be classified into major protocol deviations and minor issues.

- Major protocol deviations are a subset of protocol deviations that may significantly affect the completeness, accuracy, and/or reliability of the trial data or that may significantly affect a patient's rights, safety, or well-being. For example, major protocol

deviations may include enrolling patients in violation of key eligibility criteria designed to ensure a specific patient population or failing to collect data necessary to interpret primary endpoints, as this may comprise the scientific value of the trial.

- Minor issues are any non-compliance that does not adversely affect the study or process (i.e., does not meet the definition of major).
- Major protocol deviations will be identified by trial team review during the Data Review Meeting (DRM) prior to database lock.

Additional major protocol deviations may be defined at the Data Review Meeting (DRM) prior to database lock. During the DRM, protocol deviations as specified in this section of the SAP and all protocol deviations as reported in the CTMS system will be evaluated.

Major protocol deviations will be summarized by dose cohort, country, site, and deviation type for the Treated Set.

All major protocol deviations will be listed.

7.2.1 Protocol deviations due to COVID-19

Protocol deviations related to COVID-19 are documented in the CTMS with the preface “COVID-19” in the deviation description.

COVID-19 related protocol deviations are, for example:

- COVID-19, Visit xx on date xx of patient not conducted due to site facility re-organization related to COVID-19 disruption.
- COVID-19, missing Visit xx due to patient affected by COVID-19

The following listings of protocol deviations due to COVID-19 will be generated for the Treated Set to report the impact of COVID-19 on patients enrolled in this study:

- Patients impacted by COVID-19 related trial disruption.
- Missing visits due to COVID-19.

7.3 Subgroups

No subgroup analysis is planned for Parts 1A. This section was planned to further describe potential subgroup analysis for Part 2 through amendment when Part 2 design is available in the BNT141 CTP.

8. STATISTICAL ANALYSES

8.1 General considerations

In general, statistical analysis will be performed by dose cohort for Part 1A according to the IMP dose level CCI [redacted].

Continuous variables will be summarized using the following descriptive statistics: number of patients (n), mean, standard deviation, median, minimum, and maximum.

Categorical variables will be summarized using absolute and relative frequencies (n and %) of patients in each category. A “missing”’ category will be presented where applicable, if there is one or more missing value, with exception of by-visit summaries.

Baseline is defined as last available value prior to first dose of IMP.

Generally, only measurements at scheduled visits will be summarized and included in the tables by visit. Measurements at unscheduled visits will be included only in the listings, unless specified otherwise.

All enrolled patients will be included in the final analysis.

All relevant data will be listed. The listings will be sorted by dose level, patient number and date/time of assessment/event (if applicable). Unscheduled measurements will be included in the listings.

Programming considerations of planned summary tables, figures and listings and templates for each unique table and patient listing are provided in a separate document “DPP”.

8.1.1 Key definitions

Date/time of first IMP dose:

Is defined as date/time of first administration of BNT141.

DLT evaluation period:

The DLT evaluation period is defined as Cycle 1, i.e., 21 days for Part 1A.

For detailed definition of DLT see protocol Section 6.6.1.

Baseline Definition:

Baseline is defined as last available value prior to first dose of IMP (i.e., prior to the date and time of the first administration of IMP). Unscheduled measurements prior to the first dose of IMP will be considered in the derivation of the baseline values.

Change from baseline:

Change from baseline will be calculated as follows:

- Change from baseline = post-baseline assessment value – baseline assessment value.

Change from pre-treatment:

Change from pre-treatment will be calculated as follows:

- Change from pre-treatment = post-treatment assessment value at visit X – pre-treatment assessment value at visit X. Will be defined for each post-treatment assessment.

Age (in years) at date of informed consent:

Age is derived in the database based on the collected Year of birth as follows:

Age = (Informed consent Date – (01July + Year of birth)) / 365.25.

Age as derived in the database will be analyzed.

Body mass index (BMI):

BMI will be calculated as follows:

BMI (kq/m^2) = Weight (kg) / Height (m^2).

Duration:

Duration will be calculated as follows:

Duration (days) = last observation date – first observation date + 1

For conversion of days to months or years the following rules will be applied:

- 1 month = 30.4375 days
- 1 year = 365.25 days

Time from initial diagnosis to enrollment (in months):

Date of initial diagnosis is collected in Month/Year. Missing day will be replaced with the first day of the month. In case month is not reported, month and date will be replaced with July, 1st.

Time from initial diagnosis to enrollment (months) will be calculated as:

(Informed consent date – imputed date of initial diagnosis) / 30.4375

Trial day:

Trial day is defined as follows:

If date of assessment is on or after the date of first IMP dose:

- Date of assessment/event – date of first IMP dose +1

If date of assessment is before date of first IMP dose:

- Date of assessment/event – date of first IMP dose

Laboratory values with "< xx" or "> xx":

Any laboratory assessment values given as "< xx" or "> xx" in the database will be imputed with the numeric value of xx without the sign for the calculation of descriptive statistics and the changes from baseline (e.g., a value of < 1 will be imputed as 1 for the calculations).

Start of Follow-up Period:

Patients discontinuing from treatment for any reason had safety follow-up visits 30 days (+5 days) and 60 days (±7 days) after the patient receives the last dose of BNT141. If the patient initiated new anti-cancer treatment within 60 days of the last dose of trial treatment, the safety follow-up visit was performed prior to starting new anti-cancer treatment. Once new anti-cancer treatment was initiated, the patient moved into Survival follow-up.

Information on survival follow-up, new anti-cancer therapy (including targeted therapy and immunotherapy) and cancer-related procedures were collected for all patients via telephone calls, patient medical records, and/or clinic visits from BNT141 treatment discontinuation and approximately every 12 weeks until death (unless the patient withdraws consent, or the sponsor terminates the trial).

Planned time points for safety and survival follow-up are provided in the schedule of activities, see protocol Section 1.3.

Pooling of centers:

No pooling of centers is planned for this trial.

Conventions for imputing missing/partially missing dates:

When computations on dates are to be performed, incomplete/missing dates will be imputed using the following rules,

- Missing day, month/year present: If the month/year is the same as the month/year of the first IMP administration date, then impute missing start dates with first IMP dose date. Otherwise, for dates corresponding to a start date, impute with the first day of the month and, for dates corresponding to a stop date, impute with the last day of the month.
- Missing month/day, year present: If the year is the same as the year of the first IMP dose date, then impute missing start dates with first IMP dose date. Otherwise, for

dates corresponding to a start date, impute with the first day of the year and, for dates corresponding to a stop date, impute with the last day of the year.

- Missing month/day/year: no imputation.
- In the case imputed start date is after stop date, imputed start date is further adjusted to be equal to stop date.

This imputation method will be applied to the following dates:

- Onset date of AEs (for identification of treatment-emergent AEs purpose), incomplete AE end dates.
- Medical history start or end date to define prior medical history and concomitant diseases.
- Date of prior/concomitant medication (start dates) to define prior and concomitant medication, incomplete stop dates of prior/concomitant medications.

8.1.2 Missing data

All reasonable efforts will be made to obtain complete data for all patients. However, missing observations may occur due to patients lost to follow-up or to noncompliance with required trial visits and/or assessments. Missing data will not be imputed, and data analysis will be performed based on the observed values, unless otherwise specified.

8.1.3 Visit windows

Every attempt was made to perform evaluations at the designated time point/visit. Visit windows for visits per cycles and for follow-up (FU) visits are defined in the SoA tables (see protocol Section 1.3 and Appendix 5). All visits will be summarized according to the nominal visit.

8.2 Patient disposition

For the Screened Set, the number of patients screened, the number and percentage of patients who were eligible, those who were treated will be summarized by country, and site.

For the Treated Set, the number and percentage of treated patients included in each analysis set (i.e., Safety Set, DLT Evaluation Set, PK Set and PD set), the number and percentage of patients being excluded and the reasons for exclusion will be summarized by dose cohort.

For the Treated Set, the treatment status will be reported by dose cohort, including the number and percentage of patients having prematurely discontinued and the primary reason for premature treatment discontinuation of the IMP (e.g., AEs, disease progression, death, withdrawal of consent, lost to follow-up).

Further, the number and percentage of patients entered safety follow-up period and survival follow-up period as well as end of trial and the primary reason for discontinuation from the trial will be summarized by dose cohort. Total number of deaths will be presented by dose cohort.

All patient disposition data will be listed. Patients excluded from any of the analysis sets and the reason for exclusion from the analysis sets will be listed. In addition, screening failures patients along with their reason of screening failure will be listed. A listing of all inclusion and exclusion criteria that were not met, based on the Screened Set will be generated as well.

8.3 Baseline characteristics

8.3.1 Demographics and baseline characteristics

Demographic and baseline variables will be summarized for patients in the Treated Set. Age (years), weight (kg), height (cm), body mass index (kg/m^2), BSA (m^2) and Glomerular filtration rate (mL/min/1.73 m^2) will be summarized as continuous data. Age (<65 years, ≥65 years, ≥65 - <75 years, ≥75 years), Sex (male or female), Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reportable, Unknown), race (Black or African American, American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, White, Not Reported), BMI categories (<18 kg/m^2, ≥18 kg/m^2 - <25 kg/m^2, ≥25 kg/m^2 - <30 kg/m^2, ≥30 kg/m^2) and substance use as current alcohol use (yes, no) and current other drug abuse (yes, no) will be summarized as categorical data by dose cohort.

A listing of demographics and baseline characteristics will be provided for the Treated Set.

8.3.2 Disease characteristics

Disease characteristics will be summarized for patients in the Treated Set.

Time from initial diagnosis to enrollment (month), and time from most recent disease progression to first IMP dose (month) will be summarized as continuous data by dose cohort.

Cancer type, cancer grade, tumor stage (American Joint Committee on Cancer [AJCC], current version) at initial diagnosis, Tumor, Nodes and Metastasis (TNM) classification at initial diagnosis, Tumor status at trial entry, and Eastern Cooperative Oncology Group performance status (ECOG PS) at baseline will be summarized as categorical data by dose cohort.

Further, on the basis of the initial tumor assessment (based on RECIST 1.1) reported at the Screening visit, the following variables will be reported:

- Disease characteristics – Imaging: target lesions (absent/present), non-target lesions (absent/present), location of target lesions and sum of target lesion diameters.

The tumor type concerning the CLDN18.2 expression level at screening will be summarized as follows: IC form signed for CLDN18.2 expression (yes/no), percentage of tumor cells with a CLDN18.2 expression of 2+/3+ (%) both as continuous and as categorical data (<50.0%, 50.0% - 75.9%, 76.0% - 90.0%, >90.0%), sample type (Fresh tumor biopsy / Archival FFPE tumor tissue), Anatomical location where the sample was collected (Colon / Esophagus / Liver / Lung, etc.), laterality (Left / Right) and type of biopsy (Core / Punch / Excisional).

Disease characteristics data will be listed for the Treated Set.

8.3.3 Medical history

Medical history data will be coded using MedDRA (version 25.0 or later version). The number and percentage of patients with a medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) in the Treated Set, without distinguishing between prior medical history and concomitant diseases.

A listing of medical history data will be provided for the Treated Set.

8.3.4 Prior anti-cancer treatments

Prior cancer surgeries will be coded using MedDRA version 25.0 or later version.

Prior systemic cancer therapies will be coded using the World Health Organization Drug Dictionary (WHO-DD) drug codes of the most recent version (WHO-DD Global B3 Sep2021 or later version) resulting in Anatomical-Therapeutic-Chemical (ATC) codes indicating therapeutic classification.

A table “Prior Systemic Cancer Therapies” will be generated for the line (number) of prior systemic cancer therapies and the following information of the last systemic therapy:

- setting (adjuvant, neoadjuvant, metastatic, maintenance, unknown),
- best response (CR, PR, PD, SD/Non-PD, NE, Unknown, Not Applicable),
- disease status at the end of therapy (CR, PR, PD, SD/Non-PD, NE, Unknown, Not Applicable),
- reasons for termination of the therapy (Toxicity/Intolerance, Disease Progression, Other, Unknown, Completion of therapy)

Prior cancer surgery, prior cancer radiotherapy and prior systemic cancer therapy will be listed for the Treated Set. In addition, a listing of systemic cancer therapy, including ATC therapeutic class (ATC level 2), ATC pharmacological class (ATC level 3), and chemical class (ATC level 4) will be generated.

8.3.5 Prior and concomitant medication

All medications will be coded using the WHO-DD drug codes of the most recent version (WHO-DD Global B3 Sep2021, or later version) resulting in ATC codes indicating therapeutic classification.

Prior and concomitant medications will be defined using start and stop dates recorded relative to the first and last IMP administration dates.

Prior medications will be defined as any therapy taken prior up to (but not including) the start date of first IMP administration.

Concomitant medications will be defined as any medication either ongoing at the start date of first IMP administration or with a start date on or after the first IMP administration date, including those taken during safety follow-up.

Concomitant medications will be summarized by ATC therapeutic class (ATC level 2), ATC pharmacological class (ATC level 3), and chemical class (ATC level 4).

All medications will be listed and flagged as “Prior” or “Concomitant” for the Treated Set, including ATC therapeutic class (ATC level 2), ATC pharmacological class (ATC level 3), and chemical class (ATC level 4).

8.4 Efficacy analyses

No efficacy analysis is planned for Part 1A.

8.4.1 Primary analysis

No primary efficacy endpoints are specified for this study. The analysis of the primary safety endpoints is described in Section 8.5.1.

8.4.2 Supplementary analyses

Not applicable.

8.4.3 Secondary analyses

Not applicable.

8.4.4 Exploratory analyses

No analysis of PFS and OS is planned for Part 1A.

8.4.5 Other exploratory endpoints

Cytokine assessment data will be listed. The other exploratory endpoints such as ADAs and PK lipids will be elaborated in the “Pharmacokinetic and pharmacodynamic analysis plan”.

8.5 Safety analyses

Safety analysis will be limited to Part 1A.

Safety data analyses include extent of exposure to trial treatment, AEs, occurrence of DLTs during dose escalation in Part 1A, clinical laboratory assessments, physical examination, vital signs, ECGs and ECOG performance status.

All safety analyses will be based on the Safety Set and will be summarized by dose cohort, except for the DLT(s) analysis which will be based on the DLT Evaluation Set.

All safety data will be listed for the Safety Set.

8.5.1 Primary safety endpoints

The primary safety endpoints are the occurrence of DLTs, treatment-emergent adverse events (TEAEs), adverse events of special interest (AESI) and serious adverse events (SAE) reported by causal relationship to trial treatment, grade, and seriousness according to NCI CTCAE v5.0. The number and percentage of patients with any DLT, TEAEs, AESIs and/or SAEs will be presented.

Moreover, a patient listing will be provided with all dose exposure data of all patients enrolled, and a listing of all recorded DLTs and/or adverse events (AE) will be presented including the reported term and SOC and PT terms coded using MedDRA®, start date/time and stop date/time, causal relationship, NCI CTCAE grade, and seriousness including dose exposure data.

8.5.2 Extent of exposure

Exposure to BNT141 (for Part 1A) will be analyzed by dose cohort using the safety set as well as the DLT Evaluation set for the following dose exposure variables:

- Number of cycles
- Actual treatment duration (week) defined as follows:

  (date of last dose - date of first dose + planned duration per cycle) / 7, where the planned duration (days) is defined as the planned time between two consecutive administrations.

  Actual treatment duration (month) defined as follows:

  (date of last dose administration - date of first dose administration + planned duration per cycle) / 30.4375, where the planned duration (days) is defined as the planned time between two consecutive administrations.

  Planned treatment duration (week) is defined as follows:

(number of cycles × planned duration per cycle) / 7, irrespectively if patient was treated or not, with the exception of the last cycle which will be counted only when a patient at least partially receives an assigned dose.

- For BNT141 planned duration per cycle is 21d for Part 1A. Actual cumulative dose CCI is defined as:

  sum of all administered doses.

- Planned cumulative dose CCI is defined as:

  sum of all planned doses, irrespectively if patient was treated at cycle or not.

- Dose intensity CCI is defined as:

  actual cumulative dose CCI / actual treatment duration (week)

- Planned dose intensity CCI is defined as:

  planned cumulative dose CCI / planned treatment duration (week)

- Relative dose intensity (RDI) (%) is defined as:

  Dose intensity CCI / planned dose intensity CCI x 100

RDI will be presented as continuous parameters as well as categorically as follows: number and percentage of patients with RDI of < 60%, 60 - < 80%, ≥ 80%.

Moreover, the number and percentage of patients with any dose modification, with any dose delay, with any dose reduction, and any drug interruption will be presented.

All study drug administration data will be listed. All the above-mentioned variables related to actual exposure will be listed as well.

8.5.3 Adverse events

AEs will be coded using the MedDRA® coding system (version 25.0 or later version) to get a SOC and PT for each AE and graded for severity using NCI CTCAE v5.0.

A TEAE is defined as any AE with an onset date on or after the first administration of IMP (if the AE was absent before the first administration of IMP) or worsened after the first administration of IMP (if the AE was present before the first administration of IMP). AEs with an onset date more than 60 days after the last administration of IMP will be considered as TEAEs only if assessed as related to IMP by the investigator. TEAEs will be summarized by dose cohort as well as overall.

AEs started prior to first administration of IMP or after last administration of IMP + 60 days and not assessed as related to IMP (follow-up AEs) will be included only in the AE listings.

<u>AE leading to permanent study treatment discontinuation</u>

AE leading to discontinuation are the AEs with the items "*Action taken*" ticked "Drug withdrawn".

AE leading to dose rate reduction

AE leading to dose rate reduction are the AEs with the items "*Action taken*" ticked "Dose rate reduced".

AE leading to dose reduction

AE leading to dose reduction are the AEs with the items "*Action taken*" ticked "Dose reduced".

AE leading to drug interruption

AE leading to drug interruption are the AEs with the items "*Action taken*" ticked "Drug interrupted".

In case a patient has an AE with missing relationship status, the event will be assumed to be related and associated with the treatment received in the summaries (will be listed as collected in the listings). No imputation for missing NCI-CTCAE grades and missing seriousness will be performed.

Dose limiting toxicities

In general, a DLT for a drug or other treatment is defined as an AE that prevents an increase of the dose level of that treatment.

For the purpose of dose escalation, the DLT monitoring period will be the 21 days of Cycle 1 per CTP v4.0.

Dose-limiting toxicities are outlined in protocol section 6.6.1. Serious AEs, non-serious Grade ≥ 3 non-hematological and hematological AEs as defined per DLT criteria and clinically significant abnormal laboratory values Grade ≥ 3 will be collected and considered as a DLT if assessed by the investigator to be **at least possibly related** to BNT141 for the Part 1A of the trial. Toxicities clearly not related to BNT141 (e.g., PD, comorbidity, etc.) will not be considered a DLT. The NCI-CTCAE v.5.0 will be used to grade the intensity of AEs. DLT will be presented in a listing.

Overall summary of adverse events

The number and percentage of patients reporting at least one TEAE will be summarized for each of the following AE types:

- Any AE
- AE related to BNT141
- Grade ≥3 AE

- Grade ≥3 AE related to BNT141
- AE related to trial procedure
- DLT
- AESI
  - Infusion-related reactions (IRR)
  - AESI related to liver function (AST, ALT, bilirubin)
- SAE
- SAE related to BNT141
- SAE leading to death
- Related SAE leading to death
- AE leading to permanent treatment discontinuation of BNT141
- AE leading to drug interruption of BNT141
- AE leading to dose rate reduction of BNT141
- AE leading to dose reduction of BNT141
- Related AE leading to permanent treatment discontinuation of BNT141
- Related AE leading to drug interruption of BNT141
- Related AE leading to dose rate reduction of BNT141
- Related AE leading to dose reduction of BNT141

Adverse events by SOC and PT

The number and percentage of patients will be summarized by SOC and PT as per MedDRA. If a SOC/PT is reported more than once for a patient, the patient will only be counted once for this SOC/PT. All AE summary tables will be sorted by descending frequency (%) by SOC, by PT within SOC, and count of events where applicable in the “Total” column. If the frequencies tie, the alphabetic order will be applied. The number of AE events will be summarized in the same table.

The following tables for TEAEs by SOC and PT will be generated:

- Any AE
- AE related to BNT141
- AE related to trial procedure
- Any SAE

- SAE related to BNT141
- Related SAE leading to death
- Any non-serious AE
- AE leading to drug interruption of BNT141
- Related AE leading to drug interruption of BNT141

In addition, the most frequent TEAEs concerning PT will be summarized by number and percentage of patients as well as number of events; most frequent is defined as TEAEs for PTs which occur in at least 10% of the patients in any of the displayed dose cohorts.

Adverse events by worst NCI-CTCAE grade

The number and percentage of patients with any TEAE will be summarized by worst NCI CTCAE grade by PT nested within SOC. If a TEAE is reported more than once by a patient for an SOC/PT, the patient will be counted for the worst grade for this SOC/PT. AEs with a missing grade will be presented in the summary table as a grade category of “missing”. TEAEs related to treatment will be analyzed by the worst NCI CTCAE grade as well.

The following tables for TEAEs by worst NCI CTCAE grade by PT nested within SOC will be generated:

- Any AE
- AE related to BNT141

Deaths

Treatment-emergent AEs leading to death will be listed. All deaths will be listed as well. Deaths within 30 days of last dose of trial treatment will be flagged.

Adverse events listings

All AEs will be listed. Further, all deaths, SAEs, all SAEs leading to death, AEs leading to permanent discontinuation of treatment and AESIs will be listed.

All DLTs will be presented with the reported term, PT and SOC, its time of onset, duration, and outcome, causal relationship, NCI CTCAE grade, and seriousness based on the DLT Evaluation Set.

8.5.4 Injection/infusion-related reactions and cytokine release syndrome

Injection/infusion-related reactions (IRRs) and cytokine release syndromes (CRS) will be listed.

8.5.5 Laboratory assessments

Clinical laboratory data to be summarized include hematology, blood chemistry, coagulation factors, urinalysis, and endocrine tests. The clinical laboratory parameters to be assessed are listed in Table 4.

All laboratory parameters are reported in the clinical database using local safety laboratories. Measurements and corresponding Low and High ranges will be converted into Standard International (SI) units. Values outside the normal ranges are classified as “Not clinically significant” or “Clinically significant” by the investigator.

The last available assessment on treatment is defined as the assessment at End of Treatment Visit or the last safety assessment on treatment in case of treatment discontinuation due to death or withdrawal of consent.

The last available assessment is defined as the assessment either at Safety FU-D30, Safety FU-D60 visit or the last safety assessment before discontinuation from trial.

Continuous clinical laboratory parameters at each scheduled visit and change from baseline to each post-baseline time point will be summarized using descriptive summary statistics for each parameter by dose cohort. These summaries will apply to hematology, blood chemistry, coagulation factors, endocrine tests and blood lipids.

The number and percentage of patients reporting markedly abnormal clinical laboratory values as reported by the investigator at any point on the trial will be summarized for each parameter by visit and dose cohort using the following categories as applicable: Clinically significant low, Low, Normal, High, Clinically significant high. These summaries will apply to hematology, blood chemistry, and coagulation factors.

Urinalysis dipstick results will be reported only by number of patients and percentage for each parameter by visit and dose cohort.

All clinical laboratory data will be presented in the data listings. Abnormal clinical laboratory values and clinically significant values as reported by the investigator will be flagged in the listing. Blood lipids, pregnancy assessment (including childbearing potential), and Hepatitis B and C data will be listed as well.

Table 4: Local laboratory assessments – overview

Laboratory assessments	**Parameters**			
Hematology	• Platelet count • Hemoglobin • Hematocrit • RBC count • WBC count	**Differential WBC count:** Neutrophils Lymphocytes Monocytes Eosinophils Basophils		
Blood chemistry	**Proteins:** Total protein Albumin Glucose CRP Urate BUN or urea	**Electrolytes:** Potassium Sodium Calcium Chloride Phosphate	**Liver:** Total and direct bilirubin ALP AST ALT LDH	**Kidney:** Creatinine eGRF
Coagulation factors	• aPPT • PT time • INR			
Urinalysis (dipstick)	• Specific gravity • pH • glucose • protein • blood • ketones			
Endocrine tests	• TSH • free-T3 • Total T3 • free-T4 • total T4			
Pregnancy test	• Urine or serum pregnancy test (females of childbearing potential only)			
Tumor marker	• CA 19-9			
Hepatitis B and C	• HbsAg • HCV (if positive for HCV RNA by PCR)			
Lipids	• Total cholesterol • LDL • VLDL • HDL • Triglycerides • Apolipoprotein E			

Time points and content of the reduced blood chemistry panel are detailed in protocol Section 1.3.

ALP = Alkaline phosphatase; ALT = Alanine aminotransferase; aPTT = Activated partial thromboplastin time; AST = Aspartate aminotransferase; BUN = Blood urea nitrogen; CA 19-9 = Cancer antigen 19-9; CRP = C-reactive protein; eGFR = Estimated glomerular filtration rate; EOT = End of treatment; FU = Follow-up; HbsAg = Hepatitis B surface antigen; HCV = hepatitis C virus; HDL = High density lipoprotein; INR = International normalized ratio; LDH = Lactate dehydrogenase; LDL = Low-density lipoprotein; PCR = Polymerase chain reaction; PT = Prothrombin; RBC = Red blood cell count; RNA = Ribonucleic acid; T3 = Triiodothyronine; T4 = thyroxine; TSH = Thyroid stimulating hormone; VLDL = Very low-density lipoprotein; WBC = White blood cell.

8.5.6 Physical examination

The complete physical examination includes, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.

Weight (kg) is measured and body surface area (BSA) calculated, based on height at screening, using the equation:

BSA (m2) = √((height [cm] x weight [kg])/3600).

The symptom-directed examination is based upon the symptoms displayed, i.e on any new or worsened clinically significant abnormalities since previous assessment [Y/N].

The scheduled visits and time points for assessments are presented in the SoA (see protocol Section 1.3).

All physical examination data will be listed.

Note: depending on timing (before or after signing the ICF for trial participation), the clinically significant findings of the physical examination are recorded as medical/surgical history or as AEs.

8.5.7 Vital signs

Vital sign parameters are diastolic blood pressure (mmHg), systolic blood pressure (mmHg), oxygen saturation (%), pulse rate (beats/min), respiratory rate (breaths/min) and body temperature (°C). The scheduled visits and time for assessments are presented in the SoA (see protocol Section 1.3 and Appendix 5).

Vital sign parameters at each time point, change from baseline to each post-baseline time point will be summarized using descriptive statistics for each dose cohort. Change in vital sign parameters from pre-treatment to each time point post treatment will be summarized as well.

The last available assessment on treatment is defined as the assessment at End of Treatment Visit or the last safety assessment on treatment in case of treatment discontinuation due to death or withdrawal of consent.

The last available assessment on trial is defined as the assessment either at Safety FU-D30, Safety FU-D60 visit or the last safety assessment before discontinuation from the trial.

Vital sign values for each parameter will be assigned an LNH classification according to whether the value is lower (L), within (N) or higher (H) the reference range for that parameter (Table 5).

Table 5: Normal ranges for vital signs

Parameter	Range
Systolic blood pressure	90-140 mmHg
Diastolic blood pressure	40-90 mmHg
Oxygen saturation	95 - 100%
Respiratory rate	10-22 Breaths/min
Pulse rate	60-100 bpm
Temperature	≤ 38 °C

All vital sign data and assigned LNH flag will be presented in the data listings.

8.5.8 Electrocardiogram (ECG)

ECGs parameters and the scheduled visits for assessment are presented in the SoA (see protocol Section 1.3 and Appendix 5).

ECG parameters, i.e., ventricular heart rate (HR) [bpm]), pulse rate (PR) [msec], QRS duration [msec], QT interval [msec], and corrected QT (QTc) interval (according to Frederica) [msec], at each visit and change from baseline to each post-baseline visit will be summarized using descriptive statistics by dose cohort. The mean of the triplicates at each visit will be applied.

In addition, investigators´ interpretations of ECG parameters will be summarized by visit, and the worst-case abnormality (1=Abnormality, CS / 2=Abnormality, NCS / 3=Normal) by visit will be used. The worst-case abnormality at one visit is considered Abnormality, CS, if at least one of the triplicates at the visit is Abnormality, CS. Otherwise, the worst-case abnormality is considered Abnormality, NCS, if at least one of the triplicates is Abnormality, NCS and there is no Abnormality, CS. The worst case is Normal, if none of the triplicates is abnormal.

QTc interval according to Frederica values will be classified according to the NCI CTCAE v5.0 where possible, and summarized once as a categorical variable over all treatment visits, including unscheduled visits.

Results for all ECG parameters will be presented in listings.

8.5.9 ECOG performance status

ECOG performance status (Table 6) will be assessed according to the SoA (see protocol Section 1.3).

The following ECOG performance status grades will be reported:

Table 6: ECOG performance status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Death

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982; 5: 649-655.
Available from: https://ecog-acrin.org/resources/ecog-performance-status

The number and percentage of patients in each ECOG performance status grade will be summarized by visit and dose cohort.

All ECOG performance status data will be listed. For each patient, the best and worst post-baseline assessment values will be flagged.

8.6 Pharmacokinetics (PK) analyses

8.6.1 Primary PK endpoints

No primary PK endpoints are specified.

8.6.2 Secondary PK endpoints

PK profile of intact BNT141-encoded protein RiboMab[redacted]

The analyses of PK parameters will be performed using the PK analysis set. Individual and mean (± standard deviation) serum and plasma concentration data will be tabulated and plotted over time by dose level.

PK parameters will be estimated from the serum concentration data using a non-compartmental analysis method and will include (but are not limited to): Cmax, tmax, t1/2, Vd, AUC0-t, and CL, and Ctrough. (see definitions in Appendix 3). These parameters will be listed by individual patient and summarized using descriptive statistics (means, medians, ranges, standard deviations, and coefficient of variation as appropriate) by cohort, as appropriate. Details of the PK analysis will be provided in “Pharmacokinetic and pharmacodynamic analysis plan”.

Population PK modeling approaches may be also considered and will be reported separately.

9. CHANGES TO PROTOCOL-PLANNED ANALYSES

As of the trial termination, patients have been recruited only to Part 1A per CTP v4.0, dated on 13 June 2022.

Therefore, this SAP describes the planned analysis and statistical methods for Part 1A only. The other major changes to the analyses planned in the CTP v4.0 are as follows,

- The analyses of shift from baseline to the worst post-baseline NCI-CTCAE grade in the clinical laboratory parameters were removed.
- The analyses of secondary efficacy endpoints were removed.
- The analyses of exploratory endpoints were removed, with the exception that cytokine, anti-drug antibody and PK lipids data will be listed.

10. QUALITY CONTROL

SAS programs are developed to produce output such as analysis data sets, summary tables, data listings, figures or statistical analyses. An overview of the development of programs is detailed in Syneos Health Developing Statistical Programs SOP (3907).

Syneos Health Developing Statistical Programs SOP (3907), Conducting the Transfer of Biostatistical Deliverables SOP (3908) and the SAS Programming and Validation Plan (version 3.0, dated 25 AUG 2021) describes the quality control procedures that are performed for all SAS programs and output. Quality control (QC) is defined here as the operational techniques and activities undertaken to verify that the SAS programs produce the output by checking for their logic, efficiency and commenting and by review of the produced output.

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U.S. National Comprehensive Cancer Network (NCCN 2020; available at https//www.nccn.org/professionals/physician_gls/pdf/prostate.pdf).

12. SUPPORTING DOCUMENTATION

12.1 Appendix 1: List of abbreviations

Abbreviation	***Definition***
AE	*Adverse Event*
ALP	*Alkaline Phosphatase*
ALT	*Alanine Transaminase*
ApoE	Apolipoprotein E
aPPT	*Activated partial thromboplastin time*
AST	*Aspartate Transaminase*
ATC	*Anatomical Therapeutic Chemical*
AUC	*Area-under-the-concentration-time curve*
BMI	*Body Mass Index*
bpm	*beats per minute*
BSA	*Body surface area*
C	*Cycle*
CA 19-9	*Cancer antigen 19-9*
CI	*Confidence Interval*
CLDN18.2	*Claudin 18.2*
CR	*Complete Response*
CRF	*Case Report Form*
CRO	*Contract Research Organization*
CRP	*C-Reactive Protein*
CRS	*Cytokine release syndrome*
CS	*Clinically Significant*
CT	*Computer tomography*
CTC	*Common Toxicity Criteria*
CTCAE v5.0	*Common Terminology Criteria for Adverse Events, version 5.0*
CTMS	*Clinical Trail Management System*
CTP	*Clinical Trial Protocol*
CTR	*Clinical Trial Report*
D	*Day of cycle*
DCR	*Disease control rate*
DLT	*Dose-limiting toxicity*
DOR	*Duration of response*

DPP	*Data presentation plan*
DRM	*Data Review Meeting*
CRF	*Case Report Form*
ECG	*Electrocardiogram*
ECOG	*Eastern Cooperative Oncology Group Performance Status*
EOT	*End of Treatment*
FDA	*Food and Drug Administration*
FFPE	*(Fresh) formalin-fixed paraffin-embedded*
FU	*Follow-up*
GEJ	*Gastroesophageal junction*
h	*Hour*
ICF	*Informed consent form*
ICH	*International Conference on Harmonization*
IMP	*Investigational Medicinal Product*
IRR	*Injection/infusion-related reaction*
LNH	*Low, Normal, High*
LNP	*Lipid nanoparticles*
MAD	*Maximally administered dose*
Max	*Maximum*
MedDRA™	*Medical Dictionary for Regulatory Activities*
CCI	[redacted]
Min	*Minimum*
mmHg	*millimeter of mercury*
MRI	*Magnetic resonance imaging*
MTD	*Maximally tolerated dose*
N	*Number of Patients*
n	*Number of Observations*
NA	*Not Applicable*
NCI	*National Cancer Institute*
NCS	*Not Clinically Significant*
NE	*Not Evaluable*
NCI-CTCAE	*National Cancer Institute - Common Terminology Criteria for Adverse Events*
ORR	*Objective Response Rate*

OS	*Overall Survival*
PD	*Progressive Disease*
PFS	*Progression-Free Survival*
PK	*Pharmacokinetic*
PR	*Partial Response*
PT	*Preferred Term*
PS	*Performance status*
QC	*Quality Control*
RBC	*Red Blood Cell*
RDI	*Relative dose intensity*
RECIST	*Response Evaluation Criteria in Solid Tumors*
RNA	*Ribonucleic acid*
RP2D	*Recommended phase 2 dose*
SAE	*Serious Adverse Event*
SAP	*Statistical Analysis Plan*
SAS	*Statistical Analysis Software*
SD	*Stable Disease; Standard Deviation*
SI	*International System of Units*
SoA	*Schedule of Activities*
SOC	*System Organ Class*
SOP	*Standard Operating Procedures*
SRC	*Safety Review Committee*
TEAE	*Treatment-Emergent Adverse Event*
TFL	*Tables, Figures and Listings*
TMF	*Trial Master File*
TSH	*Thyroid Stimulating Hormones*
V	*Visit*
WBC	*White Blood Cell*
WHO-DD	*World Health Organization Drug Dictionary*

12.2 Appendix 2: List of PK parameters

Parameter	***Definition***
AUC_{0-t}	*Area under the concentration versus time curve from time 0 to time t*
AUC_{0-inf}	*Area under the drug concentration-time curve, from time zero to infinity*
AUC_{0-504}	*Area under the drug concentration-time curve, from time zero to 504 hours after the start of the infusion*
AUC_{0-tau}	*Area under the drug concentration-time curve, from time zero over the dosing interval at steady-state (Tau = 504 hours corresponding to 3-weeks administration) after the start of the infusion*
CL	*Clearance*
C_{max}	*Maximum observed concentration*
C_{min}	*Minimum concentration of a drug observed*
$C_{max, ss}$	*Maximum observed concentration at steady-state*
$C_{min, ss}$	*Minimum concentration of a drug observed*
C_{trough}	*Concentration prior to next dose*
K_{el}	*Apparent terminal elimination rate constant, estimated by linear regression of the terminal elimination phase of the log-linear drug concentration-time curve*
t_{max}	*Time to reach the maximum observed concentration* C_{max}
$t_{max, ss}$	*Time to maximum observed concentration at steady-state*
$t_{1/2}$	*Terminal half-life*
V_{ss}	*Volume of distribution, estimated as* MRT_{inf} * *CL*
CL_{ss}	*Apparent clearance at steady state*
V_{ss}	*Volume of distribution at steady state*
$RAUC$	*Accumulation ratio for AUC*
RC_{max}	*Accumulation ratio for* C_{max}

12.3 Appendix 4: Schedule of activities

Following Table 1 – Table 6 are referred to those in the CTP v4.0dated on 13JUN2022.

Table 1: Schedule of activities and procedures: Part 1A – BNT141 monotherapy dose escalation

Treatment Cycle (21 d)	Pre-screening	Screening [1] ≤ 21 d prior Cycle 1 Day 1	Cycle 1						Cycle 2			Cycle 3					Cycle 4			Cycle 5, 7, 9 etc.	Cycle 6, 8, 10 etc.		EOT [2]	Safety FU1 30d after last dose	Safety FU2 60d after last dose	Survival FU Every 12 weeks	Unscheduled [3]
Day			1	2	3	4	8	15	1	8	15	1	2	4	8	15	1	8	15	1	1	8					
Visit window (days)						+1	±1	±1	+3	±1	±1	±3		±1	±1	±1	±3	±1	±1	±3	±3	±1		+5	±7	±14	
Administrative procedures																											
ICF for pre-screening	X																										
ICF for main trial		X																									
Demographics	X																										
Tumor tissue	X[4]		X[5]							X[6]																	
Eligibility	X	X																									
Medical history [7]		X																									
Clinical procedures/interventions																											
Height, body weight [8]		X	X				X	X	X	X	X	X			X	X	X	X	X	X	X		X	X	X		X
Physical examination [9]		X	X				X	X	X	X	X	X					X			X	X		X	X	X		X
Vital signs [10]		X	X				X	X	X	X	X	X					X			X	X		X	X	X		X
ECG [11]		X	X	X	X	X	X	X	X			X	X	X	X	X	X			X	X		X	X	X		X
Tumor assessments [12]		X									X	Refer to Footnote 12											X				
ECOG Performance Status		X	X						X			X					X			X	X		X	X	X		X
AEs [13]		X	X				X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X		X
Prior/concomitant medication [14]		X	X				X	X	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X		X
BNT141 administration [15]		CCI																									
New anti-cancer treatment [16]																							X	X	X	X	
Survival follow-up [17]																										X	
Local lab: Blood sample [18]		X	X	X			X	X	X	X	X	X	X				X			X	X		X	X	X		X
Local lab: Urine sample [18]		X	X						X			X					X			X	X		X	X	X		X
Central lab: Blood sample [19]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X		X

1 If ≥ 50% moderate-to-strong CLDN18.2 protein expression is detected, patient can enter the screening phase. For screening, all laboratory assessments must be performed ≤ 7 d prior the planned treatment start with BNT141. Results of SOC test or examinations performed prior to obtaining informed consent and within 21 d prior to Cycle 1 Day 1 may be used, such tests do not need to be repeated for screening.

2 If the patient has to go off treatment per treatment withdrawal criteria, the End of Treatment Visit should be performed as soon as possible after permanent discontinuation criteria but not later than 30 d after last dose (in this latter case, due to the End of Treatment Visit occurring close to Safety FU1, Safety FU1 can be skipped). The visit at which an imaging shows disease progression resulting in treatment discontinuation may be used as the End of Treatment Visit, at which time all assessment associated with the End of Treatment Visit should be performed.

3 Unscheduled visits can be performed at any time point when clinically indicated and can include assessments as indicated.

4 Both fresh and archival biopsies will be accepted.

5 Additional tumor tissue (10 µm thick tumor curls) should be sent from all patients receiving study drug to the central laboratory for further exploratory research on CLDN18-ARHGAP6/26 fusion.

6 On-treatment biopsy should be performed in patients where feasible/without a risk of complications for the patient. Preferred on Cycle 2 Day 8 (± 1 d), but can be performed at any time during the study treatment.

7 Medical history includes cancer history (including but not limited to, prior cancer therapies and procedures and tumor characteristics such as mutation status, cancer related somatic genomic alterations and germline status, other clinically relevant diseases, surgeries, use of alcohol and/or drugs abuse and, reproductive status).

8 Height will only be measured at screening. The body weight measurement taken at the visit prior to dosing should be used for IMP preparation.

9 Full physical examinations should be performed during screening, thereafter a symptom orientated limited physical examination should be performed.

10 Includes temperature, blood pressure (systolic and diastolic), heart rate, oxygen saturation and respiratory rate.

11 A 12-lead ECG will be performed in triplicate. Single ECG recordings may be obtained at an unscheduled time point as clinically indicated.

12 The same imaging method (CT/MRI) must be used for a patient throughout the trial at screening, at Week 6 (± 7 d), then every 6 weeks (± 7 d) for 24 weeks, and every 12 weeks (± 7 d) thereafter until disease progression. Tumor assessments will not be performed at the beginning of the trial if last tumor assessment was within 4 weeks before C1D1 and those images can be used. Imaging will be assessed by an experienced radiologist at site using RECIST 1.1 criteria and sent to an external service provider for storage. Monitoring of the liver and the spleen size will be performed as described in the Imaging Manual.

13 AEs/SAEs will be reported from the start of study drug treatment until Safety FU2. During pre-screening no AEs/SAEs will be reported, with the exception of AEs/SAEs related to the procedure of collection of a fresh biopsy.

14 Prior medications are any medications and non-drug therapies (see Section 6.5) used by the patient within 21 d prior to initiation of trial treatment and during screening. Concomitant medications are any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment (including prophylactic treatment after BNT141 administration and medications as a result of an adverse event). Prior/Concomitant medications and non-drug therapies include all previous and on-trial COVID-19 vaccinations.

15 BNT141 will be administered CCI

16 New anti-cancer treatments will be collected from treatment discontinuation until death (unless the patient withdraws consent or the sponsor terminates the trial).

17 Information on survival FU, new anti-cancer therapy and cancer-related procedures will be collected for all patients via telephone calls, patient medical records, and/or clinic visits approximately every 12 weeks until death (unless the patient withdraws consent or the sponsor terminates the trial). If the patient withdraws from trial, the trial staff may use a public information source (e.g., county records) to obtain information about survival status only.

18 Local laboratory assessments can take place one day prior to patient visit apart from Cycle 2 Day 1. The screening samples must be obtained within 7 d of Cycle 1 Day 1. All Day 1 samples must be taken before study drug administration. Additional safety laboratory assessments can be performed at any time point when clinically indicated and can include assessments as indicated. Local laboratory assessments are detailed in Table 3.

19 Central laboratory assessments are given in Table 2.

AE = adverse event; ARHGAP = Rho GTPase Activating Protein 6; CLDN = Claudin; COVID = coronavirus disease; CT = computer tomography; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; FU = follow-up; ICF = informed consent form; IMP = investigational medicinal product; MRI = magnetic resonance imaging; RECIST = Response Evaluation Criteria Solid Tumors; SAE = serious AE; SOC = standard of care.

Table 2: Schedule of central laboratory assessments (PK, PD, immunogenicity and lipids) for Part 1A – BNT141 monotherapy dose escalation

Treatment Cycle (21 d)	Cycle 1									Cycle 2						Cycle 3								Cycle 4, 6, 8 etc. [1]		EOT	Safety FU1	Safety FU2	Unscheduled
Day	1				2	3	4	8	15	1				8	15	1				2	4	8	15	1	8		30d after last dose	60d after last dose	
CCI										CCI						CCI								CCI					
Blood collection window [3]	-24h	+10m	±15m	±15m							+10m	±15m	±15m			-24h	+10m	±15m	±15m					-24h					
Visit window [3]							+1d	±1d	±1d	+3d				±1d	±1d	±3d					+1d	±1d	±1d	±3d	±1d		+5d	±7d	
Pharmacokinetics (PK)																													
PK RiboMab CCI (serum)	X	X	X	X	X	X	X	X	X	X				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK lipids (plasma) [4]	X	X [4]	X	X	X			X	X	X	X					X	X			X			X						X
Pharmacodynamics (PD)																													
Cytokines/ chemokines (serum) [4, 5]	X	X [4]	X	X	X	X	X			X	X	X	X			X	X	X	X	X	X			X					X
ADCC (serum)	X						X									X					X								X
CDC (serum)	X						X									X					X								X
Immunogenicity (serum)																													
Anti-CCI lipid antibodies	X							X		X				X		X						X		X	X	X	X	X	X
Anti-RiboMab CCI antibodies	X								X	X					X	X							X	X	X	X	X	X	X
Additional samples																													
Extra sample for further analysis [6]	X							X		X				X		X						X		X	X	X	X	X	X
Apolipoprotein E	X																												

The PK sampling schedule may be adapted based on dose escalation PK results. Samples will be analyzed centrally. For details, please see the Laboratory Manual.

1 PK, PD samples should be collected only every second cycle from Cycle 4 (Cycle 4, 6, 8). No PK, PD samples should be taken in Cycle 5, 7, 9 etc.

2 CCI

3 Investigators should adhere to the given time points. However, due to possible time deviations that may occur in clinical practice, those will not be reported as protocol deviations.

4 After start of infusion, an unscheduled sampling for cytokines or PK lipids may be considered if infusion-related reactions occur.

5 Cytokines/chemokines to be analyzed include, but are not limited to IFN-γ, IFN-α, TNF-α, IL-1b, IL-12, MCP-1, MIP-1b, IL-2, IL-15, and IL-6.

6 Samples will be used either for re-testing or for future analysis if required (see Section 8.9).

ADCC = antibody-dependent cellular cytotoxicity; CCI CDC = complement-dependent cytotoxicity; d = day; EOI = end of infusion; EOT = end of treatment; FU = follow-up; h = hour; IFN = interferon; IL = interleukin; m = minute; MCP = monocyte chemoattractant protein; MIP = macrophage inflammatory protein; TNF = tumor necrosis factor.

Table 3: Local laboratory assessments: Part 1A – BNT141 monotherapy dose escalation

Treatment Cycle (21 d)	Test to be done	Screening	Cycle 1				Cycle 2			Cycle 3		Cycle 4 onwards	EOT	Safety FU1	Safety FU2	Unscheduled
Day		≤ 21 d prior C1D1	1	2	8	15	1	8	15	1	2	1		30 d after last dose	60 d after last dose	
Visit window (days)					±1	±1	±3	±1	±1	±3		±3		+5	±7	
Hematology	RBC count, hemoglobin, hematocrit, platelet count, WBC count, differential WBC count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry	**Electrolytes**: sodium, potassium, chloride, phosphate, calcium **Liver**: total and direct bilirubin, ALP, ALT, AST, LDH **Kidney**: creatinine, eGFR **Proteins**: total protein, albumin, glucose, CRP, urate, BUN or urea	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation factors	PT, aPTT, INR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endocrine	TSH, free T3, total T3, free T4, total T4	X											X	X	X	X
Pregnancy test [1]	Urine or serum pregnancy test	X	X				X			X		X	X	X	X	X
Tumor marker [2]	CA 19-9	X								X		X	X			X
Hepatitis B and C	HbsAg, HCV (if positive for HCV RNA by PCR)	X														
Lipids	Total cholesterol, LDL, VLDL, HDL, triglycerides		X													
Urinalysis (dipstick)	pH, specific gravity, glucose, protein, ketones, blood	X	X				X			X		X	X	X	X	X

Local laboratory assessments can take place one day prior to patient visit apart from Cycle 2 Day 1. The screening samples must be obtained within 7 d of Cycle 1 Day 1. All Day 1 samples must be taken before study drug administration. Additional safety laboratory assessments can be performed at any timepoint when clinically indicated and can include assessments as indicated.

1 Serum pregnancy test for women of childbearing potential must be performed and documented as negative within 7 d of Cycle 1 Day 1. Urine or serum pregnancy test (for women of childbearing potential) will be performed at specified subsequent visits. If a urine pregnancy test is positive, hold dosing and confirm the result with a serum pregnancy test.

2 CA 19-9 measurements will be performed at screening, at Cycle 3 Day 1, then every 6 weeks (± 7 d) for 24 weeks, and every 12 weeks (± 7 d) thereafter until disease progression.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CA 19-9 = cancer antigen 19-9; CRP = C-reactive protein; d = days; eGFR = estimated glomerular filtration rate; EOT = end of treatment; FU = follow-up; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL = high-density lipoprotein; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; PCR = polymerase chain reaction; PT = prothrombin; RBC = red blood cell count; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; VLDL = very low-density lipoprotein; WBC = white blood cell.

Table 4: Schedule of activities: Part 1B – Combination dose escalation

Treatment Cycle [1] (28 d)	Pre-screening	Screening [2] ≤ 21 d prior C1D1	Cycle 1, 4, 7, etc.							Cycles 2, 5, 8, etc.						Cycles 3, 6, 9, etc.				EOT [3]	Safety FU1 30d after last dose	Safety FU2 60d after last dose	Survival FU Every 12 weeks	Unscheduled [4]
Day			1	2	3	4	8	15	22	1	8	15	16	18	22	1	8	15	22					
Visit window (days)							±1	±1	±1	+3	±1	±1			±1	±3	±1	±1	±1		+5	±7	±14	
Administrative procedures																								
ICF for pre-screening	X																							
ICF for main trial		X																						
Demographics	X																							
Tumor tissue	X[5]		X[6]								X[7]													
Eligibility	X	X																						
Medical history [8]		X																						
Clinical procedures/interventions																								
Height, body weight [9]		X	X				X	X		X	X	X				X	X	X		X	X	X		X
Physical examination [10]		X	X				X	X	X	X	X	X				X	X	X		X	X	X		X
Vital signs [11]		X	X				X	X	X	X	X	X				X	X	X		X	X	X		X
ECG [12]		X	X	X	X	X	X			X		X	X	X	X	X				X	X	X		X
Tumor assessments [13]		X	Refer to Footnote 13																	X				
ECOG Performance Status		X	X							X						X				X	X	X		X
AEs [14]		X	X				X	X	X	X	X	X				X	X	X		X	X	X		X
Prior/concomitant medication [15]		X	X				X	X	X	X	X	X				X	X	X		X	X	X		X
BNT141 administration [16]		CCI																						
Nab-paclitaxel + Gemcitabine [17]			X				X	X		X	X	X				X	X	X						
New anti-cancer treatment [18]																				X	X	X	X	
Survival follow-up [19]																							X	
Local lab: Blood sample [20]		X	X	X			X	X	X	X	X	X				X	X	X		X	X	X		X
Local lab: Urine sample [20]		X	X							X						X				X	X	X		X
Central lab: Blood sample [21]			X	X[22]	X[22]	X[22]	X	X[22]	X	X[22]	X[22]	X[22]	X[22]	X[22]	X[22]	X[22]	X[22]	X[22]	X[22]	X	X	X		X

1 Trial visits will be performed weekly for Cycles 1, 2 and 4 (Days 1, 8, 15, 22). After the first 4 cycles, trial visits will be performed at the days where BNT141 and/or nab-paclitaxel and gemcitabine are administered. Treatment will continue until disease progression and until protocol-defined treatment discontinuation criteria are met.
2 If ≥50% moderate-to-strong CLDN18.2 protein expression is detected, patient can enter the screening phase. For screening, all laboratory assessments must be performed ≤ 7 d prior the planned treatment start with BNT141. Results of SOC test or examinations performed prior to obtaining informed consent and within 21 d prior to Cycle 1 Day 1 may be used, such tests do not need to be repeated for screening.
3 If the patient has to go off treatment per treatment withdrawal criteria, the End of Treatment Visit should be performed as soon as possible after permanent discontinuation criteria but not later than 30 d after last dose (in this latter case, due to the End of Treatment Visit occurring close to Safety FU1, Safety FU1 can be skipped). The visit at which an imaging shows disease progression resulting in treatment discontinuation may be used as the End of Treatment Visit, at which time all assessment associated with the End of Treatment Visit should be performed.
4 Unscheduled visits can be performed at any time point when clinically indicated and can include assessments as indicated.
5 Fresh and archival biopsies will be accepted.
6 Additional tumor tissue (10 µm thick tumor curls) should be sent from all patients receiving study drug to the central laboratory for further exploratory research on CLDN18-ARHGAP6/26 fusion.
7 On-treatment biopsy should be performed in patients where feasible/without a risk of complications for the patient. Preferred on Cycle 2 Day 8 (± 1d), but can be performed at any time during the study treatment.
8 Medical history includes cancer history (including but not limited to, prior cancer therapies and procedures and tumor characteristics such as mutation status, cancer related somatic genomic alterations and germline status, other clinically relevant diseases, surgeries, use of alcohol and/or drugs abuse and, reproductive status).
9 Height will only be measured at screening. The body weight measurement taken at the visit prior to dosing should be used for IMP preparation.
10 Full physical examinations should be performed during screening, thereafter a symptom orientated limited physical examination should be performed.
11 Includes temperature, blood pressure (systolic and diastolic), heart rate, oxygen saturation and respiratory rate.
12 A 12-lead ECG will be performed in triplicate. Single ECG recordings may be obtained at an unscheduled time point as clinically indicated.
13 The same imaging method (CT/MRI) must be used for a patient throughout the trial at screening, at Week 8 (± 7 d), then every 8 weeks (± 7 d) for 24 weeks, and every 12 weeks (± 7 d) thereafter until disease progression. Monitoring of the liver and the spleen size will be performed as described in the Imaging Manual.
14 AEs/SAEs will be reported from the start of study drug treatment until Safety FU2. During pre-screening no AEs/SAEs will be reported, with the exception of AEs/SAEs related to the procedure of collection of a fresh biopsy.
15 Prior medications are any medications and non-drug therapies (see Section 6.5) used by the patient within 21 d prior to initiation of trial treatment and during screening. Concomitant medications are any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated treatment (including prophylactic treatment after BNT141 administration and medications as a result of an adverse event). Prior/Concomitant medications and non-drug therapies include all previous and on-trial COVID-19 vaccinations.
16 BNT141 will be administered CCI
17 Nab-paclitaxel and gemcitabine will be given per SmPC after administration of BNT141 CCI
18 New anti-cancer treatments will be collected from treatment discontinuation until death (unless the patient withdraws consent, or the sponsor terminates the trial).
19 Information on survival FU, new anti-cancer therapy and cancer-related procedures will be collected for all patients via telephone calls, patient medical records, and/or clinic visits approximately every 12 weeks until death (unless the patient withdraws consent or the sponsor terminates the trial). If the patient withdraws from trial, the trial staff may use a public information source (e.g., county records) to obtain information about survival status only.
20 Local laboratory assessments can take place one day prior to patient visit apart from Cycle 2 Day 1. The screening samples must be obtained within 7 d of Cycle 1 Day 1. All Day 1 samples must be taken before study drug administration. Additional safety laboratory assessments can be performed at any time point when clinically indicated and can include assessments as indicated. Local laboratory assessments are detailed in Table 6.
21 Central laboratory assessments are given in Table 5.
22 Cycles 1 to 3 only.

AE = adverse event; ARHGAP = Rho GTPase Activating Protein 6; CLDN = Claudin; COVID = coronavirus disease; CT = computer tomography; C1D1 = Cycle 1 Day 1; d = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FU = follow-up; ICF = informed consent form; IMP = investigational medicinal product; MRI = magnetic resonance imaging; SAE = serious AE; SmPC = summary of product characteristics; SOC = standard of care.

Table 5: Schedule of central laboratory assessments (PK, PD, immunogenicity and lipids) for Part 1B – Combination dose escalation

Treatment Cycle (28 d)	Cycle 1													Cycle 2									Cycle 3			Cycle 4, 7, 10, 13, 16, etc.		EOT	Safety FU1	Safety FU2	Unscheduled
Day	1				2	3	4	8	15	22				1	8	15				16	18	22	1	8	15	1	8		30d after last dose	60d after last dose	
CCI										CCI						CCI								CCI		CCI					
Blood collection window [2]	-24h	+10 m	±15 m	±15 m							+10 m	±15 m	±15 m			-24h	+10 m	±15 m	±15 m					-24h		-24h					
Visit window [2]							+1d	±1d	±1d	+3d				±1d	±1d	+3d					+1d	±1d	±1d	+3d	±1d	+3d	±1d		+5d	±7d	
Pharmacokinetics (PK)																															
PK RiboMab CC (serum)	X	X	X	X	X	X	X	X	X	X				X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PK lipids (plasma) [3]	X	X [5]	X	X	X			X	X	X	X					X	X			X			X								X
Pharmacodynamics (PD)																															
Cytokines/ chemokines (serum) [3, 4]	X	X [5]	X	X	X	X	X			X	X	X	X			X	X	X	X	X	X			X		X					X
ADCC (serum)	X						X									X					X										X
CDC (serum)	X						X									X					X										X
Immunogenicity (serum)																															
Anti-CCI lipid antibodies	X							X		X				X		X						X		X	X	X	X	X	X	X	X
Anti-RiboMab CC antibodies	X								X	X					X	X							X	X	X	X	X	X	X	X	X
Additional samples																															
Extra sample for further analysis [6]	X							X		X				X		X						X		X	X	X	X	X	X	X	X
Apolipoprotein E	X																														

The PK sampling schedule may be adapted based on dose escalation PK results. Samples will be analyzed centrally. For details, please see the Laboratory Manual.

1 CCI

2 Investigators must adhere to the given time points. However, due to possible time deviations that may occur in clinical practice, those will not be reported as protocol deviations.

3 After start of infusion, an unscheduled sampling for cytokines or PK lipids may be considered if infusion-related reactions occur.

4 Cytokines/chemokines to be analyzed include but are not limited to IFN-γ, IFN-α, TNFα, IL-1b, IL-12, MCP-1, MIP-1b, IL-2, IL-15, and IL-6.

5 Samples will be used either for re-testing or for future analysis if required (see Section 8.9).

ADCC = antibody-dependent cellular cytotoxicity; CCI CDC = complement-dependent cytotoxicity; d = day; EOI = end of infusion; EOT = end of treatment; FU = follow-up; h = hour; IFN = interferon; IL = interleukin; m = minute; MCP = monocyte chemoattractant protein; MIP = macrophage inflammatory protein; TNF = tumor necrosis factor.

Table 6: Local laboratory assessments: Part 1B – Combination dose escalation

Treatment Cycle [1] (28 d)	Test to be done	Screening	Cycle 1, 4, 7, etc.					Cycle 2, 5, 8, etc.			Cycle 3, 6, 9, etc.			EOT	Safety FU1	Safety FU2	Unscheduled
Day		≤ 21 d prior C1D1	1	2	8	15	22	1	8	15	1	8	15		30 d after last dose	60 d after last dose	
Visit window (days)					±1	±1	±1	±3	±1	±1	±3	±1	±1	±1	+5	±7	
Hematology	RBC count, hemoglobin, hematocrit, platelet count, WBC count, differential WBC count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Blood chemistry	**Electrolytes**: sodium, potassium, chloride, phosphate, calcium **Liver**: total and direct bilirubin, ALP, ALT, AST, LDH **Kidney**: creatinine, eGFR **Proteins**: total protein, albumin, glucose, CRP, urate, BUN or urea	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation factors	PT, aPTT, INR	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Endocrine	TSH, free T3, total T3, free T4, total T4	X												X	X	X	X
Pregnancy test [2]	Urine or serum pregnancy test	X	X					X			X			X	X	X	X
Tumor marker [3]	CA 19-9	X									X			X			X
Hepatitis B and C	HbsAg, HCV (if positive for HCV RNA by PCR)	X															
Lipids	Total cholesterol, LDL, VLDL, HDL, triglycerides		X														
Urinalysis (dipstick)	pH, specific gravity, glucose, protein, ketones, blood	X	X					X			X			X	X	X	X

Local laboratory assessments can take place one day prior to patient visit apart from Cycle 2 Day 1. The screening samples must be obtained within 7 d of Cycle 1 Day 1. All Day 1 samples must be taken before study drug administration. Additional safety laboratory assessments can be performed at any time point when clinically indicated and can include assessments as indicated.

1 Trial visits will be performed at Cycles 1, 2 and 4 (Days 1, 8, 15, 22). After the first 4 cycles, trial visits will be performed at the days where BNT141 and/or nab-paclitaxel and gemcitabine are administered. Treatment will continue until disease progression and until protocol-defined treatment discontinuation criteria are met.

2 Serum pregnancy test for women of childbearing potential must be performed and documented as negative within 7 d of Cycle 1 Day 1. Urine or serum pregnancy test (for women of childbearing potential) will be performed at specified subsequent visits. If a urine pregnancy test is positive, hold dosing and confirm the result with a serum pregnancy test.

3 CA 19-9 measurements will be performed at screening, at Week 8 (Cycle 3 Day 1), then every 8 weeks (± 7 d) for 24 weeks, and every 12 weeks (± 7 d) thereafter until disease progression.

ALP = alkaline phosphatase; ALT = alanine aminotransferase; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CA 19-9 = cancer antigen 19-9; CRP = C-reactive protein; d = days; eGFR = estimated glomerular filtration rate; EOT = end of treatment; FU = follow-up; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HDL = high-density lipoprotein; INR = international normalized ratio; LDH = lactate dehydrogenase; LDL = low-density lipoprotein; PCR = polymerase chain reaction; PT = prothrombin; RBC = red blood cell count; RNA = ribonucleic acid; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; VLDL = very low-density lipoprotein; WBC = white blood cell.

Signature: PPD

Email:

PPD [redacted]

[redacted]

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