STATISTICAL ANALYSIS PLAN (SAP)
BNT411-01

Version: Final 2.0 **Date:** 21 Feb 2024
Sponsor: BioNTech SE

Protocol number:	BNT411-01
Protocol title:	Phase 1/2a, first-in-human, open-label, dose-escalation trial with expansion cohorts to evaluate safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of BNT411 as a monotherapy in patients with solid tumors and in combination with atezolizumab, carboplatin and etoposide in patients with chemotherapy-naïve extensive-stage small cell lung cancer (ES-SCLC)
Protocol version:	6.0
Protocol date:	04 JUL 2023
Compound:	BNT411
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1 SAP APPROVAL

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

2 VERSION HISTORY

Table 1: SAP Version History Summary

SAP version	Approval date	Change	Rationale
Final v1.0	01 DEC 2021	Not applicable.	
Final v2.0	08 FEB 2024	Updated following an amendment to the BNT411-01 protocol (Protocol v5.0)	Protocol amendment
		Updated the signature page with the new trial team.	Team update
		Section 3.2 • Added clarification for investigational medicinal products of and non-investigational medicinal products of Part 1B.	Clarification
		Section 7 • Updated the wording for the classification of important protocol deviation.	Clarification
		Section 8.1 • Added clarification about the denominator that should be used for percentage calculations.	Clarification
		• Added details about how to handle partial anti-cancer therapy dates.	Clarification
		Section 8.2 • Added clarification that the screened patient summary table is not by cohort.	Clarification
		Section 8.3.1 • The weight at screening was replaced by the baseline weight for consistency with the other parameters.	Update
		Section 8.3.2 • The tumor stage and TNM stage at diagnosis and at baseline was removed from summary table as it is collected with free text in the electronic Case Report Form (eCRF).	Update
		Section 8.3.3 and Section 8.3.4 • The anatomical-therapeutic-chemical (ATC) level 5 has been replaced by ATC level 4.	Update
		Section 8.4.3: • Added clarification that the confirmation of complete response (CR) and partial response (PR) is required	Clarification

SAP version	Approval date	Change	Rationale
		• Added clarification about the minimum duration time of stable disease	Clarification
		• Added clarification that only the responses prior to start of new anti-cancer therapy are used for the determination of the best overall response.	Clarification
		Section 8.4.4:	
		• Added clarification for iDOR that for the date of first occurrence of objective tumor progression.	Clarification
		Section 8.5.4:	
		• Added temperature and weight in the vital signs summary table.	New analysis
		Section 8.6.1:	
		• Added urine PK.	New analysis
		• Added some details for the derivations of the PK parameters.	Clarification
		Section 8.6.2:	
		• Updated to clarify that due to the exploratory nature of this analysis the PD and Biomarkers analyses may be conducted if there is enough data.	Update
		Section 10.5 Appendix 5: Censoring Rules:	
		• Amended 'before' to 'not after'.	Update
		• Added clarification for some event or censoring rules.	Clarification
		• Added clarification about the derivations for two or more consecutive tumor assessments.	Clarification
		Section 10.7:	
		• Removed this section and the SAS code	Not required in SAP
		Section 3.1: Updated the applicable trial parts to each trial objective	
		Section 3.2: • Updated the planned number of patients • Updated the definition of end of trial Section 7.1: Removed the analysis set for mITT as it is applicable only for Part 2 of the trial Section 8.1: Removed the general considerations related to efficacy analysis Section 8.4: Removed the details pertaining to efficacy analysis and added the below statement:	Updated for protocol amendment v6.0

SAP version	Approval date	Change	Rationale
		"Owing to the heterogeneity of cancer types and limited number of patients in Part 1A and B, no efficacy analysis will be done in Part 1" Section 8.4.3: Removed the secondary efficacy analysis as this is no more applicable for Part 1 of the trial Section 8.4.4: Remove the exploratory analysis pertaining to efficacy as this is no more applicable for Part 1 of the trial	

3 INTRODUCTION

This is an open-label, multicenter phase 1/2a dose escalation, safety, pharmacokinetics (PK) and pharmacodynamics (PD) trial of BNT411 with expansion cohorts in a mixed population of patients with solid tumors. This statistical analysis plan (SAP) describes the detailed procedures for the planned statistical analyses for Part 1 of the trial for clinical trial protocol (CTP) v1.0 dated 30 SEP 2019, CTP amendment v2.0 dated 30 OCT 2019, CTP amendment v3.0 dated 07 MAY 2020, CTP amendment v4.0, dated 13 NOV 2020, CTP addendum related to the coronavirus disease (COVID)-19 pandemic v3.0, dated 04 JUN 2021, CTP amendment v4.1, dated 14 MAY 2021, CTP amendment v4.2, dated 24 JUN 2021 and CTP amendment v5.0, dated 11 JUL 2022 and CTP amendment v6.0 dated 04 JUL 2023 to support the completion of the Clinical Trial Report (CTR). Part 2 of the clinical trial is no longer applicable therefore is excluded from this SAP.

The statistical analyses will be conducted by BioNTech or ICON using SAS® software Version 9.4 or higher.

3.1 Objectives and endpoints

Table 2: Trial design

Objectives	Endpoints
Primary	
• For Parts 1 and 2: Assess safety profile	• Occurrence of Dose-Limiting Toxicities (DLTs) within a patient during the DLT evaluation period • Occurrence of treatment-emergent adverse events (TEAEs) within a patient including grade ≥3, serious, fatal TEAE by relationship • Occurrence of dose reduction and discontinuation of BNT411 within a patient due to TEAEs
• For Part 1: Determine MTD and/or RP2D	• Maximal tolerated dose (MTD) defined as the highest tolerated dose • Recommended Phase 2 dose (RP2D) based on integrated evaluation of safety, tolerability, clinical benefit, PK, and PD data, for all dose levels tested
Secondary	
• For Parts 1 and 2: Establish PK profile	• PK parameters Area-under-the-concentration-time curve (AUC), clearance (CL) and volume of distribution (V_D), maximum concentration (C_{max}), time to C_{max} (T_{max}), trough concentration (C_{trough}), and terminal half-life ($T_{1/2}$)
• For Part 2: Evaluate anti-tumor activity according to RECIST 1.1	• Objective response rate (ORR) defined as the proportion of patients in whom a complete response (CR) or partial response (PR) is observed as best overall response. • Disease control rate (DCR) defined as the proportion of patients in whom a CR or PR or stable disease

Objectives	Endpoints
	(assessed at least 6 weeks after first dose) is observed as best overall response. • Duration of response (DOR) defined as the time from first objective response (CR or PR) to the date of the first occurrence of objective tumor progression or death from any cause, whichever occurs first.
Exploratory	
• For Part 2: Evaluate anti-tumor activity according to iRECIST	• Immune ORR (iORR) defined as the proportion of patients in whom a (immune) CR (iCR) or (immune)PR iPR is observed as best overall response. • Immune DCR (iDCR) defined as the proportion of patients in whom a iCR or iPR or (immune) stable disease (assessed at least 6 weeks after first dose) is observed as best overall response. • Immune DOR (iDOR) defined as the time from first objective response (iCR or iPR) to the date of the first occurrence of objective tumor progression (immune confirmed progressive disease (iCPD)) or death from any cause, whichever occurs first.
• For Part 2: Evaluate preliminary efficacy	• Progression-free survival (PFS) defined as the time from first dose of BNT411 to first occurrence of objective tumor progression (per Response Evaluation Criteria in Solid Tumors [RECIST 1.1]), or death from any cause, whichever occurs first. • Overall survival (OS) defined as the time from first dose of BNT411 to death from any cause.
• For Parts 1 and 2: Preliminary assessment of biomarkers that might act as pharmacodynamics, anti-tumor, and safety indicators of activity of BNT411 monotherapy and in combination with chemotherapy and atezolizumab	• Changes in selected cytokines and other activation markers compared to baseline. • Changes in systemic and intra-tumoral immune response in blood and tumor tissue compared to baseline (e.g. immunophenotyping of immune cells in peripheral blood, absolute and relative changes compared to baseline in tissues and/or peripheral blood mononuclear cells [PBMCs]).

AUC, area-under-the-concentration-time curve; CL, clearance; C_{max}, maximum concentration; (i)CR, (immune) complete response; C_{trough}, trough concentration; (i)DCR, (immune) disease control rate; DLTs, dose-limiting toxicities; DOR, duration of response; iCPD, immune confirmed progressive disease; iRECIST (Protocol Appendix 6), immune RECIST; MTD, maximal tolerated dose; (i)ORR, (immune) objective response rate; OS, overall survival; PBMCs, peripheral blood mononuclear cells; PD, pharmacodynamic; PFS, progression-free survival; PK, pharmacokinetic; (i)PR, (immune) partial response; RECIST (Protocol Appendix 5), Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; (i)stable disease, (immune) stable disease; $T_{1/2}$, terminal half-life; TEAEs, treatment-emergent AEs; T_{max}, time to C_{max}; V_D, volume of distribution.

3.2 Trial design

This is an open-label, multicenter Phase 1/2a dose escalation, safety, PK and PD trial of BNT411 with expansion cohorts in a mixed population of patients with solid tumors. The trial consists of three parts: Part 1A, Part 1B and Part 2. An overview of the trial design is provided in Table 3.

Table 3: Trial design

	Part 1A	**Part 1B**	**Part 2**
Trial design	Part 1A will be a monotherapy dose escalation in patients with advanced solid cancers until the MTD and/or RP2D of BNT411 as monotherapy are defined.	Part 1B will be a combination dose escalation in patients with chemotherapy-naïve ES- SCLC until the MTD and/or RP2D of BNT411 in combination with atezolizumab, carboplatin and etoposide are defined.	Part 2 will consist of expansion cohorts in solid cancers based on data generated in Part 1A and Part 1B.
Trial population	Patients with advanced solid cancers	Patients with chemotherapy-naïve ES-SCLC	Patients with solid cancers
Geographic regions	North America and Europe	North America and Europe	North America, Europe and Israel
Investigational medical product(s)	Name: BNT411 Dose: according to dose levels outlined in Appendix 6 Schedule: Days 1, 8 and 15 of each 3-week treatment cycle (21 days) of the first 4 cycles. In the following cycles thereafter, administration will be every 3 weeks on Day 1 of each 3-week treatment cycle (21 days)	Name: BNT411 Dose: according to dose levels outlined in Appendix 6 Schedule: Days 2, 8 and 15 of each 3-week treatment cycle (21 days) of the first 4 cycles. In the following cycles thereafter, administration will be every 3 weeks on Day 2 of each 3-week treatment cycle (21 days)	Name: BNT411 BNT411 either as monotherapy or in combination with other anti-cancer agent. Dose: This will be initiated by a CTP amendment once RP2D is reached at the end of Part 1A and Part1B Schedule: This will be initiated by a CTP amendment

	Part 1A	**Part 1B**	**Part 2**
	Route of administration: 100 mL intravenous infusion.	Route of administration: 100 mL intravenous infusion. For the purpose of this trial, in the USA and UK, atezolizumab, carboplatin and etoposide are considered as non-investigational medicinal products (NIMPs). However, the individual drugs are considered as IMPs in Spain and Germany at the request of the competent authorities due to their use in combination with BNT411. Name: Atezolizumab Dose: recommended dosage is 1200 mg Schedule: Every 3 weeks Route of administration: IV infusion. Name: Carboplatin Dose: commercially available formulation and at the label-recommended doses Schedule: every 3 weeks until cycle 4 Route of administration: IV infusion. Name: Etoposide: Dose: commercially available formulation and at the label-recommended doses (100 mg/m^2)	Route of administration: intravenous infusion.

	Part 1A	**Part 1B**	**Part 2**
		Schedule: On Day 1 of each cycle, administered over 60 minutes following carboplatin administration. On Day 2 and Day 3 of each cycle, administered intravenously over 60 minutes. Route of administration: IV infusion. For combination with atezolizumab and chemotherapy, the administration will be in the following order: Day 1: Atezolizumab > Carboplatin > Etoposide Day 2: BNT411 > Etoposide Day 3: Etoposide	
Planned number of patients	• The number of patients for Part 1A is driven by the 3+3 trial design • Between 6 to 60 DLT-evaluable patients are planned to be enrolled in Part 1A.	• The number of patients for Parts 1B is driven by the 3+3 trial design • Between 6 to 30 DLT-evaluable patients are planned to be enrolled in Part 1B.	• This will be implemented through a CTP amendment.
Randomization and blinding	This is a non-randomized, open-label trial		The expansion cohort may be a single-arm cohort or a randomized cohort. This will be documented in a CTP amendment.
Tumor assessment schedule:	Efficacy will be assessed by on-treatment imaging at screening (within 21 days prior to visit Cycle 1 Day 1)/Baseline and Week 6 (+7 days), every 6 weeks (±7 days) for 48 weeks, and every 12 weeks (±7 days) thereafter until disease progression is assessed by the investigator (unless the investigator elects to continue treatment [see Section 8.5.1 of the CTP for conditions of continued		This will be implemented through a CTP amendment.

	Part 1A	**Part 1B**	**Part 2**
	treatment]), withdrawal of consent, trial termination by the sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy.		
Other features	Not applicable		

Part 1B is planned to start before the MTD/RP2D is reached in Part 1A using a bifurcated trial design. Bifurcation is planned to start when Part 1A BNT411 monotherapy dose level 5 (2.4 µg/kg) evaluation is completed and deemed safe. At this point, Part 1B would start with one dose level below (i.e., dose level 4 [1.2 µg/kg]). Based on nonclinical data, this dose level is the anticipated minimally efficacious dose. Atezolizumab, carboplatin and etoposide will be administered at fixed doses approved for the indication of extensive-stage small cell lung cancer (ES-SCLC). The dose level of BNT411 in Part 1B at any given time will always be one dose level below that in Part 1A.

In case the MTD for BNT411 monotherapy is identified prior to dose level 5, the bifurcation will start one dose level below the BNT411 monotherapy MTD dose level. The sponsor together with the Safety Review Committee (SRC) may explore intermediate dose levels to bifurcate from monotherapy to combination dose escalation based on safety, PK, PD and preliminary efficacy data generated.

In Part 2, once a dose level is deemed safe and endorsed by the SRC, additional patients can be included at a given dose level of either BNT411 monotherapy or combination in order to explore, e.g., early efficacy in other indications and/or PD signals. Furthermore, different doses and schedules might be explored during the dose escalation and/or expansion based on the data generated in the dose escalation.

Additional indication-specific solid cancer cohorts are implemented by CTP amendments.

The design of the trial is shown in Figure 1.

Dose escalation in Part 1A

The dose escalation starts with an accelerated phase consisting of single-patient cohorts followed by larger patient cohorts informed by a classical 3+3 design. The single-patient cohorts in the first three dose levels will be expanded to 3+3-patient cohorts in case of occurrence of grade ≥2 toxicities, or the occurrence of DLTs, or based on the decision of the sponsor's SRC based on safety data generated. In addition, in the single-patient cohort phase, the next cohort can only start once the DLT period for the previous dose level has been assessed and the next dose level is proposed by the SRC and endorsed by the sponsor. Once a single-patient cohort has been expanded, all future cohorts will follow the 3+3 design. Additional details regarding the SRC can be found in the CTP. The DLT period is defined as one cycle (i.e., 21 days).

Further details can be found in the CTP.

For the assessments of each cohort, the DLTs will be collected for the first treatment cycle, i.e., a DLT evaluation period of 21 days.

Dose escalation will follow a classical 3+3 design and continue until DLTs are observed in 2/3 or 2/6 patients as described in the dose escalation table (Section 4.1.1.1 of the CTP).

Dose escalation in Part 1B

The dose escalation in Part 1B follows the classical 3+3 design as described above for dose escalation in Part 1A. However, in the case that any dose level in Part 1B is declared

as MTD, dosing in Part 1B should stop (refer to Section 6.6.5 of the CTP for stopping criteria). The monotherapy dose escalation in Part 1A can proceed independently of Part 1B until MTD and/or RP2D of BNT411 monotherapy are established.

Expansion phase (Part 2)

As described in CTP Section 4.1.2, expansion cohorts can be implemented by a CTP amendment. The decision to expand is based on the totality of data generated in both Part 1A and Part 1B. The expansion cohort can be a single-arm cohort or a randomized cohort. Further details can be seen in the CTP.

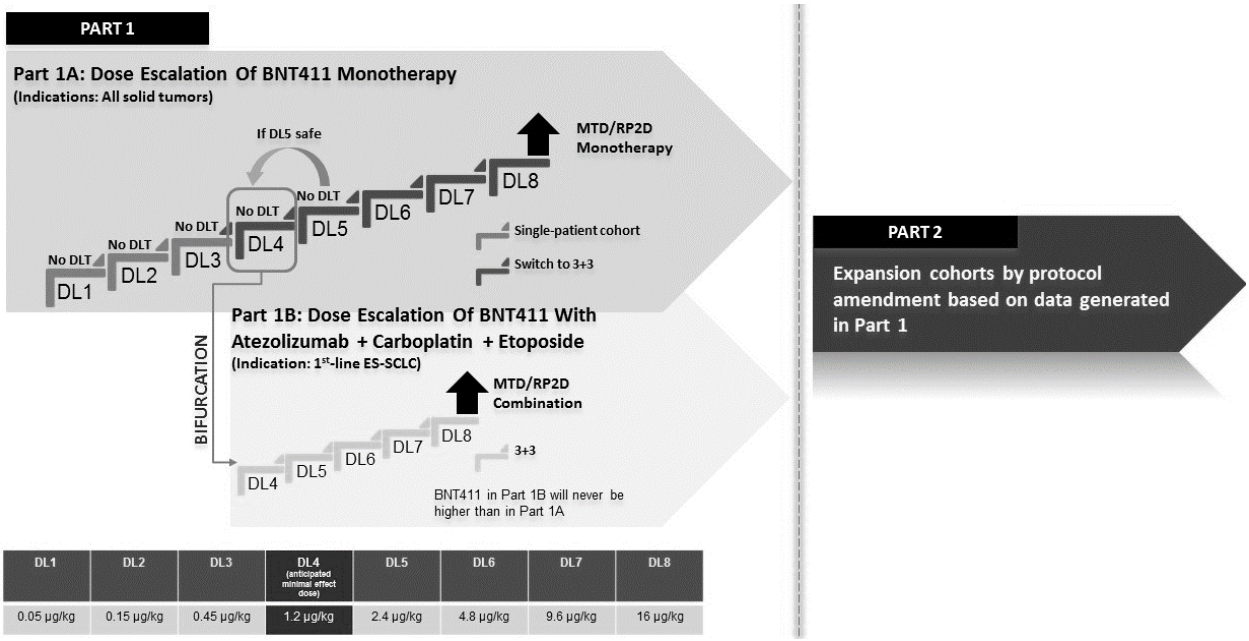
Treatment and trial duration

Patient level:

Patients will receive treatment until one of the CTP pre-defined discontinuation of treatment criteria has been met (refer to Section 7.1 of the CTP). Patients are expected to be on-treatment for up to 2 years (maximum). This will be followed by safety follow-up 1 (30 days after last dose) and a safety follow-up 2 (60 days after last dose). Survival will be followed up every 12 weeks after last dose until 1 year.

Trial level:

The trial will be considered completed once all patients have completed treatment and safety follow-ups. After the sponsor considers the data collection is completed, patients will continue to follow the SoA defined by the protocol unless the medical monitor gives approval not to do so.



DL1	DL2	DL3	DL4 (anticipated minimal effect dose)	DL5	DL6	DL7	DL8
0.05 µg/kg	0.15 µg/kg	0.45 µg/kg	1.2 µg/kg	2.4 µg/kg	4.8 µg/kg	9.6 µg/kg	16 µg/kg

Figure 1: Overall trial design

DL, dose level; DLT, dose-limiting toxicity; ES-SCLC, extensive-stage small cell lung cancer; MTD, maximal tolerated dose; RP2D, recommended phase 2 dose.

3.3 Schedule of activities

Refer to Section 10.4 for the schedule of activities.

4 STATISTICAL HYPOTHESES

There are no plans to test statistical hypotheses for this trial.

5 INTERIM ANALYSES AND ANALYSIS SEQUENCE

No formal interim analysis is planned. However, data will be reviewed by the SRC after each cohort (details are provided in the CTP). The main statistical analysis will be performed once all patients have completed treatment and safety follow-up. Preliminary statistical analyses may be performed on selected cohorts once all patients have been enrolled and are DLT evaluable.

6 SAMPLE SIZE DETERMINATION

The sample size for Parts 1A and 1B is driven by the 3+3 trial design and will range from three to six DLT-evaluable patients per cohort, depending on the number of DLTs which may occur. In total, between 6 and 60 DLT-evaluable patients are planned to be enrolled in the Part 1A, and between 6 and 30 DLT-evaluable patients are planned to be enrolled in the Part 1B.

7 ANALYSIS SETS AND SUBGROUPS

7.1 Analysis sets

Enrolled Set

Enrolled set will have the patients with a valid date of informed consent.

Safety Set

The Safety set is defined as all patients who received BNT411 (i.e., at least one dose of BNT411).

DLT Evaluation Set

The DLT evaluation set includes all patients from the Safety set who either have completed the DLT evaluation period (i.e., have been observed for minimum 21 days following the first dose) and meet the minimum exposure criterion (i.e., when the relative dose intensity [RDI] of BNT411 in Cycle 1 is 100%) or have experienced a DLT during the DLT evaluation period (Cycle 1).

Patients who do not experience any DLT during the DLT evaluation period are considered to be evaluable if they have been observed for minimum 21 days following the first dose and are considered to have sufficient safety data to conclude that a DLT did not occur.

Patients who are excluded from the DLT evaluation set will be replaced.

Pharmacokinetic (PK) Full Set

The PK Full set will consist of all patients who receive at least one dose of BNT411 and have at least one quantifiable post-dose PK sample.

Pharmacokinetic (PK) Evaluable Set

The PK Evaluable set will consist of all patients in the PK Full Set with a sufficient number of quantifiable PK samples to reliably estimate one or more PK parameters.

Pharmacodynamic (PD) Set

The PD set is defined as all patients who received IMP (i.e., at least one dose of BNT411) and have at least one valid post-dose PD assessment.

The DLT evaluation set will be used for the evaluation of DLTs in order to assess the MTD and the RP2D. The Safety set will be used for all other safety analyses. The PK Full Set, PK Evaluable Set and PD analysis set will be used for the PK and PD summaries, respectively.

Most patient data listings will be based on the Safety set. The Enrolled set will be used to summarize the patient disposition summary and some patient data listings.

For the screened patients, the summary is not by cohort, the number and percentage of patients having failed screening (reported as screen failure in the electronic Case Report Form [eCRF]) will be presented along with a summary of the primary reason for screening failure.

7.2 Protocol deviations

Protocol deviations are failures to adhere to the inclusion/exclusion criteria and protocol requirements and will be classified into important protocol deviations (IPDs) and non-important (NIPDs) protocol deviations.

The protocol deviation plan describes the classification process of the protocol deviations as “Key”/”Non-key”:

- The term “Key” deviation from protocol deviation plan is equivalent to IPDs in the SAP.
- The term “Non-key” deviation from protocol deviation plan is equivalent to NIPDs in the SAP.

IPDs will be identified by the trial team on an ongoing basis and will be finalized prior to database snapshot for the main analyses.

All protocol deviations will be presented in a listing. The IPDs will be summarized by cohort and total within each trial part for the Safety set.

7.3 Subgroups

There are no planned subgroup analyses.

8 STATISTICAL ANALYSES

8.1 General considerations

Unless otherwise specified, the details mentioned are for trial Parts 1A and 1B. The summaries will be presented as cohort and total within trial part (Part 1A and Part 1B). The presentation of data for Part 2 will be included in a SAP amendment.

No formal statistical comparisons between cohorts/trial parts will be performed.

Continuous variables will be summarized by cohort and total (as specified) using the following descriptive statistics: number of patients with non-missing data (n), mean, standard deviation (SD), median, minimum (min) and maximum (max).

Categorical variables will be summarized by cohort and total (as specified) presenting absolute and relative frequencies (n and %) of patients in each category and the number of patients with missing data (missing category will be presented if there is one or more missing value). Percentages will be calculated based on the number of patients with non-missing data (n) in the particular analysis set as the denominator. The text (N=xx) in the tables denotes the number of patients in the analysis set within each cohort. For event-driven occurrence data (e.g., adverse event, concomitant medication, etc.) the percentages will be based on the number of patients in the analysis set (N). For reported visit data (e.g., gender, [Eastern Cooperative Oncology Group] ECOG performance status, etc.) the percentages will be based on the number of patients with non-missing values (n).

All data collected during the trial will be listed, the trial day will be presented as appropriate. The data will be sorted by trial part (Part 1A, Part 1B) cohort, patient number cycle (if applicable) and date of assessment (if applicable).

All analyses will be conducted using SAS® version 9.4 or higher.

Baseline is defined as last available value prior to first dose of any trial treatment (i.e., for Part 1A BNT411 and for Part 1B BNT411 or atezolizumab or carboplatin or etoposide).

Generally, if there are multiple assessments available for a particular day, the assessment that is closest to the day (and time if collected) of the first dose of any trial treatment (i.e., BNT411 or atezolizumab or carboplatin or etoposide) will be used as the baseline value in the summary/analyses.

Multiple values at post-baseline visits: if there are multiple post-baseline assessments available within a visit/day, the earliest value and corresponding date/time will be considered.

Change from baseline: Unless and otherwise specified, will be calculated as follows:

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

If either the baseline or post-baseline assessment value is missing, the change from baseline is set to missing as well.

For the derivations of PK and PD data, see Section 8.6.1 and 8.6.2.

Duration (Other than "Trial Treatment Duration" defined in Section 8.5.1) will be calculated as follows:

- Duration = 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

Trial Day and Treatment Day will be calculated for each trial part (1A and 1B) as follows:

- Trial day:
  - If assessment date < treatment start date then trial day = assessment date – treatment start date
  - If assessment date >= treatment start date then trial day = assessment date – treatment start date + 1
- Treatment Day = treatment date – date of first dose of BNT411 +1

That is, trial day 1 indicates the date of treatment initiation.

For BNT411, it is Cycle 1 Day 1 of Part 1A and Cycle 1 Day 2 of Part 1B. For atezolizumab, carboplatin and etoposide it is Cycle 1 Day 1 of Part 1B.

All trial data will be presented as collected in the eCRF/visit assigned in external data. No windowing of data for the purposes of assigning to a visit will occur.

Unscheduled assessments will be listed only and not included in summaries/analysis.

Handling missing data:

For the purposes of assigning treatment-emergent flag for adverse events (AEs), partial or missing AE dates will be handled as follows (trial treatment date is the earliest date of BNT411 in Part 1A and earliest date of atezolizumab, BNT411, carboplatin and etoposide in Part 1B).

- If the day of the month is missing, the onset day will be set to the first day of the month unless it is the same month and year as trial treatment. In this case, in order to conservatively report the event as treatment-emergent, the onset date will be assumed to be the first date of trial treatment.

- If the onset day and month are both missing, the day and month will be assumed to be January 1, unless the event occurred in the same year as the trial treatment. In this case, the event onset will be coded to the day and month of treatment in order to conservatively report the event as treatment-emergent.
- A completely missing onset date will be assumed to be the first day of trial treatment.
- If an AE has a partial start date that is in the same month/year as the first dose of trial treatment, then the AE will be reported as treatment-emergent.

Partial anti-cancer therapy start dates will be handled as follows:

- If the start of subsequent anti-cancer therapy date is missing, this will be imputed to the date of the end of treatment (EOT) visit.
- Missing day, month/year present: If the month/year is the same as the month/year of EOT Visit date, then impute missing start dates with EOT Visit date. Otherwise, for dates corresponding to a start date, impute with the first day of the month.
- Missing month/day, year present: If the year is the same as the year of EOT Visit date, then impute missing start dates with EOT Visit date. Otherwise, for dates corresponding to a start date, impute with the first day of the year.
- If the EOT Visit date is missing, the date of last treatment will be used for imputation.

For the purposes of assigning prior or concomitant flag for medications, partial or missing medication dates will be handled as follows:

- If end day is missing and month/year are non-missing, then day is the minimum of treatment end date and the last day of the month.
- If end day/month are missing and year is non-missing, then day is the minimum of treatment end date and the end of the year (31DECYYYY).
- If imputed end date is less than the start date, use the start date as the imputed end date.

Start dates:

- If the start date year is missing, the start date is set to one day prior to treatment start date.
- If the start date year is less than the treatment start date year, then:
  - If the month is missing, the start date is assumed to be mid-year point (01JULYYYY).
  - Else if the month is not missing, the start date is assumed to be mid-month point (15MONYYYY).

- If the start date year value is greater than the treatment start date year, then:
  - If the month is missing, the start date is assumed to be the year start point (01JANYYYY).

  - Else if the month is not missing, the start date is assumed to be the month start point (01MONYYYY).

- If the start date year value is equal to the treatment start date year value:
  - If the month is missing or the month is equal to the treatment start date month, then the start date is assumed to be one day prior to the treatment start date.
  - Else if the month is less than the treatment start date month, the start date is assumed to the mid-month point (15MONYYYY).
  - Else if the month is greater than the treatment start date month, the start date is assumed to be the month start point (01MONYYYY).

If complete end date is available and the start date assumed from the steps above is greater than the end date, then the assumed start date should be set to the end date.

Missing data, other than that described for AEs/CMs/ above will not be imputed.

Listings will present all data as reported (i.e., without imputations).

For analysis of PK and PD data:

- The actual date collected will be used. If the date is not available, the value will be considered as missing.
- The actual time of sample collection will be used. If the time is not available, the value will, at the discretion of trial pharmacokinetics/pharmacodynamics analysist (in consultation with BioNTech), be considered as missing or imputed to be the nominal sampling time.

8.2 Patient disposition

Unless otherwise specified, all of the summaries will be presented by cohort and total within each trial part (Part 1A and Part 1B).

For the screened patients, the number and percentage of patients having failed screening will be presented along with a summary of the primary reason for screening failure. A summary of reason for violation of inclusion/exclusion criteria will also be presented. This summary is not by cohort.

The number and percentage of patients enrolled by site will be presented. The number and percentage of enrolled and treated patients will be presented by country and site including the number and percentage of IPDs (by cohort and total within each trial part).

The number and percentage of patients in each analysis set will be summarized by cohort and total within each trial part.

For each analysis set (e.g., Safety set, DLT evaluation set, PK Full set, PK Evaluable set and PD set) the number and percentage of patients being excluded from the analysis set will be presented by cohort and total along with a summary of the reasons for exclusion based on the Enrolled set.

For the Safety set the number and percentage of patients who are still on-treatment and percentage of treated patients who are off treatment will be summarized. Patients who are "off treatment" will be the patients who are who are discontinued from treatment. Also, for the Safety set the number and percentage of patients discontinued from each trial treatment (BNT411, atezolizumab, carboplatin, etoposide) will be presented along with a summary of the primary reason for treatment discontinuation as reported in the eCRF. All summaries will be by cohort within each trial part.

The number of patients that entered/not entered safety follow-up 1 and safety follow-up 2 (defined as had at least one data point collected in safety follow-up 1, safety follow-up 2, respectively) and the number of patients that had early discontinuation from the trial together with the primary reason for discontinuation will be summarized for the patients in the Safety set by cohort and total within each trial part.

In addition, total number of deaths will be summarized by cohort and total within each trial part for the Safety set.

A listing of patient disposition (including discontinuation from each trial treatment (BNT411, atezolizumab, carboplatin, etoposide) and discontinuation from trial) will be presented.

A listing of Enrolled set patients that are excluded from the Safety, DLT evaluation, PK and PD sets will be presented.

A listing of enrolled patients with protocol deviations will be provided.

8.3 Baseline characteristics

8.3.1 Demographics

Demographic data will be summarized by cohort for patients in the Safety set for each part of the trial (Part 1A and Part 1B).

Age (years), will be summarized as continuous data. Age category <65, ≥65 years), gender (male vs female), childbearing potential, race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Not reportable, Unknown and other) and ethnicity (Hispanic or Latino, Not Hispanic or Latino and Not reportable) will be summarized as categorical data.

A listing of demography will be provided.

Baseline characteristics will be summarized by cohort for patients in the Safety set for each part of the trial (Part 1A and Part 1B).

Height (cm), weight (kg), Body Mass Index (BMI (kg/m^2)), body surface area (BSA (m^2)), and Glomerular Filtration Rate (GFR, mL/min/1.73 m^2), will be summarized descriptively. BMI category (<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 Smoking status (has never smoked, current smoker, ex-smoker) will be summarized with frequency counts and percentage by cohort.

A listing of baseline characteristics will be provided.

8.3.2 Disease characteristics

The following disease characteristics at baseline will be summarized by cohort for patients in the Safety set for each part of the trial (Part 1A and Part 1B).

- Time from initial cancer diagnosis to enrollment (months)
- ECOG Performance Status at baseline
- Time from most recent progression (as recorded on the cancer classification and staging eCRF page) to start of any trial treatment (BNT411, atezolizumab, carboplatin or etoposide)
- Location at initial diagnosis

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

Time = date of enrollment – initial diagnosis date + 1.

In order to calculate the time from initial cancer diagnosis, the following rules will be applied for partial dates of first diagnosis:

- The first day of the month will be assumed;
- If the month is missing, January 1st will be assumed.

Time from most recent progression to start of any trial treatment to start of any trial treatment will be calculated as:

Time = date of first dose of BNT411 - date of most recent progression + 1.

A listing of disease characteristics will be provided.

8.3.3 Prior anti-cancer treatments

The summary of prior anti-cancer treatments will be based on the Safety set and will be presented by cohort and total for each trial part (Part 1A and Part 1B).

For prior systemic cancer therapy, the following will be summarized:

- The number of prior systemic therapies (0,1, 2, 3+)

The last prior systemic cancer therapy prior to treatment start date (the prior systemic therapy with start date closest to treatment start date) will be summarized as follows:

- Setting (adjuvant, neoadjuvant and metastatic)
- Intent (curative, palliative and unknown)
- Best response during the therapy (CR, PR, progressive disease, stable disease, unknown)
- Reason for discontinuation of last prior systemic therapy

The treatment intent and setting for prior cancer radiotherapy and treatment intent for prior cancer surgery will be summarized by cohort and total for each trial part.

Prior systemic cancer therapies will be coded using the World Health Organization Drug Dictionary (WHO DD) version B3 dated March 2023 resulting in anatomical-therapeutic-chemical (ATC) codes indicating therapeutic classification.

The number and percentage of patients taking prior systemic cancer therapies will be summarized by ATC therapeutic class (ATC level 2), ATC pharmacological class (ATC level 3), and chemical subgroup (ATC level 4) for each cohort and total for each part of the trial (Part 1A and Part 1B).

Prior cancer surgeries will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) coding system version 26.0 or higher and will be listed only.

A listing of prior cancer therapies (systemic cancer therapy, cancer radiotherapy, cancer surgery) will be provided.

8.3.4 Prior and Concomitant medication/Procedures/Non-drug Therapy

Prior and concomitant medications will be defined using medication start and stop dates recorded, relative to the first and last dose of trial treatment (BNT411, atezolizumab, carboplatin, etoposide) for both the trial parts (1A and 1B).

A **prior medication** will be defined as any therapy taken 28 days prior up to (but not including) the start date of trial treatment.

A concomitant medication will be defined as any medication either ongoing at the start of trial treatment in each trial part (1A and 1B) or with a start date on or after the first dose of any trial treatment up to (but not including) the last date of trial treatment (BNT411, atezolizumab, carboplatin, etoposide). See Section 8.1 for handing missing dates.

Medications will be coded using the World Health Organization Drug Dictionary (WHODrug) drug codes of version B3 dated March 2023. Resulting in ATC codes indicating therapeutic classification.

The number and percentage of patients who had prior and concomitant medications will be summarized by ATC therapeutic class (ATC level 2), ATC pharmacological class (ATC level 3), and chemical subgroup (ATC level 4) for each cohort and total within each trial part based on the Safety set. The summary will be presented alphabetically.

A listing of prior and concomitant medications will be provided.

Procedures and Non-drug therapies will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) coding system version 26.0 or higher. Procedure and non-drug therapies will be listed only.

8.3.5 Medical history

Medical history data will be coded using Medical Dictionary for Regulatory Activities (MedDRA®) version 26.0 or higher. The number and percentage of patients with each medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) for each cohort and total within each trial part based on the Safety set.

A listing of medical history data will be provided.

8.4 Efficacy analyses

Owing to the heterogeneity of cancer types and limited number of patients in Part 1A and B, no efficacy analysis will be done in Part 1.

8.4.1 Primary analysis

Not applicable for this trial as there is no primary efficacy endpoint defined for this trial. The primary endpoint is a safety endpoint, this endpoint is described in Section 8.5.2.

8.4.2 Supplementary analyses

Not applicable.

8.4.3 Secondary analyses

Not applicable.

8.4.4 Exploratory analyses

Not applicable.

8.5 Safety analyses

Safety data that will be summarized includes treatment exposure, AEs, clinical safety laboratory assessments (including hematology, biochemistry, urinalysis, coagulation endocrine tests), vital signs, electrocardiogram (ECGs), ECOG PS, Eye examinations, PD and biomarkers. All safety analyses will be based on the Safety set and will be summarized by cohort and trial part and if appropriate, by cohort and treatment, for example for summary of treatment-related AEs. For all the summaries patients will be assigned to the treatments according to the actual treatment they have received (“as treated”). The actual treatment will be derived as following:

- If a patient received at least once the planned dose during Cycle 1, then this patient will have the actual treatment assigned to the planned treatment.
- Otherwise, the actual treatment will be considered as the dose received in Cycle 1 day 1.

All safety data will be listed.

8.5.1 Extent of exposure

The following dose exposure variables will be derived and summarized for each treatment (BNT411 in Part 1A also BNT411, atezolizumab, carboplatin, and etoposide in Part 1B). The summaries will be based on patients in the Safety set and will be repeated for DLT evaluation set. The summary for the DLT evaluation set will be restricted to the exposure data from the first cycle (21 days).

- Number of treated cycles.
- Number of BNT411 infusions.

- Number of atezolizumab, carboplatin and etoposide infusions (Part 1B).
- (Actual)Treatment Duration (weeks) defined as follows: (Date of last administration - Date of first administration + Planned Duration) / 7, where the Planned Duration (days) is defined as the planned time between two consecutive administrations. In Part 1A, planned duration for BNT411 is one week for the first four cycles, followed by once every 3 weeks. In Part 1B, planned duration for BNT411 for the first four cycles is 6 days if the patients' last dose was the first dose within any cycle, 7 days if the patients' last dose was the second dose within any cycle and 8 days if the patients' last dose was the third dose in within any cycle. After 4 cycles planned duration for BNT411 is 3 weeks. Planned duration for atezolizumab is every 3 weeks, for carboplatin it is 21 days apart till Cycle 4 and for etoposide planned duration is one day till day 3 of the Cycle 4. Actual treatment duration is calculated for each treatment separately.
- Planned Treatment Duration (weeks) defined as (scheduled date of last administration - scheduled date of first administration + Planned Duration) / 7. The scheduled date of last administration is the date at which the last administration should be given according to the CTP schedule. Planned duration is as above.
- (Actual) Cumulative Dose defined as sum of all administered doses for each trial treatment. BNT411 (µg) for Part 1A and Part 1B and atezolizumab (mg), carboplatin (mg), and etoposide (mg) for Part 1B. Calculated for each treatment separately.
- Planned Cumulative Dose defined as sum of all planned doses, separately, for each trial treatment. BNT411 (µg) for Part 1A and Part 1B and atezolizumab (mg), carboplatin (mg), and etoposide (mg) for Part 1B.
- Dose Intensity is defined as Cumulative Dose for that trial treatment (unit for that trial treatment) / (Actual) Treatment Duration (weeks) for that trial treatment.
- RDI % (using units for BNT411) is defined as follows:

$$\text{RDI (\%)} = \frac{\text{Actual Dose Intensity } \left(\frac{\mu g}{\text{week}}\right)}{\text{Planned Dose Intensity } \left(\frac{\mu g}{\text{week}}\right)} \text{ x } 100 = \text{DI x TI x } 100,$$

Where

$$\text{Actual Dose Intensity} \left(\frac{\mu g}{\text{week}}\right) = \frac{\text{(Actual) Cumulative Dose } (\mu g)}{\text{(Actual) Treatment Duration (weeks)}}$$

$$\text{Planned Dose Intensity } \left(\frac{\mu g}{\text{week}}\right) = \frac{\text{Planned Cumulative Dose } (\mu g)}{\text{Planned Treatment Duration (weeks)}}$$

$$\text{Dose Index (DI)} = \frac{\text{Total Administered Dose } (\mu g)}{\text{Total Planned Dose } (\mu g)}$$

$$\text{Time Index (TI)} = \frac{\text{Planned Treatment Duration (weeks)}}{\text{Actual Treatment Duration (weeks)}}$$

The units in the derivations above are for BNT411. For atezolizumab, carboplatin and etoposide the unit is mg.

The following variables will be presented with summary statistics for each trial treatment by cohort for each trial part:

- Number of cycles received (categorical, Cycle 1-2, 3-4, 5-6, 7-8, 9-10, 11-12, 13-14, 15-16, 17-20 21-24 and so on, aligned to the tumor assessments every 6 weeks and 12 weeks respectively)
- Number of BNT411 infusions (descriptive statistics)
- Number of BNT411 infusions (categorical, 1, 2, 3 and so on)
- Number of atezolizumab, carboplatin and etoposide infusions (descriptive statistics) (Part 1B)
- Number of atezolizumab, carboplatin and etoposide infusions (categorical, 1, 2, 3 and so on) (Part 1B**)**
- Treatment duration
- Cumulative dose
- Dose intensity
- RDI

Additionally, the RDI will be presented categorically (i.e., number and percentage of patients with RDI of <60%, 60-<80%, ≥80%). Moreover, the number and percentage of patients with any dose delay, 4-7 days, > 7 days of dose delay and with any dose modification, dose reduction, dose increase, at least one dose modification and at least two dose modification and any dose interruption will be presented separately for each trial treatment for each trial part. Dose reduction and dose increase will be calculated as planned dose - given dose or total dose.

All the above mentioned dose exposure variables will be presented in a by-patient listing.

A by-patient listing of treatment administration will be presented.

8.5.2 Adverse events

This section includes the description of the analysis planned for the primary endpoints on this trial.

AEs will be coded using the most recent version of Medical Dictionary for Regulatory Activities (MedDRA®) coding system version 26.0 or higher to get a SOC and PT for each AE and graded for severity using NCI CTCAE v5.0. 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-CTC grades will be performed.

A treatment-emergent AE (TEAE) is defined as any AE with an onset date on or after the first administration of trial treatment (BNT411 in part1A and BNT411, atezolizumab, carboplatin, and etoposide in Part 1B) (if the AE was absent before the first administration of trial treatment) or worsened after the first administration of trial treatment (if the AE was present before the first administration of trial treatment). AEs with an onset date more than 60 days after the last administration of trial treatment will be considered as treatment-emergent only if assessed as related to trial treatment (BNT411 for Part 1A and BNT411, atezolizumab, carboplatin, and etoposide for Part 1B) by the investigator.

Treatment-emergent AEs will be summarized by cohort and trial part and total within trial part. In addition, treatment-related TEAEs will be summarized by cohort and trial treatment (BNT411, atezolizumab, carboplatin, and etoposide) within trial part.

Only TEAE data will be summarized for the Safety set for each trial part (Part 1A and Part 1B). Non-TEAEs will be listed only.

Dose-limiting toxicities

In general, a DLT for a drug or other treatment is defined as one or more AEs that prevents an increase of the dose level of that treatment (for details on dose escalation decision rules see Appendix 5).

Serious AEs (SAEs), non-serious grade ≥3 AEs and clinically significant abnormal laboratory values grade ≥3 will be collected and assessed for DLTs (for each dose level during the first cycle). Common Terminology Criteria for Adverse Events (NCI CTCAE) v.5.0 will be used to grade the intensity of AEs.

More details regarding DLTs can be found in the Section 6.6 of the CTP.

For the additional rules and considerations of MTD and RP2D other than what was already defined in Section 1.1, see Section 4.1.1.2 of the CTP.

The number and percentage of patients reporting DLTs will be summarized by PT nested within SOC for each cohort by trial part using the DLT evaluation set.

A separate listing of DLTs will be presented, including reported term, SOC, PT, time of onset, duration, outcome, relationship to trial treatment, NCI CTCAE grade, and seriousness including dose exposure data during the first cycle (i.e., 21 days).

Overall summary of adverse events (AE)

The number and percentage of patients reporting at least one AE will be summarized for each of the following AE types by cohort and trial part (Parts 1A and 1B). Related applies to a separate summary for BNT411 in Part 1A and BNT411, atezolizumab, carboplatin, and etoposide and any NIMP/IMP in Part 1B, unless otherwise specified :

- any TEAE
- related TEAE
- grade ≥3 TEAE
- related grade ≥3 TEAE

- any treatment-emergent serious AE (TESAE)
- related TESAE
- TESAE leading to death
- Related TESAE leading to death
- TEAEs leading to dose reduction and dose interruption (BNT411 in Part 1A or BNT411, atezolizumab, carboplatin, and etoposide in Part 1B)
- TEAE leading to permanent discontinuation of treatment (BNT411 in Part 1A or BNT411, atezolizumab, carboplatin, and etoposide in Part 1B)
- DLTs

Analyses of adverse events

The number and percentage of patients reporting at least one TEAE will be summarized by PT nested within SOC for each of the above AE categories. If an SOC / PT is reported more than once for a patient, the patient will only be counted once for this SOC / PT. Strongest relationship or worst grade will be counted if a TEAE is reported more than once by the same patient for a SOC / PT. The common TEAE occurring in ≥ 10% of the patients will be summarized separately.

All AE summary tables will be sorted in descending frequency order by SOC and PT within SOC.

Analyses of other adverse events (excluding serious AEs)

The number and percentage of patients reporting other TEAEs (excluding TESAEs) will be summarized by PT nested within SOC. 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 in descending frequency order by SOC and PT within SOC.

TEAE by relationship

The number and percentage of patients with TEAEs will be summarized by ‘ALL’ and ‘Related’ to trial treatment (BNT411, atezolizumab, carboplatin, and etoposide) by PT nested within SOC. If an AE is reported more than once by the same patient for a SOC / PT the related AE will be counted once for this SOC / PT. The relationship to trial treatment will be counted as related if relationship status is reported as missing for an AE.

TEAE by NCI-CTC grade

The number and percentage of patients with TEAEs will be summarized by worst NCI-CTC grade by PT nested within SOC. Worst grade will be counted if an AE is reported more than once by the same patient for a SOC / PT. The related TEAEs by worst NCI-CTC grade will be summarized separately.

The number and percentage of patients with grade ≥ 3 AEs and related grade ≥ 3 AEs will be summarized by PT nested within SOC. In addition, AEs with a missing grade will be presented in the summary table as a grade category of “Missing.”

Deaths

- All deaths including those that occurred on-treatment (on or after date of first dose of BNT411) and post-treatment, will be listed, post-treatment deaths will be flagged. In addition to the summary of on-treatment deaths an additional summary of all deaths (on-treatment + post-treatment) will be provided along with primary reason for death.
- A separate summary of TESAEs leading to death will be provided by PT nested within SOC.
- A separate summary of related TESAEs leading to death will be provided by PT nested within SOC.

Serious Adverse Events and Other Significant Adverse Events

The number and percentage of patients

- with any TESAE,
- with any related TESAE (separately for each trial treatment and total),
- with any TESAE leading to death,
- with any related TESAE leading to death,
- with any TEAE leading to permanent discontinuation of treatment (BNT411, atezolizumab, carboplatin, and etoposide), or
- with any TEAE leading to dose reduction or interruption

will be summarized by PT nested within SOC by cohort within each trial part.

Deaths

In addition to a summary of on-treatment (on or after date of first dose of BNT411 until…) deaths and primary reason for death an additional summary of all deaths (on-treatment + during follow-up) will be provided along with primary reason for death. by cohort for each trial part. All deaths including those that occurred on-treatment and during follow-up, will be listed, post-treatment deaths will be flagged.

AE listings

All deaths, AEs, SAEs and TEAEs leading to permanent discontinuation of treatment, and discontinuation from trial will be listed. Also a listing of TEAEs leading to death will be provided. DLTs will be flagged in all AE listings. The listings will be sorted by trial part, cohort and patient within cohort.

8.5.3 Laboratory assessments

All laboratory assessments except for PK and biomarkers will be processed by local laboratories. Summaries of all laboratory data will be based on Safety set for each trial part (Parts 1A and 1B) and total within each trial part.

For the purposes of summarizing and presentation in tables and listings, all laboratory values will be summarized by cohort and presented in System International (SI) units. If a laboratory value is reported using a nonnumeric qualifier e.g., less than (<) a certain value, or greater than (>) a certain value, the given numeric value will be used in the summary statistics, ignoring the nonnumeric qualifier. The data as collected will be presented in the listings.

Clinical laboratory data to be summarized includes hematology, biochemistry, urinalysis, coagulation factors and endocrine tests. The safety laboratory parameters to be assessed are listed in Section 10.2 of the CTP. The scheduled time points for assessment are outlined in the SoAs (Section 10.4.1)

Continuous clinical laboratory variables at each protocol scheduled visit and its change from baseline to each post-baseline visit will be summarized using descriptive summary statistics for each parameter listed in CTP Table 10-1 by cohort. Categorical variables will be summarized using n and %.

Laboratory values that are below or above the reference ranges will be flagged.

Abnormal and clinically significant, abnormal and not clinically significant, and normal laboratory values will be summarized for each parameter by visit and cohort.

All laboratory data will be presented in the data listings. Abnormal clinical laboratory values will be flagged in the listing.

Serology and pregnancy results will be listed only.

8.5.4 Vital signs

Vital sign parameters to be summarized include systolic blood pressure (SBP), diastolic blood pressure (DBP), body temperature, body weight, respiration rate and pulse rate.

Vital sign parameters collected at each visit/time-point, and its change from baseline to each post-baseline visit (for BNT411 infusion days the value collected pre-infusion will be used for this summary) will be summarized using descriptive summary statistics for each parameter by cohort and visit for each trial part.

Vital sign parameters collected on BNT411 infusion days and its change from baseline (pre-infusion value at that visit) to each post-baseline time-point will be summarized for each time-point using descriptive summary statistics for each parameter by cycle, cohort, and trial part.

Body weight, which is collected at screening and at the beginning of each cycle of treatment, will be summarized using descriptive summary statistics by cycle, cohort, and trial part.

All vital sign data will also be presented in a data listing.

8.5.5 ECG

Triplicate (during trial treatment) or single (at other time points) 12-lead ECG will be collected as shown in CTP Table1-4 and Table 1-5.

The triplicate ECG values will be listed only. For the summary at each time-point, the first assessment will be considered.

ECG variables to be summarized include heart rate, QRS, QTc. QTcF Absolute values collected at each time-point, and its change from baseline to each post-baseline time-point (for BNT411 infusion days the value collected pre-infusion will be used for this summary) will be summarized using descriptive summary statistics for each parameter by cohort, visit and trial part.

ECG variables collected on BNT411 infusion days and its change from baseline (pre-infusion value at that visit) to each post-baseline time-point will be summarized for each time-point using descriptive summary statistics for each parameter by cycle, cohort, and trial part.

In addition, the number of patients with abnormal QT, and QTcF (number of patients in the following categories <=450 ms, >450-480 ms, >480-500 ms, >500 ms, and increase <=30 ms, >30-60 ms and >60 ms over baseline) will be summarized by cohort and visit for each trial part.

Additionally, the results of ECG interpretation (normal, abnormal not clinically significant or abnormal clinically significant) will be summarized with number and percentage of patients by cohort and visit. For the triplicate assessments, only the first assessment will be considered for the summary.

A listing of ECG data will also be provided.

8.5.6 Physical examination

A listing of physical examination findings will also be presented.

8.5.7 ECOG performance status

The frequencies and percentages of patient's ECOG performance status will be provided by cohort and visit for each trial part.

Additionally, a shift table from baseline to each post-baseline visit by cohort will be provided.

A listing of ECOG performance status will also be provided.

8.5.8 Eye examinations

The eye examination data will be summarized for the patients by cohort and visit for each trial part.

- Ophthalmologic entry criteria: Presence/absence for each at baseline

- Slit-lamp examination results will be summarized with frequencies and percentages of patients

A listing of eye examination will also be provided.

8.5.9 ECHO and MUGA

ECHO and MUGA data will be listed only.

8.6 Other analyses

8.6.1 Pharmacokinetics

Plasma and urine samples will be collected for measuring concentrations of BNT411 and its metabolites as per the schedule of timing for collection of samples for PK assessments mentioned in Table 1.3 and Table 1.4 of the CTP. For urine sampling, the exact time of sampling and the volume (mL) excreted over each collection interval must be documented. Full pharmacokinetic profiles will be documented in additional patients enrolled to confirm the RP2D. The actual date and time (24-hour clock time) of each sample will be recorded.

Plasma concentrations of BNT411 and its metabolites (if available) will be listed and summarized by cycle, day, nominal time, and cohort for each part of the trial (Part 1A and Part 1B) using descriptive statistics (n, arithmetic mean, SD, coefficient of variation [CV%], geometric mean, geometric CV%, median, minimum, and maximum) for the Full PK analysis set. The geometric CV% will be calculated as the square root of the exponentiated SD of the natural log-transformed data SQRT ($\exp(sln^2)-1$), where appropriate. Mean and individual plots of plasma concentrations will be presented in both the original and semi-logarithmic scales.

All PK parameters will be summarized by cohort for each part of the trial (Part 1A and Part 1B). For $T_{1/2}$, the following descriptive statistics will be calculated, if possible, n, arithmetic mean, median, CV%, SD, minimum and maximum and, for T_{max}, n, median, minimum and max will be calculated. All other PK parameters will be summarized using n, arithmetic mean, SD, CV%, geometric mean, geometric CV%, median, minimum, and maximum.

The following PK parameters will be determined from plasma concentrations of BNT411 after the first dose on Cycle 1 Day 1 (or Cycle 1 Day 2 for Part B):

- AUC_{0-24}: partial AUC from time 0 to 24 hours calculated using the linear-log trapezoidal method.
- AUC_{0-48}: partial AUC from time 0 to 48 hours calculated using the linear-log trapezoidal method.
- AUC_{0-last}: AUC from time 0 to the last measurable time-point calculated using the linear-log trapezoidal method.
- $AUC_{0-\tau}$: AUC from time 0 to the end of the 168-hour dosing interval (τ) calculated using the linear-log trapezoidal method.

- $AUC_{0\text{-}inf}$: AUC from time 0 extrapolated to infinity, calculated as $AUC_{0\text{-}inf} = AUC_{0\text{-}last} + C_{last}/\lambda_z$, where C_{last} is the last quantifiable (measurable) concentration.
- C_{max}: Maximum (peak) concentration.
- T_{max}: Time of maximum (peak) concentration.
- λ_z: terminal elimination rate constant.
- $T_{1/2}$: terminal elimination half-life computed as $(\ln 2)/\lambda_z$.
- CL: Clearance, calculated as $Dose/AUC_{0\text{-}inf}$. Dose will be converted, as necessary, to reflect the amount of anhydrous BNT411 administered (molecular weight 439.5579 g/mole).
- V_D: Volume of distribution, calculated as $[CL/\lambda_z]$.

The following PK parameters will be determined from plasma concentrations of BNT411 after the fourth dose on Cycle 2 Day 1 (or Cycle 2 Day 2 for Part B):

- $AUC_{0\text{-}24}$: partial AUC from time 0 to 24 hours calculated using the linear-log trapezoidal method.
- $AUC_{0\text{-}last}$: AUC from time 0 to the last measurable time-point calculated using the linear-log trapezoidal method.
- $AUC_{0\text{-}\tau}$: AUC from time 0 to the end of the 168-hour dosing interval (τ) calculated using the linear-log trapezoidal method.
- C_{max}: Maximum (peak) concentration.
- T_{max}: Time of maximum (peak) concentration.
- λ_z: Terminal elimination rate constant estimated by linear regression of log concentration vs. time; at least three data points are required to compute this parameter.
- $T_{1/2}$: Terminal elimination half-life computed as $(\ln 2)/\lambda_z$.
- CL: Clearance, calculated as $Dose/AUC_{0\text{-}\tau}$. Dose will be converted, as necessary, to reflect the amount of anhydrous BNT411 administered (molecular weight 439.5579 g/mole).
- V_D: Volume of distribution, calculated as $[CL/\lambda_z]$.
- $R_{A,Cmax}$: Accumulation ratio for C_{max} computed as C_{max} after Cycle 2 Day 1 (or Cycle 2 Day 2 for Part B) divided by C_{max} after Cycle 1 Day 1 (or Cycle 1 Day 2 for Part B).
- $R_{A,AUC}$: Accumulation ratio for AUC computed as AUC_τ after Cycle 2 Day 1 (or Cycle 2 Day 2 for Part B) divided by AUC_τ after Cycle 1 Day 1 (or Cycle 1 Day 2 for Part B).
- $T_{1/2,eff}$: Effective half-life for accumulation computed as $\ln(2)\tau/\ln(R_{A,AUC}/[R_{A,AUC}\text{-}1])$.

AUC will be computed using the linear-log trapezoidal rule. When necessary, interpolation or λ_z extrapolation may be used to estimate partial AUCs and $AUC_{0\text{-}\tau}$. The value of the extrapolated portion of any AUC ($AUC_{\%extrap}$) will be less than or equal to 20% for the AUC

to be considered well estimated. If this proportion is > 20%, then the values of AUC will be treated with caution. When AUC is calculated and listed, the $AUC_{\%extrap}$ will also be listed. Where $AUC_{\%extrap}$ >20%, AUC and all related parameters (i.e., CL, V_D) will be presented but excluded from the calculation of summary statistics. All values excluded from the summaries should be flagged in the individual listings with an explanation for the exclusion.

The λ_z will be estimated by log-linear regression of the concentration-time data associated with this phase. The decision as to which data points describe the terminal phase will be reached by inspecting the semi-logarithmic plot of the data, only considering concentrations at time points beyond T_{max}. A minimum of three data points will be used for the estimation of λ_z preferably covering a time span of at least two half-lives. Ideally, the adjusted r^2 value of the estimated λ_z will be > 0.80. If λ_z is poorly estimated (i.e., if a time span of at least two half-lives is not used or adjusted $r^2 \leq 0.80$), the corresponding $T_{1/2}$ and other parameters derived using λ_z (i.e., $AUC_{0\text{-inf}}$, CL, and V_D) will be flagged in the report and excluded from summaries for PK parameters dependent on λ_z.

In addition to the two plasma PK profiles collected for doses administered on Cycle 1 Day 1 (or Cycle 1 Day 2 for Part B) and Cycle 2 Day 1 (or Cycle 2 Day 2 for Part B), sparse PK samples will be collected at additional times throughout the trial (see CTP Table 1-3 and Table 1-4). Concentrations of BNT411 in pre-dose samples will be considered C_{trough} values provided they are collected between 156 and 180 hours after the start of the prior dose (i.e., 168 ± 12 hours). Concentrations of BNT411 collected within 5 minutes after the end-of-infusion will be considered end-of-infusion concentrations (C_{eoi}). Values of C_{trough} and C_{eoi} will be summarized longitudinally in tabular and graphical format by nominal elapsed time since the start of first infusion of BNT411.

After a pre-dose void, all urine will be collected over the interval 0 to 6 hours after the start of dosing on Cycle 1 Day 1 in Part 1A and Cycle 1 Day 2 in Part 1B. Actual start and end times and total volumes of urine collections will be recorded.

The following PK parameters will be determined from urine volumes (Vu) and BNT411 concentrations (Cu) on Cycle 1 Day 1 and Cycle 2 Day 1 of Part 1A and Cycle 1 Day 2 and Cycle 2 Day 2 of Part 1B:

- $Ae_{0\text{-}6}$: amount of BNT411 excreted in urine over the collection interval between start and end times calculated as Cu × Vu for the interval.
- $fe_{0\text{-}6}$: fraction of the administered BNT411 dose excreted in urine over the collection interval between 0 and 6 hours calculated as $Ae_{t1\text{-}t2}$/Dose. Dose will be converted, as necessary, to reflect the amount of anhydrous BNT411 administered (molecular weight 439.5579 g/mole).
- $CL_{R,0\text{-}6}$: renal clearance of BNT411 over the collection interval between 0 and 6 hours calculated as $Ae_{0\text{-}6}/AUC_{0\text{-}6}$. Partial AUCs will be computed for plasma as described above.

Since BNT411 cannot be present in urine until after dosing, the start of the 0- to 6-hour urine collection interval will be the start of BNT411 infusion at Cycle 1 Day 1 in Part 1A or Cycle 1 Day 2 in Part 1B.

BNT411 dosing and concentration data will be combined with relevant extrinsic and intrinsic covariates and used to develop a population-based pharmacokinetic (PopPK) model suitable for subsequent simulation and exploration of exposure-response trends. The methods to be used in the development of the PopPK model, and its subsequent application, will be described in a separate Modeling and Simulation Analysis Plan (MSAP) and results reported in a separate PopPK report.

Treatment of outliers:

Individual concentration-time points, if considered anomalous, may be excluded from the analysis at the discretion of the pharmacokineticist following a review of the available documentation. Any such exclusion will be discussed with BioNTech and clearly outlined in the trial report.

Entire individual treatment profiles for a patient may be excluded following review of the available documentation and discussion with the sponsor. However, results of analysis with and without the excluded profiles may be presented in the trial report. Any such exclusion will be clearly listed in the trial report along with justification for exclusion.

Non-quantifiable concentrations:

All concentration values reported as no results (not collected or not determined) values will be treated as missing. For the calculation of concentration summaries, all concentrations below the quantifiable limit (BLQ) will be treated as 0. For the purpose of calculating PK parameters and plotting mean and individual concentration-time profiles, BLQ values will be treated as 0 prior to the first measurable concentration. After the first measurable concentration, subsequent BLQ values within the PK profile will be treated as missing. Descriptive statistics at any point will only be calculated if at least 2/3 of the individual data were measured and were quantifiable.

Dose-proportionality analysis:

The dose-proportionality of the PK parameters $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} for the single-dose PK profile and $AUC_{0\text{-}\tau}$ and C_{max} for the multiple-dose PK profile will be investigated over the administered dose range using the following power model,

ln(parameter) = a + b * ln(dose), where a is the intercept and b is the slope.

Dose proportionality will be assessed for Cycle 1 Day 1 (or Cycle 1 Day 2 for Part B) and Cycle 2 Day 1 (or Cycle 2 Day 2 for Part B) of the trial separately.

Each log-transformed PK parameter will be fit with a power model with a fixed effect term for log-transformed dose. For each PK parameter, the slope and associated 90% CI will be presented. Dose proportionality will be assessed based on whether the 90% CI includes 1.0.

8.6.2 Pharmacodynamics and biomarkers

Due to the exploratory nature of this analysis the PD and Biomarkers analyses may be conducted if there is enough data.

8.6.3 New anti-cancer treatment

New anti-cancer treatment as collected at trial withdrawal, safety follow-up and survival follow-up will be listed.

9 REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline E3: Note for Guidance on Structure and Content of Clinical Study Reports (CPMP/ICH/137/95), July 1996. Retrieved on 30 January 2018 from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf
2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline E9: Statistical Principles for Clinical Trials (CPMP/ICH/363/96), March 1998. Retrieved on 21 April 2019 from http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf
3. Brookmeyer R. and Crowley J. A confidence interval for the median survival time. Biometrics 38:29-41, 1982
4. Clopper, CJ and Pearson, ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26: 404-413, 1934
5. Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. FDA December 2018.

10 SUPPORTING DOCUMENTATION

10.1 Appendix 1: Changes to protocol-planned analyses

- An ‘enrolled set’ was defined to summarize the patient disposition summary and patient data listings of screen failures and exclusion from analysis sets.
- The protocol mentions summarizing adverse events, it was clarified during SAP development that only TEAEs should be summarized. All AEs will be listed.

10.2 Appendix 2: List of abbreviations

AE	Adverse event
Ae_{t1-t2}	Amount of BNT411 excreted in urine over the time interval from time=t1 to time=t2
AJCC	American Joint Committee on Cancer Staging
ATC	Anatomical-Therapeutic-Chemical
AUC	Area Under the Curve of concentration versus time
$AUC_{\%extrap}$	Extrapolated portion of any AUC
AUC_{0-24}	Area Under the Curve of concentration versus time calculated from the time of dosing to 24 hours post-dose
AUC_{0-48}	Area Under the Curve of concentration versus time calculated from the time of dosing to 48 hours post-dose
AUC_{0-inf}	Area Under the Curve of concentration versus time calculated from the time of dosing to infinity
AUC_{0-last}	Area Under the Curve of concentration versus time calculated from the time of dosing to the last measurable concentration
$AUC_{0-\tau}$	AUC from time 0 to the end of the 168-hour dosing interval (τ)
BCVA	Best Corrected Visual Acuity
BMI	Body Mass Index
bpm	Beats per minute
BSA	Body surface area
C_{eoi}	End-of-infusion concentrations
CI	Confidence interval
CL	Clearance, calculated as $Dose/AUC_{0-inf}$
$CL_{R,t1-t2}$	Renal clearance of BNT411 over the collection interval between t1 and t2
C_{max}	Maximum concentration
CR	Complete response
C_{trough}	Trough concentration
CRO	Contract Research Organization
CTR	Clinical Trial Report
C_u	BNT411 concentrations
CV	Coefficient of Variation
DBP	Diastolic blood pressure
DCR	Disease control rate
DEC	Dose-expansion cohort
DI	Dose intensity
DLT	Dose-limiting toxicities
DMC	Data monitoring committee

DOR	Duration of response
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
ES-SCLC	Extensive-stage small cell lung cancer
FDA	Food and Drug Administration
fe_{t1-t2}	Fraction of BNT411 dose excreted in urine over the time interval from time=t1 to time=t2
GFR	Glomerular Filtration Rate
GGT	Gamma-Glutamyl-Transpeptidase
IPD	Important Protocol Deviations
iRECIST	immune Response Evaluation Criteria in Solid Tumors
IRR	Infusion-related Adverse Events
ITT	Intent-To-Treat
irAE	Immune-related Adverse Events
kg	kilogram
KM	Kaplan-Meier
LLN	Lower Limit of Normal
LLOQ	Lower limit of quantification
LNH	Low, Normal, High
MedDRA®	Medical Dictionary for Regulatory Activities
mL	millilitre
mmHg	millimeter of mercury
MSAP	Modeling and Simulation Analysis Plan
MTD	Maximal tolerated dose
MUGA	Multigated acquisition
N	Number of Patients
n	Number of Observations
NCI CTCAE	National Cancer Institute - Common Terminology Criteria for Adverse Events
NIPD	Non-Important Protocol Deviations
ORR	Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral blood mononuclear cells
PD	Pharmacodynamics
PFS	Progression-Free Survival

PopPK	population-based pharmacokinetic
PK	Pharmacokinetics
PR	Partial Response
PT	Preferred Term
$R_{A,AUC}$	Accumulation ratio for AUC computed as AUC_{τ} after Cycle 2 Day 1 divided by AUC_{τ} after Cycle 1 Day 1
$R_{A,Cmax}$	Accumulation ratio for C_{max} computed as C_{max} after Cycle 2 Day 1 divided by C_{max} after Cycle 1 Day 1
RDI	Relative dose intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SBP	Systolic Blood Pressure
SD	Standard Deviation
SI	International System of Units
SOC	System Organ Class
SRC	Safety Review Committee
SQRT	Square Root
$T_{1/2}$	Terminal phase half-life
$T_{1/2,eff}$	Effective half-life for accumulation computed as $\ln(2)\tau/\ln(R_{A,AUC}/[R_{A,AUC}-1])$
TCR	T-cell receptor
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
T_{max}	Time from dosing to the maximum observed plasma concentration
ULN	Upper Limit of Normal
V_D	Volume of distribution
V_u	Urine volume
WHO DD	World Health Organization Drug Dictionary
λ_z	Terminal elimination rate constant
µg	Microgram

10.3 Appendix 3: Reporting conventions

SAS version 9.4, or higher, will be used to produce all tables, listings, and figures.

For summary statistics, the mean and median will be displayed to one decimal place greater than the original value and the measure of variability (e.g., SD) will be displayed to two decimal places greater than the original value. Minimum and maximum will be reported to the same decimal places as the original value. Percentages (%) will be displayed with one decimal place and 95% CIs will be displayed with one decimal place greater than the original value.

Cohort in the Table 4 will be used for the Tables/Figures/Listings display as appropriate:

Table 4: Treatment Descriptors

Trial part	Cohort	Cohort label	Treatment code
Part 1 A – Monotherapy dose escalation	BNT411 0.05 (µg/kg)	Dose escalation BNT411 0.05 (µg/kg) cohort	1
	BNT411 0.15 (µg/kg)	Dose escalation BNT411 0.15 (µg/kg) cohort	2
	BNT411 0.45 (µg/kg)	Dose escalation BNT411 0.45 (µg/kg) cohort	3
	BNT411 1.2 (µg/kg)	Dose escalation BNT411 1.2 (µg/kg) cohort	4
	BNT411 2.4 (µg/kg)	Dose escalation BNT411 2.4 (µg/kg) cohort	5
	BNT411 4.8 (µg/kg)	Dose escalation BNT411 4.8 (µg/kg) cohort	6
	BNT411 6.0 (µg/kg)	Intermediary dose escalation BNT411 7.2 (µg/kg) cohort	7
	BNT411 7.2 (µg/kg)	Intermediary dose escalation BNT411 6.0 (µg/kg) cohort	8
	BNT411 9.6 (µg/kg)	Dose escalation BNT411 9.6 (µg/kg) cohort	9
Part 1B – combination (Atezolizumab + carboplatin + etoposide + BNT411) dose escalation	BNT411 (1.2 µg/kg) combination therapy	atezolizumab + carboplatin + etoposide + BNT411 (1.2 µg/kg) Dose escalation cohort	101
	BNT411 (2.4 µg/kg) combination therapy	atezolizumab + carboplatin + etoposide + BNT411 (2.4 µg/kg) Dose escalation cohort	102

Note: The treatment code will be used in the statistical procedures.

Trial part	Cohort	Cohort label	Treatment code
Part 1A	Same as above table	Same as above table	Same as above table
Part 1B	Atezolizumab	atezolizumab 1200 mg	201
	carboplatin	carboplatin (mg)	301
	etoposide	etoposide 100 mg/m^2	401

BNT411	BNT411 DL x.x	50x

For Part 1B, x.x in BNT411 ranges from 1.2 µg/kg to 2.4 µg/kg.

10.4 Appendix 4: Schedule of activities

10.4.1 Dose Escalation Phases (Parts 1A and 1B)

Table 5 and Table 6, respectively, list all of the assessments to be performed in Parts 1A and 1B (dose escalation phases) of the trial.

Table 5: Schedule of Activities – Part 1A

Treatment Cycle	**Screening**	**Cycle 1 to 2**					**Cycle 3 to 4**			**Cycle 5 to N**			**Treatment discontinuation1**	**Safety follow-up 1**	**Safety follow-up 2**	**Survival follow-up2**	**Unscheduled**
Day (D)	**≤21 days prior to Visit C 1 (D1)**	**D1**	**D 2**	**D3 24**	**D8**	**D15**	**D1**	**D8**	**D15**	**D 1**	**D8**	**D15**	**-**	**30 days after last dose**	**60 days after last dose**	**Every 12 weeks**	
Visit window		**±D 3**	**-**	**+D 2**	**±D 1**	**±D 1**	**±D 3**	**±D 1**	**±D 1**	**± D 3**	**±D 1**	**±D 1**	**-**	**+D5**	**±D7**	**±D14**	
Informed consent	X																
Informed consent for genetic testing	X																
Eligibility criteria	X																
Demographics	X																
Medical history[19]	X																
Height	X																
Body weight	X	X					X			X			X	X			X[3]
Physical examination[4]	X	X			X	X	X	X	X	X	X	X	X	X			X[3]
Eye examination[5]	X	X[6]								X[6]			X	X			X[7]
Vital signs[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X[3]
ECHO or MUGA scan[9]	X																X[3]
ECG	X	Refer to CTP Section 8.6.3 and Table 1-3 for details on ECG assessments															
CT/MRI scan	X[10]	Refer to CTP Section 8.5.1 for details on Imaging assessments[11]															
ECOG performance status[12]	X	X			X	X	X	X	X	X	X	X	X	X	X		X[3]
Adverse events[13]	X	CONTINUOUS														X[14]	X[3]
Prior/concomitant medications and non-drug therapies[21]	X	CONTINUOUS														X[22]	X[3]
BNT411 administration[15]		X			X	X	X	X	X	X							
End of treatment													X				
New anti-cancer treatment													X	X	X	X	
Survival follow-up																X[2]	
LABORATORY ASSESSMENTS (to be performed up to 3 days before administration days, unless indicated otherwise)																	
Hematology	X[16]	X[17]	X	X	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[3]	X	X	X		X[3]

Treatment Cycle	**Screening**	**Cycle 1 to 2**					**Cycle 3 to 4**			**Cycle 5 to N**			**Treatment discontinuation1**	**Safety follow-up 1**	**Safety follow-up 2**	**Survival follow-up2**	**Unscheduled**
Day (D)	**≤21 days prior to Visit C 1 (D1)**	**D1**	**D 2**	**D3 24**	**D8**	**D15**	**D1**	**D8**	**D15**	**D 1**	**D8**	**D15**	**-**	**30 days after last dose**	**60 days after last dose**	**Every 12 weeks**	
Visit window		**±D 3**	**-**	**+D 2**	**±D 1**	**±D 1**	**±D 3**	**±D 1**	**±D 1**	**±D 3**	**±D 1**	**±D 1**	**-**	**+D5**	**±D7**	**±D14**	
Biochemistry	X[16]	X[17]	X	X	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[3]	X	X	X		X[3]
Coagulation factors	X[16]	X[17]			X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[17]	X[3]	X	X	X		X[3]
Endocrine[18]	X[16]	X[17]					X[17]			X[17]		X[3]	X				X[3]
Urinalysis	X[16]				X[17]		X[17]		X[17]	X[17]		X[3]	X	X	X		X[3]
Pregnancy test[19]	X[16]	X[17]					As indicated clinically per investigator's assessment and per local guidelines and regulations.						X	X	X		X[3]
Serology [16]	X[23]																
PK sampling (includes blood and urine)	Refer to CTP Table 1-3 for details of PK samplings																
Tumor biopsy, biomarkers	Refer to CTP Table 1-7 for detailed biomarker assessment schedule																

1 If the patient has to go off treatment per treatment withdrawal criteria (refer to CTP Section 7.1), the treatment discontinuation visit should be performed as soon as possible after permanent discontinuation of BNT411.

2 Survival follow-up starts after all other protocol required visits have been completed and may be performed as telephone, email, or clinic visit.

3 Only if relevant or clinically indicated.

4 Full physical examination should be performed at screening, thereafter a limited physical examination is performed as indicated by the patient's symptoms, AEs, or other findings as determined by the investigator. Physical examination should be performed before drug administration.

5 To be performed by an ophthalmologist. Must at least include visual acuity testing, slit-lamp examination and direct or indirect ophthalmoscopy to help diagnose cataracts, glaucoma, detached retina, macular degeneration, and cornea injuries. Patients who wear glasses must have their baseline visual acuity properly documented. Further examinations such as visual field testing, non-contact tonometry and retinal tomography can be done if required.

6 Eye examination will be done at baseline (during screening), up to 3 days before Cycle 2 and thereafter up to 3 days before every third cycle (i.e., C2, C5, C8, C11, etc.).

7 The investigator should schedule eye examination with an ophthalmologist if there is suspicion of worsening of the eyesight, or if the patient complains about decrease in visual acuity or ocular discomfort. Patients should be referred to an ophthalmologist at the investigator's discretion at any time-point of the trial.

8 Temperature, blood pressure, pulse rate and respiratory rate as according to Section 8.6.2 and Table 1-6 of the CTP on BNT411 administration days. On days when BNT411 is not administered, vital signs only need to be obtained once any time during the visit.

9 Evaluation of left ventricular function, either by echocardiogram (ECHO) or multigated acquisition (MUGA) scan, will be performed within 21 days prior to Screening and as clinically indicated at other time points. Note: country specific information for Germany, left ventricular function should only be assessed by an ECHO scan (see CTP Section 12.2.1).

10 All patients will have a CT scan with contrast agent or MRI of thorax, abdomen, and pelvis during screening. Head and neck imaging is also required for patients with squamous cell carcinoma of the head and neck (SCCHN). Imaging of the pelvis is not required for patients with SCCHN but is strongly recommended. If a CT scan or MRI has been performed within 21 days before the Cycle 1 Day 1 visit as part of standard procedures, then this scan will be acceptable as a screening scan for the trial. If brain metastases/tumors are indicated, a CT scan or MRI of the brain will be performed within 21 days before the Cycle 1 Day 1 visit. Scans that exceed the 21-day window may be used for trial enrollment with sponsor approval.

11 On-treatment imaging will be performed at Week 6 (+7 days), every 6 weeks (±7 days) for 48 weeks, and every 12 weeks (±7 days) thereafter until disease progression is assessed by the investigator (unless the investigator elects to continue treatment [see CTP Section 8.5.1 for conditions of continued treatment]), withdrawal of consent, trial termination by the sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy. Refer to CTP Sections 10.5 and 10.6 for RECIST 1.1. and iRECIST imaging and treatment guidelines.

12 ECOG status should be assessed before drug administration.

13 Adverse events (AEs) and serious adverse events (SAEs) should be reported from the time of signing the informed consent to 60 days (±7 days) after the patient receives the last dose of BNT411.

14 Suspected BNT411-related AEs only. Furthermore, in Germany only, all SAEs that occur in the patient throughout his or her lifetime should be reported – refer to CTP for further details.

15 Patients who experience a delay in the administration of BNT411 should return to the clinic at least every 2 weeks (±3 days) and assessments listed under ‘unscheduled visit’ should be performed and reported in the eCRF. Unscheduled visit assessments should be performed at the investigator’s discretion.

16 All labs at the screening visit must be obtained within 7 days of Cycle 1 Day 1. All lab assessments except for PK and biomarkers are done locally.

17 Laboratory samples should be obtained up to 3 days before treatment administration.

18 TSH, free-T3 and free-T4 will only be measured at screening, Cycle 1 Day 1, Cycle 2 Day 1, and on Day 1 of every evenly numbered cycle thereafter.

19 Serum pregnancy test is performed at screening. Thereafter, urine pregnancy test is sufficient unless indicated otherwise. The frequency of testing during treatment phase may depend on clinical indication per investigator's assessment and may also depend on local guidelines and regulations.

20 Medical history includes cancer history.

21 Prior/Concomitant Medications and Non-Drug Therapies include all anti-cancer pre-treatments.

22 Prior/Concomitant Medication and Non-Drug therapies only for BNT411 related AEs.

23 Country specific procedure for Germany: To confirm that a patient would be eligible to participate in the trial, an active infection with HIV/Hepatitis B or C should be ruled out by serum blood test of hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis B surface antigen (anti-HBs), antibody against hepatitis C virus (anti-HCV), antibody against HIV-1 and -2 (anti-HIV 1/2).

24 The visit window of +2d on Day 3 should only be used if absolutely necessary due to immune phenotyping.

Table 6 Schedule of Activities – Part 1B

Treatment Cycle	Screening	Cycle 1-2					Cycle 3- 4					Cycle 5–N				Treatment discontinuation[1]	Safety follow-up 1 [27]	Safety follow-up 2 [27]	Survival follow-up[2]	Unscheduled
Day (D)	≤21 days prior to Visit C1 (D1)	D1	D2	D3	D8	D15	D1	D2	D3	D8	D15	D1	D2	D8	D15		30 days after last dose	60 days after last dose	Every 12 weeks	
Visit window		±D3	-	+D2	±D1	±D1	±D3	-	+D2	±D1	±D1	±D3	-	±D1	±D1		+D5	±D7	±D14	
Informed Consent	X																			
Informed Consent genetic testing	X																			
Eligibility Criteria	X																			
Demographics	X																			
Medical History[23]	X																			
Height	X																			
Body weight	X	X					X					X				X	X			X[3]
Physical Examination[4]	X	X			X	X	X			X	X	X	X	X	X	X	X			X[2.,3]
Eye Examination[5]	X	X[6]										X[6]				X	X			X[7]
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			X[3]
ECHO or MUGA scan[9]	X																			X[3]
ECG	X	Refer to CTP Section 8.6.3 and Table 1-3 for details on ECG assessments																		
CT/MRI Scan	X[10]	Refer to CTP Section 8.5.1 for details on Imaging assessments11																		
ECOG Performance Status[12]	X	X			X	X	X			X	X	X		X	X	X	X	X		X[3]
Adverse Events[13]	X	CONTINUOUS																	X[14]	X[3]
Prior/Concomitant Medications and Non-Drug Therapies[24]	X	CONTINUOUS																	X[25]	X[3]
BNT411 Administration[15]			X		X	X		X		X	X		X							
Atezolizumab Administration[16]		X					X					X								
Carboplatin Administration[17]		X					X													
Etoposide Administration[17]		X	X	X			X	X	X											

Treatment Cycle	**Screening**	**Cycle 1-2**					**Cycle 3- 4**					**Cycle 5–N**				**Treatment discontinuation[1]**	**Safety follow-up 1 [27]**	**Safety follow-up 2 [27]**	**Survival follow-up[2]**	**Unscheduled**
Day (D)	**≤21 days prior to Visit C1 (D1)**	**D1**	**D2**	**D3**	**D8**	**D15**	**D1**	**D2**	**D3**	**D8**	**D15**	**D1**	**D2**	**D8**	**D15**		**30 days after last dose**	**60 days after last dose**	**Every 12 weeks**	
Visit window		**±D3**	**-**	**+D2**	**±D1**	**±D1**	**±D3**	**-**	**+D2**	**±D1**	**±D1**	**±D3**	**-**	**±D1**	**±D1**		**+D5**	**±D7**	**±D14**	
Prophylactic cranial irradiation												X[18]								
End of Treatment																X				
New anti-cancer treatment																X	X	X	X	
Survival follow-up																			X[2]	
LABORATORY ASSESSMENTS (to be performed up to 3 days before administration days, unless indicated otherwise)																				
Hematology	X[19]	X[20]	X	X	X[20]	X[20]	X[20]			X[20]	X[20]	X[20]		X[20]	X[20]	X	X	X		X[3]
Biochemistry	X[19]	X[20]	X	X	X[20]	X[20]	X[20]			X[20]	X[20]	X[20]		X[20]	X[20]	X	X	X		X[3]
Coagulation factors	X[19]	X[20]			X[20]	X[20]	X[20]			X[20]	X[20]	X[20]		X[20]	X[20]	X	X	X		X[3]
Endocrine[21]	X[19]	X[20]					X[20]					X[20]				X				X[3]
Urinalysis	X[19]				X[20]		X[20]				X[20]	X[20]				X	X	X		X[3]
Pregnancy Test[22]	X[19]	X[20]					As indicated clinically per investigator's assessment and per local guidelines and regulations.									X	X	X		X[3]
Serology [19]	X[26]																			
PK Sampling (includes blood and urine)	Refer to CTP Table 1-3 for details of PK samplings																			
Tumor biopsy, biomarkers	Refer to CTP Table 1-7 for detailed biomarker assessment schedule																			

1 If the patient has to go off treatment per treatment withdrawal criteria (refer CTP Section 7.1), the treatment discontinuation visit should be performed as soon as possible after permanent discontinuation of BNT411. A separate treatment discontinuation visit should also be done after discontinuation of atezolizumab, carboplatin and etoposide, if it occurs ≥21 days later than BNT411 (this visit will be entered as unscheduled visit in the eCRF).

2 Survival follow-up starts after all other protocol required visits have been completed and may be performed as telephone, email, or clinic visit.

3 Only if relevant or clinically indicated.

4 Full physical examination should be performed at screening, thereafter a limited physical examination is performed as indicated by the patient's symptoms, AEs, or other findings as determined by the investigator.

5 To be performed by an ophthalmologist. Must at least include visual acuity testing, slit-lamp examination exam and direct or indirect ophthalmoscopy to help diagnose cataracts, glaucoma, detached retina, macular degeneration, and cornea injuries. Patients who wear glasses must have their baseline visual acuity properly documented. Further examinations such as visual field testing, non-contact tonometry and retinal tomography can be done if required.

6 Eye examination will be done at baseline (during screening), up to 3 days before Cycle 2 and thereafter up to 3 days before every third cycle (i.e., C2, C5, C8, C11, etc.)

7 The investigator should schedule an eye examination with an ophthalmologist if there is suspicion for worsening of the eyesight, or if the patient complains about decrease in visual acuity or ocular discomfort. Patients should be referred to an ophthalmologist at the investigator's discretion at any time-point of the trial.

8 Temperature, blood pressure, pulse rate and respiratory rate as according to CTP Section 8.6.2 and Table 1-6 on BNT411 administration days. On days when BNT411 is not administered, vital signs only need to be obtained once any time during the visit.

9 Evaluation of left ventricular function, either by echocardiogram (ECHO) or multigated acquisition (MUGA) scan, will be performed within 21 days prior to Screening and as clinically indicated at other time points. Note: country specific information for Germany: left ventricular function should be assessed by an ECHO scan (see CTP Section 12.2.1)

10 All patients will have a CT scan with contrast or MRI of thorax, abdomen, and pelvis during screening. Head and neck imaging is also required for patients with squamous cell carcinoma of the head and neck (SCCHN). Imaging of the pelvis is not required for patients with SCCHN but is strongly recommended. If a CT scan or MRI has been performed within 21 days prior to visit Cycle 1 Day 1 as part of standard procedure, it is acceptable as a screening scan for the trial. If there is suggestion of brain metastases/tumors, a CT scan or MRI of the head and neck will be performed within 21 days prior to the Cycle 1 Day 1 visit. Scans that exceed the 21-day window may be used for trial enrollment with sponsor approval.

11 On-treatment imaging will be performed at Week 6 (+7 days), every 6 weeks (±7 days) for 48 weeks, and every 12 weeks (±7 days) thereafter until disease progression is assessed by the investigator (unless the investigator elects to continue treatment [see CTP for conditions of continued treatment]), withdrawal of consent, trial termination by the sponsor, or death, whichever occurs first, regardless of whether patients start a new anti-cancer therapy. Refer to CTP Sections 10.5 and 10.6 for RECIST 1.1. and iRECIST imaging and treatment guidelines.

12 ECOG status should be assessed before drug administration.

13 Adverse events (AEs) and serious adverse events (SAEs) should be reported from the time of signing the informed consent to 60 days (±7 days) after the patient receives the last dose of BNT411, or atezolizumab, or carboplatin or etoposide, whichever occurs later.

14 Suspected BNT411 related AEs only. Except for Germany and Spain, where AEs related to atezolizumab, carboplatin, and etoposide should also be reported. Furthermore, in Germany only, all SAEs that occur in the patient throughout his or her lifetime should be reported – refer to CTP Table 1-5 and Section 10.3.4 for further details.

15 Patients who experience a delay in the administration of BNT411 should return to the clinic at least every 2 weeks (±3 days) and an unscheduled visit should be performed and reported in the eCRF. Unscheduled visit assessments should be performed at the investigator's discretion.

16 After discontinuation of chemotherapy, atezolizumab will be administered in combination with BNT411.

17 The recommended number of chemotherapy cycles is 4. If the investigator decides to administer more than four cycles, this should be discussed with the Medical Monitor.

18 After 4 cycles, prophylactic cranial irradiation (PCI) is permitted as per local guidelines and will be reported on the cancer radiotherapy eCRF. No systemic anti-cancer therapies should be administered concurrently with PCI. A delay of ≤21 days in administering systemic anti-cancer therapies due to PCI is not considered a protocol deviation.

19 All labs at the screening visit must be obtained within 7 days of Cycle 1 Day 1. All lab assessments except for PK and biomarkers are done locally.

20 Laboratory samples should be obtained up to 3 days before treatment administration.

21 TSH, free-T3 and free-T4 will only be measured at screening, Cycle 1 Day 1, Cycle 2 Day 1, and on Day 1 of every evenly numbered cycle thereafter.

22 Serum pregnancy test is performed at screening. Thereafter, urine pregnancy test is sufficient unless indicated otherwise. The frequency of testing during treatment phase may depend on clinical indication per investigator's assessment and may also depend on local guidelines and regulations. Pregnancy testing should also be done after discontinuation of atezolizumab, carboplatin, and etoposide if it occurs ≥21 days later than BNT411.

23 Medical history includes cancer history.

24 Prior/Concomitant Medications and Non-Drug Therapies include all anti-cancer pre-treatments.

25 Prior/Concomitant Medications and Non-Drug Therapies only for BNT411 related AEs.

26 Country specific procedure for Germany: an active infection with HIV/Hepatitis B or C should be ruled out by serum blood test of hepatitis B surface antigen (HBsAg), antibody to hepatitis B core antigen (anti-HBc), antibody to hepatitis B surface antigen (anti-HBs), antibody against hepatitis C virus (anti-HCV), antibody against HIV-1 and -2 (anti-HIV 1/2).

27 A separate safety follow-up visit should also be done after discontinuation of atezolizumab, carboplatin and etoposide, if it occurs ≥21 days later than BNT411 (this visit will be entered as unscheduled visit in the eCRF).

28 The visit window of +2d on Day 3 should only be used if absolutely necessary due to immune phenotyping.

10.5 Appendix 5: Dose escalation table

Number of evaluable patients with DLT at a given dose level after the first treatment cycle	Escalation decision rule
0 out of 3 OR 1 out of 6	Enter patients at the next higher dose level
1 out of 3	Enter more patients at this dose level to a total of at least six evaluable patients or two patients with DLT
2 out of 3 OR at least 2 out of 6	Dose escalation will be stopped, the MTD will be considered to be reached at the one before the last dose level explored. The sponsor will decide, based on a discussion between the investigators and the sponsor at a dose escalation meeting, if additional patients need to be enrolled and at which dose to finalize the trial
Any condition which would require further clarification of safety	A cohort of 6 patients can eventually be extended and more patients can be enrolled in a cohort if decided by the sponsor based on a discussion between the investigators and the sponsor at a dose escalation meeting

DLT = dose-limiting toxicity; MTD = maximal tolerated dose.

The dose escalation will potentially (dependent on data collected during the trial) evaluate BNT411 at eight main dose levels as shown in Appendix 6.

10.6 Appendix 6: BNT411 dose increments

Dose level	Dose of BNT411* (µg/kg/administration)	Dose increment*
1**	0.05	Starting dose
2**	0.15	200%
3**	0.45	200%
4	1.2	166%
5	2.4	100%
6	4.8	100%
7	9.6	100%
8	16.0	66%

* Can be reduced or increased as a function of the observed biologic activity and based on other data generated during the trial for dose optimization.

** Accelerated titration (single-patient cohorts). Will be expanded to 3+3-patient cohorts in case of occurrence of grade ≥2 toxicities, or the occurrence of DLTs, or based on the decision of the sponsor's SRC based on safety data generated.

In addition to the above mentioned dose level, BioNTech proposes seven optional, intermediate dose levels at 0.075, 0.225, 0.9, 1.8, 3.6, 7.2 and 12.8 µg/kg.